DRUG BENEFITS AND RISKS

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Drug Benefits and Risks

International Textbook of Clinical Pharmacology

Revised 2nd edition

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Foreword to the Second Edition

The second edition of this textbook of clinical pharmacology is welcome in a world of evidence-based pharmacotherapy and guidelines. The key concept of the textbook continues to be the emphasis on drug benefit to risk ratio. The book is divided into three sections. Section I contains general principles, such as medicines and society, pharmacoepidemiology and drug evaluation, pharmacoeconomics, drug regulation, sources of drug information, and concepts essential to drug utilization in different populations. Section II incorporates an overview of drug classes discussed under a mechanistic point of view, providing the best possible evidence-based information on pharmacological issues. Section III is an evidence-based approach to the treatment of specific health problems. Benefits and risks of biologicals are also discussed. Finally, critical information is given on drugs that have been withdrawn in western countries, but are freely available in low income countries. Included in this section are chapters on symptomatic treatment and emergency medicine. The textbook provides a practical and useful expert guidance on patient treatment, and by offering a mechanistic description of most important drugs, it presents a basis to individualise dosages.

The textbook will be an excellent tool for optimal drug utilisation, not only by clinical pharmacologists but also by medical practitioners. This is of great importance because evidence-based pharmacotherapy and the profusion of guidelines have contributed to weaken the therapy individualisation approach. As a result, even if the benefits of drugs may have increased, the ratio benefit/risk may be decreasing. For instance, adverse drug events still account for 2.5% of estimated emergency department visits for all unintentional injuries, and for 2.1, 6.7 and 30% of hospitalisations in the paediatric, adult and elderly populations, respectively (BMJ 2004;329:15-9; JAMA 2006;296:1858-66). The incidence of drug-related deaths in university hospitals is around 0.5% (Eur J Clin Pharmacol 2002;58:479-82). It is distressing that 33% of adverse drug effects are still associated to warfarin, insulin and digoxin (Ann Int Med 2007;147:755-65). Approximately half the adverse effects reported are preventable. The cost of adverse drug effects to society is colossal, e.g. close to one billion $/year for a population of 60 000 000 (BMJ 2004;329:15-9).

Evidence-based pharmacotherapy provides a succinct appreciation of the benefits of a drug, but rarely takes into account the patient's quality of life. For instance, intensive statin therapy is recommended because it reduces the incidence of cardiovascular death (odds ratio 0.86), myocardial infarction (odds ratio 0.84), and stroke (odds ratio 0.82); however, the increased risks for any adverse event (odds ratio 1.44), for abnormalities on liver function testing (odds ratio 4.48), for elevations in CK (odds ratio 9.97) and for adverse events requiring discontinuation of therapy (odds ratio 1.28) are less often taken into account by the prescriber. This example emphasises that individualisation is of the utmost importance to keep an acceptable benefit/risk ratio (Clin Ther 2007;29:253-60). The benefits of evidence-based pharmacotherapy may be obtained whenever concordance/compliance of the patient is adequate. However, concordance rate is slightly higher than 30% for chronic conditions, such as hypertension (Curr Hypertens Rep 2007;9:184-9), indicating that the patient has to be educated about the use of drugs, and therapy has to be individualised.

Evidence-based pharmacotherapy and guidelines alone cannot solve the problems highlighted above, since individualisation, the risk of medication, as

well as quality of life are insufficiently taken into account. *Rational drug individualisation* is required and the textbook will be a practical and easy tool to achieve this goal.

Montréal, December 2007

Patrick du Souich, MD, PhD
Chairman, Division of Clinical Pharmacology
International Union of Basic and Clinical Pharmacology

Foreword to the First Edition

It is a great honour to endorse this international textbook in clinical pharmacology, particularly as the first ideas regarding the book were presented by the authors to the Council of the Division of Clinical Pharmacology, International Union of Pharmacology (IUPHAR) at its meeting in Buenos Aires in 1996 during the VIth World Congress in Clinical Pharmacology. The key concept of the book, to balance benefits and risks of drugs, was applauded by the council. Another idea of the authors has been to focus on the educational needs of students and prescribers in the developing world, while at the same time producing a text of interest to students in the Western World. In fact, developed and emerging countries seem to share a number of problems leading to irrational use of drugs, such as old-fashioned cook-book teaching in pharmacology and drug information that is product- rather than problem-oriented and dominated by the pharmaceutical industry. A third timely idea is to highlight the Cochrane concept of evidence-based pharmacotherapy, which in a way can be regarded as a rediscovery of the principles of the controlled clinical trial that were outlined by the first generation of clinical pharmacologists 40 years ago.

The pedagogic ideas of the three editors therefore harmonize with the main aim of the Division of Clinical Pharmacology, IUPHAR, to encourage rational use of drugs in society. The most appropriate drug should be prescribed to the right patient in an individualized dosage-schedule at a reasonable cost and with the right information. The latter includes a convincing explanation that the benefits of the treatment outweigh its potential risks. This is particularly important in view of the fact that in the Western World drug induced morbidity consumes a significant part of the health budget and that this is preventable to a large extent. A recent commentary by John C. Somberg, the editor of the *American Journal of Therapeutics* (1998, **5**, 135), is entitled Reactions to prescribed drugs kill thousands annually. The editorial points out that a new paradigm is needed in medical therapeutics and that better educated physicians in clinical pharmacology and drug selection are a must. Rational drug therapy must be based on the understanding of principles in clinical pharmacology and therapeutics, not the least a thorough knowledge of the mechanisms involved in interindividual and interethnic differences in drug response.

The future drug scenario implies that new and important drugs will be developed at increasing costs. At the same time, many new drugs will be introduced that offer small, if any, advantages compared to older and less expensive products. It will become even more important to spend the taxpayers' money on the right drugs. The responsibility of the prescribers will increase regarding pharmacotherapeutic competence, integrity versus drug promotion and awareness of the galloping drug bill. A remedy to achieve these goals is relevant educational material of the kind that is presented in this book.

Stockholm, November 2000

Folke Sjöqvist, MD, PhD, FRCP
Immediate Past Chairman, Division of Clinical Pharmacology
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Preface to the Second Edition

In the Preface to the First Edition we emphasised some key factors that led us to produce another text book in the general area of pharmacology and pharmacotherapy. For those who make decisions on the general availability of medicines, as well as those who provide treatment for individual patients, the essential need to be aware of and to balance the benefits and risks of medicines is paramount. Errors in these judgements will prove costly both financially and in terms of additional morbidity and mortality.

We stressed the ideal of equity in the provision of essential knowledge and information globally as part of the much larger ideal of striving for equity in health care. We want this Second Edition to be of good quality and useful content, but to be as cheaply and widely available as possible. To this end, an alliance between a new publisher, IOS Press, and the WHO Foundation Collaborating Centre for International Drug Monitoring should take us further in achieving this. The latter organisation will promote and distribute the book via its global network of cooperating national pharmacovigilance centres, using its contacts with academia as well, rather than using expensive retailers.

We believe the need for the Second Edition is even greater than before. Whilst we stress our concern for its availability in the developing world, we are ever conscious of the bewildering growth of information for everyone, particularly via the web. The world-wide-web is a major leveller across the world in information provision. On the other hand the very profusion is daunting and difficult to assimilate: not all the information is accurate or unbiased. Meanwhile, the number of therapeutic options becomes greater, more complex, and often more expensive. In this information explosion, our hope is that a fundamental text such as this will provide some of the essential approaches to the challenges of modern therapeutics, to enhance best possible therapy for the least risk.

Discussions on the clinical pharmacological profiles of medicines and therapeutic options that are currently available based on the best scientific evidence, will be incomplete without looking into the existing health care systems and the social environment. Specifically, whether the health system can ensure the accessibility to and affordability of the needed medicines, ensure the quality of medicines in the market, and ensure the effective and safe use of those medicines?

Access to health care is a fundamental human right, enshrined in international treaties and recognized by Governments throughout the world. But without equitable access to essential medicines for priority diseases the fundamental right to health can not be fulfilled. WHO estimates that over 10.5 million lives a year could be saved by 2015 – also by boosting economic growth and social development – by expanding access to existing interventions for infectious diseases, maternal and child health, and non-communicable diseases (*WHO Medicines Strategy – Countries at the Core 2004–2007*. Geneva, WHO, 2004). In the text of this Second Edition we incorporate also some policy perspectives of the WHO in promoting equitable access to essential medicines, in promoting rational use, and in combating counterfeit medicines. Assuring quality of medicines through effective medicines regulation is of the utmost importance, considering that the quality of medicines varies greatly, especially in low- and middle-income countries.

Where appropriate we have asked authors to explicitly discuss biologicals as both the benefit, but also the risks, of biopharmaceuticals are becoming increasingly important. During the last years a substantial part of the FDA- and EMEA-approved compounds has belonged to this class of drugs. These remedies have a number of characteristics that set them aside from low molecular weight drugs. Often their mechanisms of action are intimately related

to their complicated shape and associated with secondary, tertiary and (sometimes) quaternary structures of the molecule. These structures cannot be fully defined with our present set of analytical techniques. Drug analysis is further complicated by the fact that the exogenous compounds often are the same as (or closely resemble) endogenous proteins. This implicates that the performance of biopharmaceuticals relies on strict production protocols and close monitoring of their activity in the clinical situation. It also means that in safety testing and clinical test programs questions have to be addressed regarding species-specific responses, selection of routes of administration and dosing schedules. The possible occurrence of immunogenicity is an other challenging issue. Toxicity problems associated with monoclonal antibodies have included lymphokine release syndrome, reactivation of tuberculosis and other infections, immunosuppression but also anaphylactic shock. More insidious, but nonetheless devastating, antibodies to a recombinant hormone or cytokine have been shown to neutralize not only the product, but also the endogenous factor.

It has to be noted that many of these novelties are highly effective and also that mostly they are extremely expensive. Undoubtedly, as the usage of biologicals will increase, the cost should come down. However, this does not seem to be happening at an impressive rate and a new form of inequality between rich countries and low-income countries is becoming a threat. Academic leadership should persuade authorities to reduce customs duties and manufacturers to reduce prices for developing countries.

The so-called biologicals have received some special attention in this Second Edition of Drug Benefits and Risks as we feel that their appearance on the global market in the past decennium might signify a milestone in the history of pharmaceutical medicine.

Chris J. van Boxtel
Budiono Santoso
I. Ralph Edwards

Preface to the First Edition

This is a book about practical therapeutics and the surrounding general and pharmacological knowledge. The ultimate goal of the book is to give expert guidance on how to treat patients. Whilst the book is concerned with the best possible evidence-based therapy and information, it also aims to be a practical and useful guide wherever in the world patients are treated. To achieve this, authors of the various sections have been brought together from around the world, and have peer-reviewed each other's contributions.

As editors we would claim that part of problem-based learning is to have a starting point where practical information is given and also some of the adjoining philosophy. We want to emphasize that it is only knowledge that can prevent examples becoming models and that at the very moment students begin to think that there are model-answers to pharmacotherapeutic questions the whole concept of interindividual variability, so crucial for clinical pharmacology and thus for effective and efficient pharmacotherapy, is lost and one starts teaching cookbook therapy.

Where problem-based learning has been developed, the discussion and interaction with a local expert is usually an initial part of the exercise. Sadly, there are many places in the world where this practical expert advice is not easily available for a variety of reasons. A considerable need for more clinical pharmacological expertise has been observed and that such a need exists has been confirmed in the recent past by members of the Division of Clinical Pharmacology of the International Union of Pharmacology IUPHAR and by the International Network for the Rational Use of Drugs. It is also a fact that pharmacological texts in general and especially texts on basic principles are either not accessible or are not suitable for the circumstances in emerging countries. Often only texts provided by the pharmaceutical industry are available. If we believe that it is good to give young, intelligent students in the Western world access to books with 500–1500 pages of information on Clinical Pharmacology and Pharmacotherapy why then would that not be the case for students in the developing world? One could even argue that those countries might need more information because at the moment they are highly interesting markets for the industry, markets which at the same time often appear to be only poorly regulated at best.

On the other hand it would not be advisable to think of a teaching aid only fit to be used by people in the third world. Problems with respect to a responsible handling of drugs are not fundamentally different in emerging countries compared to the western world. However such problems exist on a much wider scale and there are special difficulties that doctors have to conquer when they prescribe medicaments in the developing world. More and more people all over the world are confronted with the same drugs, with the same policies of multinational industries and by the same limitations of financial possibilities. And for all clinical pharmacologists in the global village of today it is good to be reminded of the fact that outside the privileged world of Western countries extra difficulties exist with respect to the use of drugs. Therefore, what we wanted to provide to the developing world is an easy accessible text that at the same time should be of interest to students in the Western world.

Apart from inviting for several chapters first authors from non-Western countries, for each chapter advice was asked from experts in the developing world about items that are important for them and which are often not alluded to in texts aimed at students in the Western world. Often their input was of such importance that they are mentioned as co-authors.

We have preferred for the book to be standard in its format mainly for two reasons. We are aware of

the fact that nowadays in many curricula there is a trend to put less accent on pharmacology and more on pharmacotherapy and to integrate pharmacology teaching with the teaching of clinical medicine. We have not chosen for this option. Being teachers ourselves we more than once experienced that during the integration process time originally available for the explanation of rational drug use was lost to make place for lengthy discussions about diagnostic problems. The other reason is that the style and kinds of questions that could be asked to reinforce learning will vary all over the world and it was felt that teachers should have as much freedom as possible to formulate their own strategy for using this book in their teaching.

We all should be concerned about the huge socioeconomic impact of irrational prescribing and of medication errors. It is estimated that in the Western world some 10% of the health budgets is spent on drug induced or drug use related morbidity and that 50% of those costs are preventable. Such prevention would of course involve adequate pharmacology and pharmacotherapy teaching. We have expressed our concern in the title of this book which wants to underline that together with the benefits also the risks of medicaments should always be taken into account. Drug safety and the balance between benefits and risks have been of central interest throughout the text.

The most important ingredient of safe and efficacious pharmacotherapy is knowledge. Three areas of knowledge are involved. Firstly, knowledge of the basic principles of Clinical Pharmacology is needed. Secondly, a carefully dosed amount of knowledge about our pharmacotherapeutic tools should allow for appropriate choices. However, as a selection from the $\pm 80{,}000$ preparations that are traded world wide as medicaments is bound to be subjective, the limited factual information on individual drugs that is given is only meant to serve as an example. We fully realize that a serious problem for pharmacology teaching and thus for he rational use of drugs is the sheer volume of pharmacological and pharmacotherapeutic facts. Finally, knowledge about pharmacotherapeutic strategies in the various medical disciplines is required. The division of the book into three sections, **General Pharmacology**, both on a macro and on a micro level, **Specific Pharmacology** with an emphasis on drug groups rather than on individual agents and **Therapeutic Problems**, is based on the identification of these three areas of knowledge.

Section I, General Principles, basically deals with the questions how to handle drugs in society and in individuals. Conventionally, the scope and function of clinical pharmacology are more focused on individual patients, especially at a clinical setting or in a clinical research environment. This can be understood from the original definition that "clinical pharmacology is the scientific study of drugs in man". However, since the ultimate goal of clinical pharmacology is "the effective, safe and rational use of drugs", there now is clearly a need to expand the scope of clinical pharmacology and the discipline should also cover drug problems in communities as well as in populations. The development of pharmacoepidemiological and pharmacoeconomic tools has enabled clinical pharmacologists to study and influence the use of drugs at a macro and population level, not only to improve the safe and effective use of drugs but also their cost effectiveness. With the increasing challenges in many developing countries, especially with regards to access and rational use of drugs, the discipline of clinical pharmacology should be enriched with sufficient public health perspectives on how to provide the needed essential medicines of assured quality to the population and to ensure their appropriate use. Therefore, those who are interested in clinical pharmacology should also know the elements of policies, whether macro national policies or micro institutional policies, to achieve these objectives.

Section II, Pharmacotherapeutic Products, really wants to provide a birds eye view over our therapeutic armamentarium and give information about the drug groups which are available and useful. The emphasis is on the chemical similarities and the clinically important mechanistic differences. And again, it should be stressed that the colossal amount of simple facts that is available on individual compounds makes commemoration absolutely impossible.

Section III, Treatment of Health Problems, is about therapeutics and summarises evidence-based pharmacotherapeutic indications and drug regimens. The objective of this section is to allow experts to say, in their own way, what they think is important in their discipline. We are convinced that, especially for dealing with the safety issues of drugs, a solid knowledge of clinical pharmacology is mandatory and therefore for this section we also invited mostly authors with training in clinical pharmacology. The authors were asked to scrutinize the Cochrane database to look for the available evidence at the time of

writing. We do however agree with Professor Silvio Garattini that in many instances we should ask ourselves the question "Is the evidence there is really the evidence we need?".

Launched in 1991 in Geneva, the International Medical Benefit/Risk Foundation (IMBRF) was established to address the weighing of medical benefits, risks, and costs with a special focus on the pharmaceutical aspects of health care. Although forced in 1995 to reduce and later to discontinue its operations completely, over the years the Foundation has served, among others, as an international resource for patient organizations, technical experts, and the news media. Independent foundations that could operate in close contact with the IMBRF were initiated in England, Japan, Greece and Australia and also in the Netherlands the Risk Benefit Assessment of Drugs – Analysis and Response (RAD-AR) Foundation, in short the Dutch RAD-AR Council, was established.

Although the publishers have tried to keep the price low, so allowing as many as possible to have access to the book, through sponsorship by the Dutch RAD-AR council 800 free copies will be made available for emerging countries via the member National Centres of the WHO Programme for International Drug Monitoring. It is hoped they will find it useful, and even promote its use in their countries.

We would like to acknowledge The RAD-AR Council of the Netherlands for sponsorship. We particularly would like to thank our contributors for all the gratuitous efforts they put into the completion of this book. Those who, at our request, had to collaborate with colleagues on the other side of the globe, and were thus confronted with the special problems connected with such cooperation, earned our special gratitude. We are grateful to Professor Bill Lowrance, the former Executive Director of the IMBRF, for his much appreciated advice over the years. We are indebted to Dr. Jan Ufkes for his careful review of the chapters in Section II. Our thanks also go to Michael Davis, Deborah Reece, Michael Lewis and Hannah Bradley and all those other people at Wiley who had confidence in this project and who helped us to finish it.

Chris J. van Boxtel
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Section I

General Principles

Part A: Medicinals in Society

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Chapter 1

The Role of Therapeutic Agents in Modern Medicine
A: Drug Benefits

Ronald D. Mann

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I. INTRODUCTION

The subject of both sections of this chapter is complex. In the first place because after marketing the spectators in the therapeutic scene have a tendency to see different plays. Healthy people see something different from patients and the perspectives of governments, health insurers and manufacturers are all different. Furthermore we know that with respect to drug use important differences between countries exist and that intercultural and interethnic variations can have a decisive influence on the final outcome of drug use. It might therefore be good to first cite some figures to illustrate that in the modern world pharmaceuticals cannot and should not be considered as trivialities.

In most Western countries 70% to over 90% of visits to a general practitioner result in the writing of a prescription. Also in the Western world the prescription of 9 drugs on medical wards is common procedure and 20% of patients are using more than 4 agents in the period before they are admitted.

And finally, in the Western world total drug costs range between 6 and 10% of the health budget and in developing countries this percentage can even be much higher.

Drugs and vaccines can affect the outcome of disease in individual subjects and in populations. An example of this is shown in Fig. 1 relating to notifications of poliomyelitis in the UK. Poliomyelitis changed in the early 20th Century from a disease that was endemic in young children (infantile paralysis) to a disease that became epidemic in young adults (paralytic poliomyelitis). This change was associated with improvements in hygiene and sanitation which tended to limit the faecal–oral spread of the virus in infants and young children. As a result fewer children grew up with naturally acquired immunity and a pool of susceptible young adults accumulated in the population. Figure 1 shows the dramatic increase in notifications of poliomyelitis in the early years following World War II and the dramatic effect of the Salk killed virus vaccine which was given by injection and the Sabin live attenuated vaccine which was given orally. Many of the small number of cases reported after the vaccines had become available and were widely used had, in fact, been acquired overseas. Figure 1 shows the dramatic effect of the anti-poliomylitis vaccines on the incidence of the illness in the UK community. Figure 2 shows deaths due to all forms of tuberculosis in the

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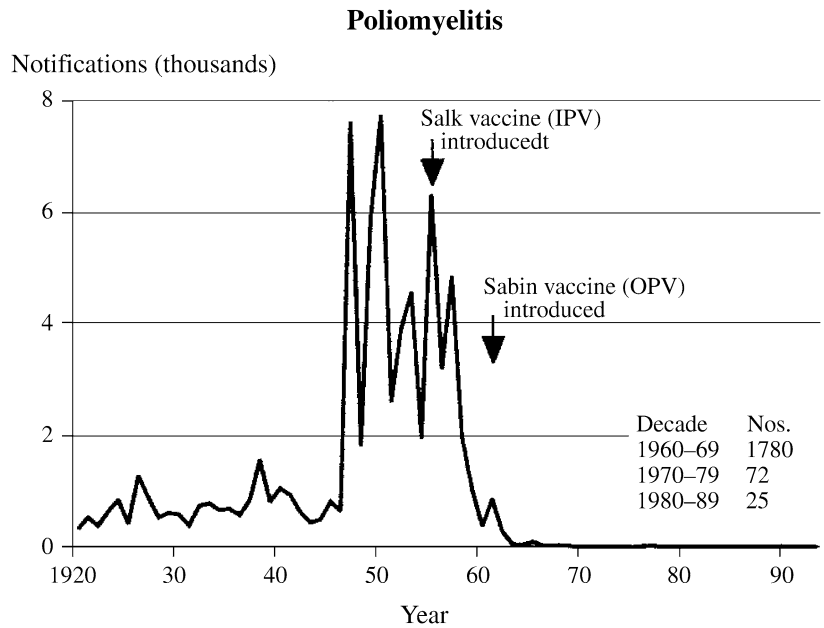


Fig. 1. Notifications (thousands) of poliomyelitis (from Galbraith et al., 1997).

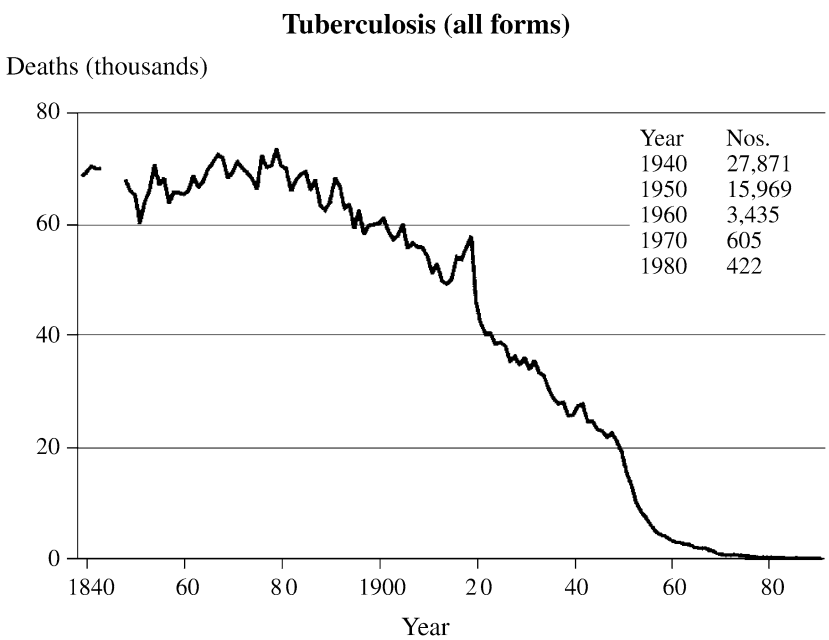


Fig. 2. Deaths (thousands) due to tuberculosis (from Galbraith et al., 1997).

UK from 1840 until near the end of the 20th Century. Horton Hinshaw and William Feldman's paper on "Streptomycin in treatment of clinical tuberculosis: A preliminary report" appeared in the Proceedings of the Mayo Clinic in 1945. For his work on antibiotics and the discovery of streptomycin Selman Waksman received the Nobel Prize in 1952. Streptomycin and the later anti-tuberculosis drugs made a very dramatic differerence to the prognosis of individual tuberculous patients in the early post-

War years following their introduction into clinical medicine. However, the dramatic decline in the number of deaths due to tuberculosis in the years from 1940 to the end of World War II – as shown in Fig. 2 – was due to continuing improvements in hygiene, housing, sanitation, diet and the rising standards of living. Thus Fig. 2 very nicely demonstrates the dramatic effect of a very serious disease such as tuberculosis in response to improvements in the social environment of the community. The specific anti-tuberculosis drugs, once they became available, made a dramatic difference to the outcome of infection in individual patients and thus to the pool of infection affecting the UK community.

II. THE BEGINNING

Modern medicine can be said to have begun with a cluster of events that marked the last decade or two of the 18th Century. One of these events was the publication in 1785 by William Withering (1741–1799) of his "An account of the foxglove, and some of its medical uses". This book, the first monograph devoted to a single drug in the English medical literature, remains startlingly modern when read through today.

Withering's discovery of the clinical use of digitalis was important, but it may well be that his contribution to the methodology of pharmacology and therapeutics was of even greater importance. His rejection of polypharmacy, his attention to pharmaceutical product quality and to the standardization of his remedy, and his development of the technique of dose-titration enabling a drug with the narrowest of therapeutic ratios to be used safely – were recorded in a way that seems as fresh today as it ever was. These aspects of his work, the careful and detailed nature of his clinical observations, and the aphoristic nature of his splendid "Inferences" continue to excite one's admiration today (see Mann, 1985).

III. THE MILESTONES

Serturner reported the isolation of morphine in 1805; Pelletier and Magendie published on the isolation of emetine in 1817; the paper by Robiquet on the isolation of codeine was dated 1832 and that by Mein on the isolation of atropine in pure form was dated one year later. These four papers typify the isolation of active principles and pure substances that characterized the opening decades of the 19th Century – decades that were marked by the availability of pure substances available for experimentation and clinical usage. The pharmacopoeia was beginning to change from its essentially herbal content of previous years.

In 1831 and 1832 Soubeiran, Guthrie and Liebig independently reported the discovery of chloroform and in 1852 Gerland published on the synthesis of salicylic acid – these activities heralding the mid-century beginnings of the use of anaesthetics and the synthesis of new agents of therapy.

The first edition of the first official *British Pharmacopoeia* was dated 1864: the contents of its 1867 edition included acetate of morphia, carbolic acid, ether, atropine, extracts of belladonna, chloroform, cinchona bark, digitalin, ergot, extract of male fern, granulated sulphate of iron, iodine, leeches, lemons, magnesia, opium, proof spirit, quinine pills, squill, suppositories of morphia, valerian and zingiber. The modern doctor cast up on a desert island with the contents of this pharmacopoeia might find all of these of use if there was anyone there to treat. Apart from these items the modern doctor would find little use for the still largely herbal contents of the medicine chest of that time. Today's doctor would want to weed out pretty quickly, from the 1864 pharmacopoeia, the obvious poisons, such as aconite, antimony, arsenic and so on down a long list of strange ingredients still in use here in the West one and a half centuries ago.

There was a long way to go before the doctor, in the presence of serious disease, could do more than motivate the patient to be composed in the face of the benign or malign forces of nature.

IV. THE 20TH CENTURY

Dreser introduced acetylsalicylic acid into medicine in 1899. Langley, in 1905, brought in the concept of a receptor substance with which a drug has to interact in order to exert its biological effect. Sir Henry Dale and his colleagues reported on their studies of histamine in 1910. Jacobs and Heidelberger introduced tryparsamide in 1919 – and so, in the years before and during World War I, we began to reach towards the modern era of drugs targeted at the identified causes of disease. Of these pioneers none are

remembered more clearly than Paul Ehrlich (1854–1915) whose work began the chemotherapeutic revolution and led, in 1911, to the use of his compound 606 ('Salvarsan' arsphenamine) in the treatment of human syphilis.

The period between the two World Wars of 1914–1918 and 1939–1946 was marked by the discovery by Banting and Best of insulin and the epoch-making discovery by Sir Alexander Fleming of penicillin. The idea that the latter discovery was a happy accident is almost certainly wrong. Fleming had for long been working on lysozyme and there can have been few people in the world more used to seeing the effects, in culture plates, of bacteriolytic or bacteriostatic substances. The period between the two wars saw many other advances, including the publication in 1934 of Von Euler's work on prostaglandins and the first description by Bovet and Staub, in 1937, of the stucture and action of an antihistamine.

V. POST-WAR DEVELOPMENTS

Progress in the years following World War II has been exponential and greatly affected by two fundamentally important developments. These have been, firstly, the progress made by medicinal chemists and pharmacologists in rational drug design and discovery and, secondly, the discovery and development of the computer.

One of the most remarkable exponents of drug design using receptor theory and antagonism at receptor sites has been Sir James Whyte Black. In 1962, Black reported the development of pronethalol, a specific adrenergic beta-receptor antagonist relatively free from sympathomimetic activity on the cardiovascular system. Pronethalol, the lead candidate of the beta-blocking antihypertensive, antiangianal, anti-arrhythmic drugs of today, was discarded due to clinical side effects and the finding that it produced, in the mouse but not in the rat or dog, lymphosarcomas and reticulum-cell sarcomas.

A large number of compounds were then made and tested in order to develop a drug candidate with a wider therapeutic ratio and no carcinogenic potential. Black and his colleagues, in 1964, as a result of these exertions, which were akin to the persistence of Ehrlich, finally were able to introduce the resulting drug, propranolol. Propranolol then became the agent that introduced the concept of the adrenergic beta-blockers into clinical medicine. It thus is a major place in the history of 20th Century medicine.

Black then went to work on the antihistamines, his interest having been aroused by the fact that these drugs had no effect on histamine-induced gastric acid output. This suggested that there must be more than one kind of histamine receptor. In 1972 Black postulated that the pharmacological receptors involved in the histamine responses that could be blocked by conventional antihistamines, such as mepyramine, might be termed the H1-receptors. Work to find blockers for the H2-receptors concerned with gastric acid secretion involved the synthesis and testing of some 700 compounds – and resulted in the introduction of cimetidine.

It seems worthwhile to have a closer look at the birth and coming of age of the computer as this device has gained such a prominent place, not only in daily life, but also in the realm of pharmacotherapeutics.

Charles Babbage (1792–1871) is generally held to be the pioneer of today's computer. He conceived a number of machines such as the Difference Engine and the Analytical Engine, that were mechanical devices used to compute mathematical tables. Limited by the available technology only a section of the Difference Engine was ever built. World War II saw the introduction of the German 'Enigma' message coding machines and the British 'Colossus' code-breaking machine.

Early stored-program electronic machines were developed in the mathematics departments of a number of universities, specifically for the solution of complex or repetitive calculations. In the UK, both Manchester and Cambridge conducted research programmes into data storage techniques. It was in January 1954 that the first high speed stored-program commercial computer, LEO-1, based on the Cambridge technology, was completed in the UK (see Simmons, 1962). This monstrous machine contained 6000 thermionic valves and occupied a large air-conditioned room with suspended flooring. It was, however, the first machine to regularly process the payroll of a significantly large work force and undertake other substantial data processing operations for a major commercial organization.

By the late 1950s the transistor, and devices such as magnetic core storage systems, made it possible to manufacture considerably faster and smaller 'mainframe' computers. The late 1960s saw the introduction of integrated circuits making it possible for many transistors to be fabricated on one silicon substrate. The microprocessor, and random access

memory, became a reality in the mid-1970s and with the introduction of 'large-scale integration' many thousand transistors could be etched on to one substrate. LEOs mercury delay line store, its only store, for there was no hard disk, was 2048 words, each 17 bit. Today's PCs have their storage measured in megabytes and their hard disks in gigabytes – a thousand or even ten thousand fold difference!

This vast difference in computertational power and data storage capability is the strength that has permitted many of the undertakings of contempory epidemiology and bio-statistics.

Developments with respect to the automation of medical practices, especially in western Europe, the USA and Canada, and the creation of new useful databases in many places in the world, together with increased demands both by regulatory agencies and pharmaceutical companies for more quantitative information on the performance of drugs, have stimulated an enormous increase in interest in pharmacoepidemiology. To create the large databases needed for case-control and cohort studies a variety of approaches is used in different countries. The future of pharmacoepidemiology will, to a large extent, depend on the development of new and improved databases and improvement of the existing databases. An important database to be mentioned in this context is that of the Uppsala Monitoring Centre. In the late 1960s and early 1970s the World Health Organisation (WHO) started to create a database of spontaneous reports of suspected adverse drug reactions. This began on a small scale in Geneva and later in the WHO Collaborating Centre for International Drug Monitoring in Uppsala, Sweden. It is now called the Uppsala Monitoring Centre. The system is based on interchange of adverse reactions information between national drug monitoring centres virtually worldwide. Together these centres annually provide over 200,000 individual reports of suspected adverse drug reactions. Without modern computer facilities data gathering on this scale would be absolutely impossible.

Automated pharmacy services as they exist in several European countries also facilitate the study of drug use to a considerable extent.

It has been shown that computerized physician order entry substantially decreases the rate of non-missed-dose medication errors.

Another completely computer-dependent endeavour is the Human Genome Project, an international research effort to sequence and map all of the genes – together known as the genome – of members of our species, *Homo sapiens.* Completed in April 2003, the Human Genome Project gave us the ability to read nature's complete genetic blueprint for building a human being. Closely related to this project is the rapidly expanding field of pharmacogenomics. New technologies in both combinatorial chemistry and combinatorial biology promise to unlock new opportunities for drug discovery and lead optimisation. Using genome based technologies to measure the dynamic properties of pharmacological systems, pharmacogenomics can provide an objective measure of a drug's biological efficacy, including its potential adverse effects.

Computer-aided modelling for drug design is another approach for drug discovery that has become standard and the advantages and limitations of a neural networks for computer-aided molecular design and sequence analysis are a hot topic today.

Finally, we must consider the Internet. There is no area in medicine and in pharmacotherapy where the World Wide Web System will not provide an extensive source of information.

VI. THE CLOSE OF THE 20TH CENTURY

It is quite obvious that the doctor today has a range of therapies available which can cure or control or beneficially affect a very wide range of illnesses. An example of a group of drugs that beneficially affect the lives of vast numbers of people is the oral contraceptives. The first practical demonstration of such a contraceptive used in a mammal was reported in 1953. From those beginnings have arisen a group of drugs which, with minimal known risk, allow women to control their own fertility.

First-generation gene medicines and genetic vaccines represent a promising new class of therapeutics that have the potential to prevent, correct, or modulate genetic or acquired diseases. Biopharmaceuticals are becoming increasingly important medicines in many therapeutic areas. Nowadays a substantial part of the FDA-approved drugs belong to this class of agents. Undoubtedly, as the use of biologicals will increase, the cost will also come down. However, biopharmaceuticals deserve special attention as they have a number of characteristics that set them aside from low molecular weight drugs. Their activity and their kinetic behaviour depend on their complicated shape based on secondary, tertiary and

(sometimes) quaternary structures. These structures cannot be fully defined with our present set of analytical techniques and approaches. They often are the same as (or closely resemble) endogenous proteins. Those are challenging issues but those challenges need to be met.

VII. NON-DRUG EFFECTS

Although we rejoice in the modern pharmacopoeia we must remember that beneficial drug effects cannot be separated from effects due, in communities, to improvements in nutrition, housing, hygiene, clean water, better food storage, antenatal and infant welfare care, improved economic security, improved education – and a whole host of such important factors which affect the natural history of disease. As has already been mentioned, tuberculosis provides a prime example of the effects of these factors on disease. However, constant vigilance is needed for complacency, social depravation, and poor care of the public health can allow these killing diseases of the past to creep back by means which include the development of drug resistant micro-organisms.

VIII. CONCLUSION

Pharmaceutical innovation, together with rising education, sanitation and wealth, prolonged life expectancy in industrialised countries throughout the 20th Century. At the turn of the 21st Century, with many, formerly common, lethal diseases confined to the developing world, the benefits of medical intervention are taken for granted in industrialized countries. Notwithstanding estimates which indicate that the efficacy of drugs and vaccines has resulted in an increase of life expectancy of some 15 years while, on average, drug toxicity costs us approximately 40 minutes of our lives (see Heilman, 1988), there are some problems in therapeutics that seem to attract our attention and affect or limit the role of therapeutic agents in modern medicine. What are these problems? Each individual will have his or her own list and any such list must be conditioned by what that individual has experienced and learnt in medical practice.

Therapeutic agents have a vast and exponentially expanding role in modern medicine. Devices also showing dramatic developments and are becoming increasingly important. However we should not become overly melioristic. There are serious questions to be asked and we should, while it is still possible, check unreasonable expectations where these have been fostered by those who gain by promising an utopia that is still, in reality, some considerable distance away.

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Chapter 1

The Role of Therapeutic Agents in Modern Medicine B: Drug Risks

Jerry Avorn

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I. INTRODUCTION

Despite all the good that prescription drugs do, evidence continues to mount that adverse drug events are a common, costly, and often preventable cause of illness, disability, and even death. The challenge is to appreciate this downside of drug therapy, to define it, and to understand how the problems associated with it can be prevented. More and more data are becoming available concerning the frequency, clinical consequences, and cost of adverse drug events. At a time in which measures of quality and expenditures in the healthcare system are being scrutinized with great care, these are particularly important issues. Perhaps most importantly, adverse drug events are preventable in many instances. For healthcare resources to be used as efficiently as possible, preventing drug induced illness is one of the most promising areas for future efforts. This does not require rationing or withholding of care; it just requires better clinical decision making. In order to accomplish this, it is necessary to understand the causes of drug induced illness.

Most drug-induced illness comes about through one of four mechanisms: (a) poor prescribing decisions by physicians, despite the availability of clear evidence; (b) errors in dispensing or administration of a drug; (c) poor compliance by the patient resulting in under use, overuse, misuse, or complete cessation of therapy; and (d) the occurrence of previously unanticipated adverse drug reactions, whose existence was not clearly predicted by pre-marketing clinical trials. For each of these causes one must consider the origin, its consequences, and, perhaps most important, what can be done for each cause to prevent it.

II. PHYSICIAN PRESCRIBING

If one had to assess the burden of disability from drug induced illness, poor prescribing decisions by doctors would probably account for the largest piece. The causes of poor prescribing are fairly well understood, and each leads to some important conclusions. In all countries for which there is enough information on this matter, there is ample evidence that medical students are poorly trained to use drugs. The conventional excuse is that the drugs that are used during the span of their studies will not be in use by the time the students finish their training. So, why teach them about these medications? To some extent this is true. But it is still imperative to teach trainees how to think about prescribing issues: how to balance risks and benefits, and increasingly, how to balance risks and benefits and cost; how to develop an

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approach to prescribing; how to evaluate data about new drugs. These are all timeless lessons that belong in the medical school curriculum, perhaps more than almost anything else. Without this information young doctors are often subject to whatever demands their patients come in with, or whatever arguments are made to them by a cost-container or by a sales representative, and they are not adequately equipped to translate this information into arguments that they can assess and act on rationally.

Another reason for major problems with physician prescribing is information overload. Powerful and effective biomedical research in medical centers all across the world is generating new information at a staggering pace, and is the source of many vital new treatments. But this avalanche of data can result in too much information for any one human being to assimilate and use in a practical way on a day to day basis. This has important policy aspects as well. Most countries impose very small or even zero requirements for physicians to demonstrate ongoing competency once they are in practice. This is true in any area of medicine, but is most important in the area of prescribing. There is a need for much better certification processes reviewing whether doctors are keeping up with new knowledge, as part of any comprehensive approach to reducing poor prescribing.

Many practicing physicians also have difficulty in finding good sources of information about drugs. It would take many hours a day, hours that are just not available, to read even just the very best journals. A strong need exists for evidence-based sources of information that would scan the continuously evolving collection of clinical and epidemiologic data on drug effects and that would be constantly updated, not by a payor (whether governmental or otherwise), for whom cost containment may be the uppermost priority, nor by a manufacturer, for whom sales promotion may be the key motivation, but by a nonprofit entity with no such secondary motivations. In this way, doctors could be provided with a continuing synthesis of new information, well referenced, but boiled down to a succinct, user-friendly format and they could feel comfortable that the purveyors of such prescribing information are providing unbiased, non-product-based information about common drug choices.

At the moment such guidance is hard to come by simply because we have too much information. Although most governments remain rather passive in their expectations about what they want doctors to know about therapeutics, other groups are very concerned with what is prescribed, and those concerns are not necessarily the same as those of patients. If only cost containment initiatives by payers drive prescribing, then doctors are at risk of not using good new drugs that are available. Conversely, commercial pressures from manufacturers can also distort drug choices and increase costs unnecessarily. Direct-to-consumer advertisements, increasingly common in the United States, can bring the doctor's attention to a product that he or she had not been using, or cause them to work up a previously unaddressed problem. But more often it also may merely oblige the doctor to get into long discussions with patients about why the drug they saw advertised is not appropriate for them.

A related problem of poor prescribing is the undertreatment of treatable disease. This is an area in which some direct-to-consumer advertising could turn out to be a good thing. Examples of diseases that are undertreated include depression, hypertension and incontinence. Here too, a better flow of information to doctors could make a big difference in improving appropriate drug use.

Poor prescribing may also involve using a new costly drug when a more established product would work as well. Conversely, physicians who do not keep up with new drug discoveries may keep their patients on drugs that are less effective or are causing side effects when newer, better alternatives are available.

One useful approach to tackle this problem of drug-induced illness caused by bad prescribing is known as "academic detailing", in which a trained health professional meets with the physician in his or her office and functions as a source of neutral, academically oriented, evidence-based knowledge (see www.RxFacts.org).

Another positive development is the proliferation of evidence-based guidelines, although sufficient evidence is often not available to base guidelines on. The work of the Cochrane collaboration throughout the world is a very useful approach to deal with the growing mass of clinical evidence that is being generated. As drug ordering on the computer becomes more common, the best available information on drug choices can be presented at the time a prescribing decision is being made, opening the door to an exciting new era in quality improvement and continuing medical education.

III. DRUG DISPENSING AND ADMINISTERING

The second major cause of drug-induced illness, and one that has captured a great deal of attention, comprises errors made in drug dispensing and administering after the prescription has been written. A growing body of data documents that which things go wrong with distressing frequency during dispensing and administering drugs. With the publication of seminal papers in recent years, this problem has come out of the closet and people are talking about it more openly. This is good because problems like this tend to improve if people talk about it; if the issue is ignored, it is likely to persist or get worse.

While medicine is a special profession in many ways, it also shares some aspects with other industries. Researchers who have seen this connection have been doing exciting work in bringing the tools of those industrial models to bear in understanding drug dispensing and administering. It has been argued that no airline would be allowed to fly if it had error rates comparable to those that prevail in health care. Because problems of medication errors occur one at a time, among sick people, and often under circumstances where only healthcare professionals know what really happened, it becomes more difficult to discern a pattern or define a rate. Another part of the problem is that many in medicine do not see their mission the way airlines see theirs. Airlines understand that because they are an industrial concern they must have quality management procedures in place at every step in the production line. Industrial consultants help them to do this, figure out how often should a jet plane be inspected, what to do if you find a faulty part. The medical profession needs to learn the same kinds of systems approaches to thinking about medication administration errors.

Some simple but powerful solutions have come from this industrial model of quality assurance. For example, just the removal of concentrated potassium chloride solutions from hospital wards can prevent a toxic dose of potassium from being accidentally injected intravenously. Making the color of the tubing different may prevent epidural lines and IV lines being interchanged so that medication intended to go into a vein does not go into the epidural space,or vice versa.

There are many other examples of such a systems approach to reducing drug-induced illness caused by this kind of error.

The computer is also an attractive tool to prevent errors, and one that is coming into widespread use in relation to drug prescribing and administration. The entire prescription can easily be translated into digitized information and barcodes. A number of hospitals now have barcoded not just medications, but also a patient's identification bracelets and the nurse as well, to verify who gave a certain medication to a certain patient, with the date and the location recorded automatically. Hospitals and health care systems are increasingly eager to invest in this approach because the technology is becoming so cheap and efficient and ubiquitous; the consequences of just one patient having a major side effect from a drug that was not theirs or was given in the wrong dose are so terrible as to justify the difficulty and cost of putting these systems into place.

IV. PATIENT COMPLIANCE

Poor compliance by patients is another important cause of drug-induced illness. In research from our group and many others, a similar disheartening pattern is repeatedly seen. About 50% of what doctors prescribe for chronic illness does not get taken,and roughly this same number was found for every indication studied: hypertension, congestive heart failure, glaucoma, hypercholesterolemia. Why is this problem so prevalent? Part of the difficulty is that we physicians are not living up to our responsibilities as teachers. The word "doctor" comes from the same root as the word "teacher", and teaching has traditionally been a very important part of the doctor's role. This was particularly true during the times when doctors were not able to do very much for their patients, except prognosticate and tell them about their illness. Now, so much can be done that doctors often don't get around to teaching their patients very much. Yet they are sentd home with prescriptions for large quantities of potentially toxic chemicals that can either cure them or kill them, and it is often assumed that somebody else will fill in the details. That is a role in which pharmacy can play an important part, but this doesn't take the responsibility off the prescriber's shoulders as well.

Part of this relates to the problem of polypharmacy. Some patients take 9 medications and they need every one of those 9. But the worrisome kind of polypharmacy is the unbridled, undisciplined use of a large number of drugs, especially in a frail older

patient, when not all of them are truly needed. It is ludicrous to expect that a patient will be able to go home and readily be able to keep track of 9 different medications takenconcurrently. We know that the more drugs prescribers add to a patient's regimen, the more likely it is that something will not get taken as directed. The best way to reduce this risk of poor compliance is to get the regimen stripped down to the necessities.

V. UNANTICIPATED ADVERSE DRUG REACTIONS

A final area to consider among the underlying causes of drug-induced illness is the occurrence of previously unanticipated adverse drug reactions. The past few years have seen an unprecedented rash of drug withdrawals because of potentially fatal side effects: the cox-2 inhibitors Vioxx and Bextra, which doubled the risk of myotrcardial infarction or strike; the non-steroidal antiinflamatory drug Duract which caused fulminant hepatic failure, the antihypertensive Posicor which caused severe bradycardia and hypotension, and the anorexiant fenfluramine which resulted in pulmonary hypertension and cardiac valve damage. What these agents have in common is that each of them was found to cause life-threatening problems only after they were in widespread use. In the United States, the concern has been raised that this mini-"epidemic" of post-marketing drug disasters has occurred following legislative attempts to speed new drugs through the approval process at FDA, and to shorten review times.

Whatever the relationship between unexpected adverse events and the drug approval process, it is clearly the case that many important adverse events will escape detection in even the most careful, painstaking pre-marketing clinical trials. Such trials generally enroll only modest numbers of patients, do not follow them over many years, and usually do not include the frail and complex patients who are at greatest risk of experiencing an adverse drug event. Other limitations of pre-marketing studies are even more important in understanding their limited ability to detect important side effects, but there is little evidence that they will be addressed in the near future. These include the active exclusion of adequate numbers of elderly patients, and the astonishingly short timeframe (often measured in terms of just a few months) of pivotal studies of chronic medications. For all these reasons, a full understanding of a drug's potential for risk can become apparent only after it has begun to be used in large populations. It is here that the science of pharmacoepidemiology takes center stage, and can teach us much more than we could possibly know, even under ideal conditions, from randomized trials. As pre-approval clinical studies and review times become ever smaller, there will have to be a corresponding increase in the intensity and rigor of mandatory post-marketing surveillance programs to help redress this balance. Sadly, there is no compelling evidence at present that this is taking place.

Medications remain among the safest and most cost-effective technologies in all of medicine, and our growing understanding of the frequency and importance of drug-induced illness should not obscure this fact. Rather, concern about this potential for harm from medicines should awaken new interest in the root causes which have been briefly outlined above, since each aspect of drug-induced illness is the product of its own underlying forces. By trying to better understand these forces, we can seek to reduce the frequency and severity of drug-induced illness, and allow our ever-expanding armamentarium to maximize patient benefit at the same time that it minimizes risk.

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Chapter 2

Therapeutics as a Science

Marcus M. Reidenberg

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I. HISTORY

Interest in the treatment of disease can be found in documents as old as records exist. Folklore accumulated about outcomes following use of presumed medicines. These outcomes were thought to be due to the drug. The Ebers papyrus, written in Egypt around 1550 BC, was a compilation of some of this folklore.

In India, Ayurveda, a whole conceptual system of living, including dealing with disease, may have started around 1500 BC. The codification of this system of medicine, including the concept of a formulary in which herbal remedies and recipes for them are described, was written in Sanskrit around 100 BC–100 AD or possibly earlier.

Chinese legend states that the first herbal formulary was developed by an emperor around 2700 BC. The written record of a Chinese herbal formulary comes from the Han dynasty (206 BC–220 AD).

In the Americas, lack of a written record makes dating the origins of Native American medicine difficult. European explorers wrote about some experiences. In the winter of 1535–1536, ships of Jacques Cartier were stuck in ice near Montreal. Scurvy occurred in the crew and a local chief told of a tree that produced 'a juice and sap' that cured the disease. An extract of the leaves and bark was made and it cured the scurvy in the crew. Early explorers in Peru wrote of the effects of coca leaves. Curare was used in the Amazon region for its muscle paralyzing effect as an arrow poison. Many other plant preparations used for medicinal purposes were described by early explorers in the Americans but dating their origins is impossible today.

Physicians throughout history described events that occurred after taking medication and assumed that the medication caused the event. They did not understand that even though an effect followed a dose of a medicine, the effect was not necessarily caused by the medicine. To gain confidence that an effect was really caused by the drug, controlled trials were needed and an evaluation of the likelihood that the effects were due to chance had to be made.

The idea of the comparative trial was described in the Bible. In 1 Kgs. 18: 21–24:

> And Elijah came near unto all the people and said: How long halt ye between two opinions? If the Lord be God, follow Him; but if Baal, follow him. And the people answered him not a word. Then said Elijah unto the people: I, even I only am left a prophet of the Lord; but Baal's prophets are four hundred and fifty men. Let them, therefore, give us two bullocks; and let them choose one bullock for themselves, and cut it in pieces, and lay it on the wood, and put no fire under; and I will dress the other bullock, and lay it on the wood.

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> and put no fire under. And call ye on the name of your god, and I will call on the name of the Lord, and the God that answereth by fire, let him be God.

The Bible goes on to describe the failure of Baal to start a fire under his bullock. When Elijah called upon the Lord, a fire promptly started, consuming the offering and thereby presumably proving to the assembled people which was the true God.

While this idea of a comparative trial was known in the time of Elijah in the ninth century BC, it took 2500 years for physicians to learn this biblical lesson. In 1774, James Lind did his famous trial comparing several different recommended treatments of scurvy and showing that one worked while all of the others were worthless. It is important to recognize that each of these treatments was recommended by recognized authorities of the day. One must assume that these intelligent physicians had reasons why they thought the remedies they recommended worked. It was just that they were wrong. But it took the comparative trial, not 'clinical observations' to prove that citrus juice cured scurvy and the other treatments were worthless.

An example of the kind of thinking of 18th century physicians that could lead to such ineffective or positively harmful recommendations is Benjamin Rush's treatment of the yellow fever epidemic in Philadelphia in 1793 (see Powell, 1949). Dr. Rush was one of the most highly respected physicians in North America in the 18th century.

Powell wrote:

> When the usual remedies failed and the death rate soared, Rush became desperate. 'I gave bark in all its usual forms of infusion, powder and tincture. I joined wine, brandy, and aromatics with it. I applied blisters to the limbs, neck and head. Finding them all ineffectual, I attempted to rouse the system by wrapping the whole body, agreeably to Dr. Hume's practice, in blankets dipped in warm vinegar. To these remedies I added one more: I rubbed the right side with mercurial ointment, with a view of exciting the actions of the vessels in the whole system through the medium of the liver'.

This, too, failed. Then Rush read a manuscript of John Mitchell's description of yellow fever in Virginia in 1741. 'Rush received its doctrine as revelation. He realized that the trouble had been, not that he purged, but that he purged too gently. He must boldly empty the abdominal viscera. He must purge with a mighty effect'.

This new system seemed to work. Indeed, it far exceeded Rush's expectations. It 'perfectly cured' four out of five patients, he declared. Thus, Dr. Rush fell for the fallacy that events following a drug were due to the drug. In fact, Philadelphia vital statistics showed that the people with yellow fever in Philadelphia in 1793 who were unable to receive the medical attention of Dr. Rush or the others following his teachings had a better chance for survival that those who were treated.

II. DEVELOPMENT OF PHARMACOLOGY

Chauncey Leake, in his presidential address to the American Association for the Advancement of Science in 1961, named the accumulation of lore about medicines proto pharmacology. Real pharmacology, he wrote 'could not develop until the rise of modern chemistry'. Compounds could be purified by the end of the 18th century. Setuner, early in the 19th century, isolated morphine from opium. He found in experiments on animals and on himself that this was the active principle in opium.

The ability of investigators to work with pure compounds gave them the opportunity to give reproducible doses of active principles. This made studying dose–response possible and was the start of scientific pharmacology. The fundamental issues of pharmacology, as defined by Leake, are:

1. The relationship between dose and biological effect.
2. The localization of the site of action of a drug.
3. The mechanism(s) of action of a drug.
4. The absorption, distribution, metabolism, and excretion of a drug.
5. The relationship between chemical structure and biological activity.

By addressing these fundamental issues, the science of pharmacology produces a body of valid facts about drugs and a series of generalizations about drugs that are the basis of therapeutics. Yet therapeutics, dealing with the treatment of disease, requires more than basic pharmacology. An understanding of disease, of pathophysiology, and of human nature are all required to make the response to a therapeutic intervention more predictable. This is the essence of therapeutics as a science, Therapeutics as a science

is determined by the degree of predictability of the response to an intervention and to the understanding of this degree of predictability. It is this predictability that enables one to assess the safety and efficacy of a drug or to do a risk to benefit analysis. This also lets valid comparisons of new treatments to old be made, enabling therapeutics to evolve rather than remain static. An understanding of the factors to be considered in predicting a response enables one to choose a drug rationally or to adjust a dose to a particular person's individuality. Addressing these issues has led to the development of the discipline of clinical pharmacology.

III. DEVELOPMENT OF CLINICAL PHARMACOLOGY

III.a. Placebo-Controlled Trials

While Lind described the method of the comparative trial, he was not concerned with issues that we now call the placebo effect. The first placebo controlled trial was published by Evans and Hoyle in 1933. They evaluated drugs used in the treatment of angina pectoris. Their comments almost 75 years ago are appropriate today.

> The value of remedies in relieving anginal pain cannot be judged unless the observations are properly controlled. The literature on the treatment of angina gives no indication that this side of the problem has been considered, although it is recognized that the disease pursues a varying course in regard to severity quite apart from any form of treatment.
> No facts seem to be available on variations in the severity of symptoms during the course of angina of effort over weeks or months. This knowledge is essential if we are to have control of therapeutic investigations. A contribution to this problem is furnished by our control observations. Sixty-six patients were treated with a placebo for periods of 4–26 weeks. In some patients the periods of placebo treatment were consecutive, but usually they were separated by periods during which active drugs were taken.
> Of the 66 patients who received placebo treatment for more than one test period of fourteen days, 18 (27%) showed great improvement which included complete relief from attacks for one or more observation periods. Seven (10.5%) showed moderate improvement, 22 (33.5%) showed no improvement, and 19 (29%) were worse.

Evans and Hoyle then described their findings in the study of 15 different drugs used by the conscientious physicians of the 1920s to treat patients with angina. Their conclusions were:

> With one exception, they (the drugs) show that a measure of improvement appears to result from every remedy tried, and at least as great an improvement during treatment with placebo. This universal efficacy can only be explained by natural variations in the severity of the symptoms, which give a spurious value to each remedy. If any drug had proved to be superior there might have been grounds for recommending it in the continuous treatment of the disease, but no such precedence could be made out.

Thus, Lind showed the importance of the comparative trial and Evans and Hoyle showed the importance of the placebo effect in evaluating drug response. Gold et at. then showed the importance of observer bias and introduced the concept of the double-blind study in 1937 in a study of treatments for angina patients. They wrote:

> The method of securing data proved to be by far the most laborious aspect of the whole work. The validity of the results in the study depends chiefly on the nature of the questions that the patient was asked and the accuracy of the answers. No effort was spared in the endeavor to secure the patient's most accurate judgments, since these judgments regarding changes in the severity of a subjective symptom formed the factual data on which the analyses are based. It was fully realized that the study could be no better than this part of the work.

Patients were questioned by the examining physician.

> It was found that, in the initial reply regarding changes in pain, patients often failed to take into account all the necessary factors on which the judgment was to be based, and, not infrequently, more thorough questions resulted in their revision of their first appraisal. Therein

> was appreciated an important source of error of another kind; namely, the leading question. Various devices were employed to guard against directing the patient's judgment. Usually they were frankly informed that the examiner was uncertain as to whether the medicine would prove helpful or not, and the idea was conveyed to them that, in any case, subsequent planning for their treatment depended on the accuracy of their statements regarding their condition during the period that had elapsed. *In a further attempt to eliminate the possibility of bias, the questioner usually refrained from informing himself as to the agent that had been issued until after the patient's appraisal of the period had been obtained.*

This was the origin of the double blind study to avoid bias on the part of the observer as well as the patient.

The issue of compliance (or adherence), of whether or not patients even take their medicine, has only been of concern to physicians since medications of scientifically proven efficacy have been available. Mohler and colleagues studied patients prescribed penicillin for streptococcal pharyngitis or otitis media. All patients or their parents were interviewed after the end of a course of oral penicillin. Thirty-four percent admitted taking less than the prescribed dose. The most frequent reason given for not completing the full course of treatment was that the patient felt well after one or two days of therapy and though that continuing to take the penicillin was unnecessary. Modern studies have shown that compliance is good for once a day or twice a day medication schedules. Compliance falls off for medication scheduled more frequently than twice a day.

III.b. Use of Statistical Analysis

While the concepts related to pharmacology and to the humanness of patients had been articulated in these studies by the middle of the 20th century, the idea that a difference between two groups could be due to chance was slower to be accepted. The first clinical trial to use a formal statistical analysis was a study of antibody production following yellow fever vaccination by two different methods. Several years later, Schor and Karten wrote a vigorous critique of the lack of proper study design or data analysis in the papers being published in major medical journals. In this critique, they appear to have set the criterion of $P < 0.05$ for a difference between two groups that is not due to chance that has become the rigid criterion for statistical 'significance'.

This is the way the methods for the scientific study of drugs in humans, the first theme of clinical pharmacology, were developed. The thalidomide disaster of 1961 stimulated the acceptance of the need for scientific evidence of efficacy and safety of drugs before they are marketed and promoted. Requiring this evidence by government agencies before approval for marketing then followed.

A limitation of interpreting a study as significant when the difference between the groups is unlikely to be due to chance is that it ignores the magnitude of the difference. A trial that includes many subjects, often in the thousands, can find a very small difference not due to chance. For instance, the AFCAPS/TexCAPS study of Lovastatin involved 6605 subjects for an average of over 5 years each. The drug-treated subjects had 67 fewer heart attacks during this time than the placebo-treated subjects. While the difference was less likely than 1 in 1,000 ($P < 0.001$) due to chance, the magnitude of the difference required that 256 people needed to be treated for a year to prevent one heart attack.

III.c. Individualization of Drug Therapy

The thalidomide disaster of 1961 also focussed the world on the subject of adverse drug reactions. This lead to the development of the second theme of clinical pharmacology, individualization of therapy. In 1951, two hematologists, Wintrobe and Sturgeon, each noted a few cases of aplastic anemia in patients who had taken chloramphenicol. Checking with colleagues, they learned of a few more cases. This lead to the formation of the American Medical Association's Committee on Blood Dyscrasias in 1955, the AMA blood dyscrasia registry and the start of systematic study of adverse drug reactions.

Observational studies of adverse drug reactions identified two clinical factors that appeared to predispose to a high frequency of adverse drug reactions. These were the total number of different drugs the patient was taking and the presence of pre-existing kidney failure.

The first factor lead to the studies of drug interactions. These had been preceded by studies of factors that modified drug metabolism and were focused primarily on pharmacokinetic drug interactions

The second factor, pre-existing kidney failure, also received further attention. Initially, concern was

with antibiotic doses, drugs that were excreted by the kidney, and nephrotoxins. Subsequently, other pathways of drug disposition were studied in renal failure and how renal failure modified pharmacodynamic sensitivity to drugs was considered. This information was collected in a monograph (see Reidenberg, 1971) which presented data for how to individualize drug therapy for a wide variety of conditions for patients with poor renal function. In addition, an evaluation of drug metabolism in renal failure was part of this book. In it, a classification of drugs based on their major pathways of metabolism was developed. Then, by analyzing the metabolism rate of drugs utilizing the same biotransformation pathways, generalizations about the effect of uremia on the rates of these pathways could be made. This concept of evaluating a drug-metabolizing pathway and studying it so that the kinetics of any drug metabolized by that pathway could be predicted has been continued as the identification of specific pathways has evolved.

The refining of drug metabolizing pathways to specific genetically determined enzyme activities began with the observation of prolonged apnea following succinyl choline and the relationship of the duration of succinyl choline effect with the activity of plasma pseudocholinesterase. The information on genetically determined variability in drug response was assembled in book form by Kalow, titled Pharmacogenetics, a name coined by Vogel.

In addition to individual variation in susceptibility to adverse effects of drugs, there is substantial variation in degree of effectiveness. Silber pointed out that in trials of many different drugs for many different conditions, the rates for poor and nonresponders frequently exceeded 50% of the treated subjects. But these drugs are considered effective because the response rate in the treated was greater than that of the controls in a way unlikely due to chance.

The concept of individualization of drug therapy to allow for differences between individuals in their response to medications and information about how to do this was assembled in a book in 1974.

IV. THE SCIENTIFIC BASIS OF THERAPEUTICS

These studies and those that followed developed the discipline of clinical pharmacology which was added to the discipline of pharmacology to develop a science of therapeutics. The properly controlled clinical trial with appropriate statistical analysis gives valid information about drug effects in humans. Studies of pharmacogenetics, drug interactions, etc., give valid information about drug effects in specific humans. Combining these two themes of the discipline of clinical pharmacology, the scientific study of drugs in humans and individualization of therapy with the themes of the discipline of pharmacology as articulated by Leake, provide the scientific basis of therapeutics. The therapeutic goal of its scientific base is to make the response of a specific person to a specific dose of a specific drug more predictable than it would be without this scientific base. The scientific method also allows one to compare one drug to another. This ability to accurately determine if one treatment is better than another is what has enabled therapy to evolve to its present state of effectiveness from the largely toxic placebo therapy of the past.

V. HIERARCHY OF KINDS OF INFORMATION

Oliver Wendell Holmes wrote, probably correctly, in 1861 that ‘if the whole materia medica, as used now, could be sunk to the bottom of the sea, it would be all the better for mankind – and all the worse for the fishes’. The information that doctors used at that time was whatever personal experience in practice they could recall plus the recalled experiences told to them by friends or written in the medical books of the time. Single memorable cases or series of cases made up the evidence on which medicine was practiced. Today, the term ‘evidence-based medicine’ generally means that the practice is based on research-generated scientific evidence, primarily prospective randomized properly (placebo or standard therapy versus new therapy) controlled clinical trials analyzed with statistical rigor. Such a clinical trial gives the best evidence for the effects of a drug. Unfortunately, this ‘best evidence’ is only valid for patients that are like those in the trial (i.e. meet the entry criteria for the trial). As patients in practice vary from those in the trial, the generalizing of the trial results to the particular patient becomes less predictable. Some kinds of information, important in practice, can never be obtained from a controlled clinical trial. (Examples of these would be the dose–response relationship for large overdose such as in attempted suicide, the teratogenicity of the

drug when given to women in the first trimester of pregnancy, and the multitude of potential drug interactions when the drug is given to patients with various concurrent illnesses taking multiple drugs.) To obtain this kind of information, other techniques are needed.

To understand the context of these other techniques, one should put them in perspective. One can rank methods for obtaining information in order of increasing confidence that the conclusions are valid. The order would be: a single memorable case, a series of memorable cases, and a series of consecutive cases. The control observations for these would be historical controls, either articulated by the observer or merely understood. The assumption with the use of historical controls is that the controls are comparable to the patients and that the outcome of the treated patients if not given the new treatment would be identical to the historical controls. Often initial therapeutic trials of new cancer drugs are done in a consecutive series of treated patients and compared to historical controls. In these studies, the controls are usually not articulated. The authors assume that the natural course of the disease is so predictable in these patients that change from the predicted course is due to the drug. The validity of this assumption must be carefully examined when one interprets any study that is a case series.

The next level of confidence is the more formal epidemiologic study. These can be divided into cohort and case-control studies.

Cohort studies are studies in which a group of patients receiving one drug is compared to a group of patients receiving another drug. Usually, the comparison is the difference between the groups in an outcome. The validity of concluding that any difference in frequency of the outcome is due to the drug used depends on how similar the two groups were at the beginning. In a randomized prospective trial, the randomization procedure is for the purpose of making the two groups the same at the beginning. One checks this by seeing if every relevant factor is the same between the groups. Examples include age and sex distributions, fraction of the group who smoke, frequency of other illnesses in the groups, socioeconomic factors like educational level and income, and factors relevant to the specific disease being treated like severity scores (Hamilton Depression Score, New York Heart Association heart failure class, TNM stage of cancer patents, etc.). In a cohort study, one can do the same checks for similarity of the groups after they have been assembled but one can never know if some additional unidentified factor is present that affects the outcome and that is not equally distributed between the groups. In a randomized trial, the randomization procedure is intended to make this possibility very unlikely. In an observational cohort study in which the drug choice was made in any other way, one cannot be as confident that meaningful differences between the groups at the beginning are unlikely.

Large problems occur when one tries to interpret a cohort study in which there are identified differences between the cohorts at the beginning. While statistical 'adjustments' are often made, they cannot fully restore the confidence in the validity of the conclusions that one would have if the groups were really the same at the beginning.

Case-control studies start with patients that had the event of interest, often an adverse event (such as phocomelia), and compare the previous events (such as medications used) in the patients' lives to those in a group of control patients who did not have the event of interest. These studies are especially useful to generate ideas about causes of uncommon events. The example of thalidomide-induced phocomelia is a classic example of the use of this epidemiological approach.

Another issue is how to interpret a clinical trial with equivocal results. While Schor and Karten established the probability of less than 1 in 20 ($P < 0.05$) that a difference between two groups was due to chance as meaning that it was due to the drug, they did not establish criteria for how to properly interpret studies that failed to find this big a difference. Can this lack of evidence of effect be considered as evidence of lack of effect? People have settled on the convention that a clinical trial must include enough patients to have at least an 80% chance of finding an effect if an effect really exists. Failure to find an effect in this large a trial is considered evidence of true lack of effect. This has been named the 'power' of the study. How can we handle studies that do not have this power?

Traditionally, one did a review of those studies writing a narrative about them and drawing conclusions based on the subjective evaluation of this information by the reviewer. A different way to write review articles, named meta-analysis, was introduced into clinical medicine by Chalmers. It has been defined as 'a systematic review of studies that uses quantitative statistical procedures to combine, synthesize, and integrate information across these studies'. What this methodology does is take a group of

different studies and analyze them together as if they were a single multicenter study following a single protocol.

The strength of meta-analysis is that by combining a series of small equivocal studies, into one analysis of all the patients, an unequivocal result could be obtained. There are several issues in meta-analysis. One is whether all of the small clinical trials of the drug were included or only the published 'positive' trials while the small negative trials that were done were never published. This would be like excluding the data from selected centers in a multicenter trial. While this would be intentional misconduct in an analysis of a multicenter trial, it can happen through 'publication bias' in a meta-analysis. Another issue is whether the separate studies can really be combined. Since the studies were not done with identical protocols, it is a judgment decision on the part of the reviewer to decide which studies were sufficiently similar to be combined appropriately for analysis as if they were from a single multicenter study. Recognizing the limitations, the techniques of meta-analysis adds an additional level of rigor to a review paper.

One special ongoing meta-analysis is the Cochrane Collaboration (http://www.updateusa.com/clibip/clib.htm). This is a continuing voluntary association of medical scientists who periodically update systematic reviews of the effects of health care interventions. These are critical summaries of all randomized controlled trials about a given subject. Each is done by a group of people particularly interested in the specific topic and agree to continuously monitor the field and regularly update their review. A large number of topics are reviewed, and the number increases with time, but every *possible* subject of randomized controlled trials is not covered. In addition, because of the voluntary nature of the collaboration, and limited funding, the long-term future of each of the continuously updated systematic reviews is not predictable. Even with its limitations, the Cochrane reviews are an excellent source of information about the effects of health care interventions and a good place to go first for the most current information.

VI. 'EVIDENCE-BASED MEDICINE'

In the 1980s, several commentators declared that only 10–20% of physicians' interventions were supported by objective evidence that they were beneficial. In 1990, an assessment of 126 diagnostic and therapeutic technologies concluded that only 21% were based on solid research-based scientific evidence. From this public debate, the name 'evidence-based medicine' emerged. The meaning is that the use of any medical intervention either diagnostic or therapeutic should be based on valid scientific evidence that justifies the use of the intervention. Ellis and coworkers (see Ellis et al., 1995) evaluated the degree of evidence supporting the treatments given on a general medical inpatient service. They categorized the level of evidence as: (1) randomized controlled trials; (2) convincing non-experimental evidence; and (3) lack of substantial evidence. They found that 53% of the treatments were based on randomized controlled trials, 29% on convincing non-experimental literature, and only 18% lack substantial evidence that the treatment given was better than some alternative or placebo. Thus, modern medical care is largely based on scientific evidence of its value for the patients like those in the clinical trials. The World Health Organization developed its Essential Medicines program to make evidence-based medicine advice and suggestions available universally (http://who.int/medicines/en). Often, treatment for a disease must be modified from that used in the trial to account for the differences between the specific patients and the patients in the trial. Factors like concurrent drugs, multiple diseases, age, and genetic differences are examples of the types of variables that must be considered in individualizing therapy for a specific person. Personalized medicine is the current name given this concept, especially when it relates to relevant genetic differences between people.

The interest in all sorts of 'alternative and complementary' interventions is in contrast to 'evidence-based' medicine. These are interventions, often commercially promoted, that do not have a scientific basis for their proposed efficacy, and usually have not been evaluated scientifically for their safety and efficacy. The National Center for Complementary and Alternative Medicine of the NIH (http://nccam.nih.gov) was established in 1999 to bring scientific methods to bear on these interventions.

A weakness in the whole area of 'alternative therapies' is that one cannot determine, even on a statistical basis, either the benefits or harms that the treatment may cause. It is this lack of valid knowledge about the intervention's effects that separates alternative methods from scientific medicine. Furthermore, because of the variable natural course of

most illness and the variable placebo response of most human beings, one can only assess the effects of any therapy with a properly designed scientific study. When 'alternative' methods show efficacy and safety by scientific study, they move into conventional therapy and no longer 'alternative'.

VII. CONCLUSION: THERAPEUTICS AS A SCIENCE

The therapeutic goal of the scientific base of therapeutics is to make the response of a specific person to a specific dose of a specific drug more predictable than it would be without this scientific base. Therapeutics as a science is based on one's ability to predict, at least in a statistical way, the response of a patient to a medication. This predictability requires the accumulation of a body of facts arranged systematically to give generalizations that enable one to predict. Pharmacology produces this body of facts systematically arranged about drugs. Clinical pharmacology focuses on the scientific evaluation of drugs in humans and difference between individual humans in their response to drugs.

Together they have produced this body of knowledge which makes therapy more predictable, and more predictable is what makes therapy both safer and more effective. This is the scientific basis of therapeutics.

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APPENDIX: NEWCOMERS' GUIDE TO THE COCHRANE COLLABORATION[1]

The Organisation

What Is the Cochrane Collaboration?

The Cochrane Collaboration is an international, non-profit, independent organisation, established to ensure that up-to-date, accurate information about the effects of healthcare interventions is readily available worldwide. It produces and disseminates systematic reviews of healthcare interventions, and promotes the search for evidence in the form of clinical trials and other studies of the effects of interventions. Documents about its history include a chronology of the organisation (www.cochrane.org/docs/cchronol.htm), and an article describing the evolution of *The Cochrane Database of Systematic Reviews* and *The Cochrane Library* (www.update-software.com/history/clibhist.htm) between 1988 and 2003. This shows how Cochrane Reviews were conceived as electronic publications from the outset, and designed to take advantage of features unique to electronic publishing. The constitution of The Cochrane Collaboration is contained in its Memorandum and Articles of Association (www.cochrane.org/admin/artassoc.htm).

The Meaning of the Name

The Cochrane Collaboration was established in 1993, and named after the epidemiologist, Archie Cochrane (1909 to 1988), a British medical researcher who contributed greatly to the development of epidemiology as a science (www.cochrane.org/docs/archieco.htm). The organisation benefits from thousands of contributors worldwide, working collaboratively from within many independent groups of people ('entities'). For this reason, the term 'collaboration' is used. The Cochrane Collaboration's principles include fostering good communication, open decision-making and teamwork; reducing barriers to contributing, and encouraging diversity (www.cochrane.org/resources/leaflet.htm). These things cannot be achieved without people co-operating with each other, setting aside self-interest, and working together to provide evidence with which to improve health care.

[1] From http://www.cochrane.org/docs/newcomersguide.htm by permission of the Cochrane Collaboration.

What the Organisation Does

The Cochrane Collaboration prepares Cochrane Reviews and aims to update them regularly with the latest scientific evidence. Members of the organisation (mostly volunteers) work together to provide evidence to help people make decisions about health care. Some people read the healthcare literature to find reports of randomised controlled trials; others find such reports by searching electronic databases; others prepare and update Cochrane Reviews based on the evidence found in these trials; others work to improve the methods used in Cochrane Reviews; others provide a vitally important consumer perspective; and others support the people doing these tasks. The Cochrane Collaboration website provides information on a variety of ways of registering interest or becoming directly involved www.cochrane.org/docs/involve.htm#involve.

Size and Geographic Spread

Data from *The Cochrane Library* in 2004 show that there are more than 11,500 people working within The Cochrane Collaboration in 91 countries, half of whom are authors of Cochrane Reviews. The number of people has increased by about 20% every year for the last five years. The increase in the number of contributors from low, lower-middle and upper-middle income countries has been even greater, to more than 1000 (9.3%) in 2004 – up by 42% since 2003, and by 248% since 2000. See 'Reference Centres by country' (www.cochrane.org/contact/country.htm) and a world map showing the locations of the Cochrane Centres (www.cochrane.org//contact/entities.htm#centres).

Structure and Management

The members of The Cochrane Collaboration are organised into groups, known as 'entities', of which there are five different types (www.cochrane.org/contact/entities.htm):

- *Collaborative Review Groups* (www.cochrane.org/contact/entities.htm#crglist) are made up of people who prepare, maintain and update Cochrane Reviews, and people who support them in this process. Each Group has an 'editorial base' where a small team of people supports the production of Cochrane Reviews. These Groups focus on particular areas of health (for example, Breast Cancer, Infectious Diseases, Multiple Sclerosis, Schizophrenia, Tobacco Addiction).

- *Cochrane Centres* (some of which have additional branches) support people in their geographic and linguistic area (www.cochrane.org/contact/entities.htm#centres). Newcomers are encouraged to contact their local Cochrane Centre for information about The Cochrane Collaboration; this can save a lot of time and effort.
- *Methods Groups* are made up of people who develop the methodology of Cochrane Reviews (www.cochrane.org/contact/entities.htm#mglist).
- *Networks* (some are called '*Fields*') focus on dimensions of health care other than specific health problems, such as the setting of care (for example, primary care), the type of consumer (for example, older people), or the type of intervention (for example, vaccines) (www.cochrane.org/contact/entities.htm#fieldlist).
- *The Consumer Network* (www.cochrane.org/consumers) provides information and a forum for networking among consumers, and a liaison point for consumer groups around the world.

The Cochrane Manual (www.cochrane.org/admin/manual.htm) contains detailed descriptions of the responsibilities of each of these groups of people ('entities'). Cochrane entities receive their funding from different sources, but agree to follow the policies and practices of The Cochrane Collaboration (also contained in The Cochrane Manual).

The development and implementation of policy affecting The Cochrane Collaboration are the responsibility of the Cochrane Collaboration Steering Group (CCSG), after Collaboration-wide consultation:

- *The Steering Group* (www.cochrane.org/contact/entities.htm#ccsg) is guided by the goals and objectives contained in the Collaboration's Strategic Plan (www.cochrane.org/admin/stratplan.htm) in developing policy. Steering Group members serve for one or two three-year terms and there is an election for about a third of the members each year. This election uses a system of proportional representation, and each member of the Steering Group represents people from one of the types of Cochrane entity (www.cochrane.org/ccsg/2004electionprocedure.doc). The new members of the Steering Group take office at the Annual General Meeting (www.cochrane.org/ccsg/report). The Steering Group meets face-to-face twice a year, and between these meetings it conducts its business by telephone conference and e-mail. The Steering Group has three sub-groups and seven advisory groups (www.cochrane.org/admin/structure.htm).

There are several other official roles:

- Two *Ombudsmen* help to resolve areas of conflict that arise between people or entities, for which the usual process of involving their Centre Director has not been sufficient.
- The *Publication Arbiter* helps people to reach a mutually acceptable agreement in areas of dispute between the editorial teams of Collaborative Review Groups (for example, on the appropriate home for a specific Cochrane Review), and between authors of Cochrane Reviews and their editorial team (for example, when authors and editors cannot agree on some aspects of the review).
- The *Funding Arbiter* (a member of the Steering Group) and two other people who form a Funding Arbitration Panel to give guidance on difficult issues referred to them with respect to the organisation's policy on commercial sponsorship.
- The *Company Secretary*, whose responsibilities are fulfilled by the Secretariat Administrator, holds office for both the charity and its trading subsidiary (see Section 2.2.7.1 of The Cochrane Manual (www.cochrane.org/admin/manual.htm)).

The *Secretariat* is the administrative office of The Cochrane Collaboration, and supports the work of the Steering Group and its sub-committees, manages the central finances of the organisation, and facilitates communication (www.cochrane.org/contact/entities.htm#secretariat). It is based in Oxford, England, and has four full-time members of staff: the Chief Executive Officer, Secretariat Administrator, Deputy Administrator and Administrative Assistant.

Funding

The Cochrane Collaboration's central functions are funded by royalties from its publishers, John Wiley and Sons Limited, which come from sales of subscriptions to *The Cochrane Library*. The individual entities of The Cochrane Collaboration are funded by a large variety of governmental, institutional and private funding sources, and are bound by organisation-wide policy limiting uses of funds from corporate sponsors (www.cochrane.org/news/articles/2004.04.06.htm). There is a Funders' Forum to help facilitate discussions between The Cochrane Collaboration and funders (www.cochranefunders.

net/). This is a partnership between The Cochrane Collaboration, those who fund its infrastructure, and those representing institutions with an interest in using the outputs of The Cochrane Collaboration in the development of health policy, guidelines and other major publications based on high quality reviews of evidence. Enquiries regarding funding should be directed to the Collaboration's Chief Executive Officer (www.cochrane.org/contact/entities.htm#secretariat).

International and Intercultural Work and Communications

The Cochrane Collaboration is committed to involving and supporting people of different skills and backgrounds, to reducing barriers to contributing, and to encouraging diversity. A document entitled 'Cross-cultural team working within The Cochrane Collaboration' gives advice on communicating with people from other cultures (www.cochrane.org/docs/crossculturalteamwork.doc). Members of the organisation often work in teams spread across great distances, and so they communicate largely by e-mail (www.cochrane.org/admin/maillist.htm). Information of widespread interest is disseminated via an e-mail discussion list called 'CCInfo' which anyone can join (www.cochrane.org/admin/maillist.htm#ccinfo), and in printed newsletters such as 'Cochrane News' (www.cochrane.org/newslett). Meeting other members of the organisation at our annual conferences (Cochrane Colloquia) (www.cochrane.org/colloquia), and regional meetings of Cochrane contributors, are other ways of fostering good communication.

Cochrane Reviews

What Are Cochrane Reviews?

Cochrane Reviews are systematic assessments of evidence of the effects of healthcare interventions, intended to help people to make informed decisions about health care, their own or someone else's. Cochrane Reviews are needed to help ensure that healthcare decisions throughout the world can be informed by high quality, timely research evidence. This is described in 'Systematic reviews and The Cochrane Collaboration' (www.cochrane.org/docs/whycc.htm). Cochrane Reviews are published in full in *The Cochrane Database of Systematic Reviews*, one of several databases in *The Cochrane Library* (www.thecochranelibrary.com).

Their Impact Around the World

The main output of The Cochrane Collaboration, the Cochrane Reviews, has had a real and significant impact on practice, policy decisions and research around the world. Many examples are given in 'The Dissemination of Cochrane Evidence' (www.cochrane.org/reviews/impact).

Where to Find Them

The main output of The Cochrane Collaboration, Cochrane Reviews, is contained in *The Cochrane Database of Systematic Reviews*, published electronically by John Wiley and Sons as part of *The Cochrane Library* (www.thecochranelibrary.com). *The Cochrane Library* is a collection of high quality evidence-based healthcare databases, providing instant access to over 2000 full text articles reviewing the effects of healthcare interventions. It is published every three months with new and updated Cochrane Reviews, and is available by subscription, on the Internet and CD-ROM; people wishing to subscribe should contact www.cochrane.org/contact/wileycontacts.htm. An increasing number of countries have a national subscription to *The Cochrane Library*, which allows everyone in those countries to access *The Cochrane Library* for free (www.update-software.com/cochrane/provisions.htm). Abstracts and consumer summaries of Cochrane Reviews are freely available to everyone on the Internet (www.cochrane.org/reviews/clibintro.htm#abstracts). *The Cochrane Library* provides links to MEDLINE abstracts and the ISI Web of Science, and from references in Cochrane Reviews to journal articles cited within them. Advice on publishing Cochrane Reviews in paper journals as well as in *The Cochrane Library* is available in Section 2.2 of The Cochrane Manual (www.cochrane.org/admin/manual.htm). BesidesCochrane Reviews, *The Cochrane Library* contains a number of additional databases (www.cochrane.org/reviews).

- Specialist subsets of Cochrane Reviews: Cochrane Reviews are listed by Collaborative Review Group on the website (www.cochrane.org/cochrane/revabstr/crgindex.htm). Several subsets of Cochrane Reviews published in *The Cochrane Library* are also published separately, namely: *The WHO Reproductive Health Library* (available in both English and Spanish) (www.update-software.com/RHL/); *The Cancer Library* (www.update-software.com/cancer/); *The Mental*

Health Library (www.update-software.com/mhl/mhlogon.htm); and *The Renal Health Library* (www.update-software.com/renalhealth).

- Versions of Cochrane Reviews in languages other than English: *The Cochrane Library is available in Spanish: La Cochrane Library Plus en español (www.update-software.com/clibplus/). For information on translations of reviews and their abstracts into other languages, contact the Collaboration's publishers, John Wiley and Sons (mcouat@wiley.co.uk).*
- Cochrane methodology reviews: As well as Cochrane Reviews of the effects of healthcare interventions, there are also Cochrane methodology reviews of the ways in which health care can be evaluated and, from 2006, there will be Cochrane Reviews of the accuracy of diagnostic tests.

How They Are Created

The Cochrane Collaboration has special software for processing Cochrane Reviews called 'RevMan' (Review Manager), managed by the Information Management System (IMS) team at the Nordic Cochrane Centre (www.cc-ims.net/IMSG).

Learning to Prepare Them

Information on how to prepare a Cochrane Review is contained in the Cochrane Reviewers' Handbook (www.cochrane.org/resources/handbook). Preparing a Cochrane Review requires skills that may be new to the author. The Cochrane Collaboration's Open Learning Material (www.cochrane.org/resources/openlearning), together with the Cochrane Reviewers' Handbook, helps people to prepare a Cochrane Review, and the Cochrane Centres and some Collaborative Review Groups provide or facilitate training through workshops (www.cochrane.org/news/workshops.htm).

Getting Involved

Finding Help

A large amount and variety of information is available:

- For *newcomers* (www.cochrane.org/docs/involve.htm#involve), perhaps without any healthcare experience. Some online training is available for people who want to help by searching the healthcare literature (www.webct.brown.edu/public/dickersin01). People without a healthcare background can also contribute as authors of Cochrane Reviews.
- For *editorial teams of Collaborative Review Groups* (www.cochrane.org/crgprocedures). This password-protected material contains many procedural resources, including examples of checklists, forms, etc. In addition, the Cochrane Style Guide (www.liv.ac.uk/lstm/ehcap/CSR/home.html) provides guidance to enable people to copy edit Cochrane Reviews and other documents produced within The Cochrane Collaboration in a consistent manner.
- For *consumers*, the Consumer Network 'CCNet' has a website providing information on the role of health consumers, patients and the general public in the work of The Cochrane Collaboration (www.cochrane.org/consumers).
- *Job opportunities* within the organisation are advertised on the website from time to time (www.cochrane.org/jobs).
- *Frequently asked questions* (www.cochrane.org/docs/faq.htm).

Meeting People in the Organisation

Newcomers are enthusiastically welcomed at The Cochrane Collaboration's annual conferences, the Cochrane Colloquia, which take place around the world. Colloquia were held in Barcelona, Spain, in 2003, and in Ottawa, Canada, in 2004. Future Colloquia are scheduled to take place in Melbourne, Australia (2005); in Dublin, Ireland (2006); and in São Paulo, Brasil (2007). Further information on these, and all previous Colloquia, is on the website (www.cochrane.org/colloquia), with the abstracts of presentations.

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Chapter 3

Pharmacoepidemiology and Drug Evaluation

Supornchai Kongpatanakul, Brian L. Strom

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I. INTRODUCTION

Modern drugs are generally evaluated according to three major criteria: efficacy, safety, and cost-effectiveness. Studies to address these criteria begin once a compound is discovered. At any stage of drug development, the process can be terminated if the compound fails to meet these criteria. Even if a drug survives the pre-market testing and is introduced to the market, it can be withdrawn if adverse effects later prove to be unacceptable. Drug evaluation includes 4 phases that – in stepwise manner of number of patients, characteristics of patients and trial design, and complexity of patients and trial design – aim to provide the information for eventual product. With the introduction of more and more modern drugs and the dramatic increase in drug consumption and health care costs, more demand is being placed on the tools and techniques needed for generating data for decision makers at the various stages of drug evaluation. Pharmacoepidemiology, which specifically addresses this need, is an important discipline that has gained recognition and prominence in recent decades.

Pharmacoepidemiology is traditionally defined as the discipline concerned with the study of the use and effects of drugs in large numbers of people. It applies epidemiologic methods, knowledge, and reasoning to the subject of clinical pharmacology and therefore can be considered a subdiscipline of both clinical pharmacology and epidemiology. The epidemiologic methods used by this discipline range from single case reports to the observational or non-experimental population-based approach with several years of follow-up, to large-scale randomized clinical trials. Historically, the field of pharmacoepidemiology began with a focus on safety evaluation or the study of adverse drug reactions, particularly Type B reactions, which tend to be uncommon, dose-unrelated, unpredictable, and potentially more serious than Type A, i.e., dose-related and pharmacologic, reactions. It has evolved to include the study of the effectiveness of new drugs and the use of drugs post-marketing, such as patterns of and variations in prescribing in a particular health care facility or area, and strategies to improve the use of the drug. Recent extended applications that apply the population perspective to improve rational drug therapy have enhanced the impact of the field, and include studies of drug utilization, evaluating and improving physician prescribing, the development of treatment guidelines, drug utilization review, risk management, and the development of national drug policies. Another major area of drug evaluation, economic assessment, is discussed elsewhere in this book.

The field of pharmacoepidemiology has expanded enormously since the publication of the last edition

Drug Benefits and Risks: International Textbook of Clinical Pharmacology, revised 2nd edition
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of this book. Numerous research articles have been published and there are now many journals competing to accommodate those works. In addition, interest in further training in this discipline is rapidly increasing, as well as the number of training programs. The essence of the discipline has been incorporated into many postgraduate training programs in the medical sciences, such as clinical epidemiology, public health, clinical pharmacology, etc. Pharmacoepidemiology has contributed significantly to the area of regulatory approval and control, and it will continue to impact this area as long as drugs are permitted to enter the market with potentially unknown adverse side effects. The objective of this chapter is to summarize and describe important methods and applications in the field of pharmacoepidemiology, with a focus on developing countries.

II. HISTORY AND EVOLUTION OF PHARMACOEPIDEMIOLOGY

The history of drug therapy dates back to ancient times, when empiric medicine was the core of many treatments. The earliest evidence of drug therapy is the Egyptian Medical Papyrus of Smith, dating from approximately 1600 BCE. Opium and castor oil have been used for 3500 years. Later developments include vaccination in India in 550 BCE, the compilation of materia medica of 500 plants and remedies in 57 CE, the Theory of Disease by Galen in 130–201 CE and, much later, the isolation of morphine in 1805. The history of drug regulation in the US and in most of other developed countries, however, is only about a century old. In 1906, the initial drug-oriented US law, the Pure Food and Drug Act, was passed. This law gave the federal government the right to eliminate any product from the market that was adulterated or misbranded. There were no requirements for proof of efficacy or safety of marketed drugs. In 1937, more than 100 people died from renal failure as the result of using elixir of sulfanilamide dissolved in diethylene glycol. Consequently, the 1938 Food, Drug, and Cosmetic Act was enacted, requiring manufacturers to submit clinical data about drug safety to the US Food and Drug Administration (FDA) prior to drug marketing. However, data about drug efficacy was not yet required.

Perhaps the singular event that has had the most profound impact on the drug regulation process to date was the infamous ‘thalidomide disaster’ in the early 1960s. As a mild hypnotic, thalidomide was given (in many countries but not the US) to pregnant women as an antiemetic. Soon after it was marketed, there was a significant increase in those countries in the number of cases of phocomelia, a previously rare and serious congenital anomaly affecting the limbs of newborns. Awareness of this unexpected hazard was first triggered by a 15-line document published in *The Lancet* in December of 1961. Subsequent epidemiologic studies demonstrated the causal relationship of *in utero* exposure to thalidomide and this once rare birth defect. Even though the US FDA had never allowed the sale of this drug, the Kefauver–Harris Amendments were passed in response, in 1962. These amendments basically required more extensive non-clinical pharmacologic and toxicologic testing before a drug could be tested in humans. In addition, three explicit phases of clinical testing were required for providing evidence that a drug is safe and effective. The field of pharmacoepidemiology is often considered to have originated during the 1960s.

Although three phases of clinical testing are required for drug approval before marketing, much information is still lacking at the time a drug enters the market. First, since even phase III clinical trials generally involve relatively small numbers of selected groups of patients, rare but possibly serious adverse events may remain undetected. A new drug for a common indication such as hypertension generally requires a phase III study population of 1000–3000 subjects. This means that adverse events with a frequency less than 1 in 1000 will likely not be detected. Second, before marketing the drug is used under close medical supervision. The generalizability of such use to the conventional clinical context is uncertain. Third, a relatively short period of drug administration in phase III clinical trials, lasting in most cases no longer than 18 months, means that longer-term effects are undetectable. A good example is the effect of *in utero* exposure to diethylstilbestrol in causing carcinoma of the vagina and cervix in exposed offspring.

Therefore, epidemiologic techniques have been widely applied after marketing, known as phase IV or post-marketing studies. For example, in the early 1970s the Boston University Drug Epidemiology Unit (today called the Slone Epidemiology Unit) was developed, using a hospital-based approach of collecting lifetime drug exposure history to perform hospital-based case-control studies. In 1976,

the Joint Commission on Prescription Drug Use was formed to review the status of the field of pharmacoepidemiology (then called drug epidemiology) and to provide recommendations for the future. In 1977 the Computerized Online Medicaid Analysis and Surveillance System (COMPASS) was developed as the first Medicaid billing database, of which many are now used to perform pharmacoepidemiology studies. In 1980, the Drug Surveillance Research Unit (now the Drug Safety Research Trust) was formed in the UK to conduct Prescription Event Monitoring. All these developments have been important events in the field of pharmacoepidemiology in developed countries. Although the field originated mainly from concern about documenting and minimizing adverse drug reactions (ADRs), subsequent development has expanded into drug utilization studies and strategies to improve physicians' prescribing.

Since the 1980s, the number of pharmacoepidemiology studies informing major regulatory decisions as well as commercial decisions has increased significantly, with an even greater rise since 2000. Often presenting as 'drug crises', these include, among many others, tricrynafen (a non-steroidal anti-inflammatory drug that caused death from liver diseases), zomepirac (another non-steroidal anti-inflammatory drug that increased risk of anaphylactic reactions), terfenadine (an antihistamine that caused arrhythmia), cerivastatin (a statin associated with a disproportionately increased risk of rhabdomyolysis), and rofecoxib (a Cox2 specific non-steroidal anti-inflammatory drug that increased the risk of myocardial infarction). Clearly, pharmacoepidemiology has demonstrated a profound impact on the safety and efficacy of many new drugs entering the market in recent years.

Recent decades have also witnessed the additional contributions of pharmacoepidemiology to the study of beneficial drug effects, the economic impact of drug use and effects, quality-of-life studies, and meta-analysis. Findings from such work have undoubtedly helped to promote the rational use of drugs that lead to a better quality of health care.

III. CURRENT DRUG APPROVAL AND REGULATORY PROCESS

The drug evaluation process begins long before a drug gets market approval. Over the past 50 years, regulations have been passed in response to the crises with the use of pharmaceutical products, as mentioned above. On average, developing a new drug now takes more than 10 years and costs more than 1 billion US dollars. The process includes preclinical testing (mainly in animal and laboratory models), followed by three phases of clinical testing, before a successful application to allow the drug to enter the market can be filed with the regulatory agencies. During the preclinical stage, researchers evaluate the compounds, performing pharmacological, toxicology, and safety testing.

The clinical drug development process required by the US FDA, arguably the most stringent in the world, starts with the investigational new drug (IND) application prior to human testing. It reveals information about all known compounds to be used and includes the description of the clinical research plan for the product as well as the protocol for phase I studies. Preclinical study results also need to be revealed.

Once the IND application is accepted, three phases of human trials must be conducted. Phase I studies are typically performed on a small number of normal subjects, usually not more than 30 volunteers, generally by clinical pharmacologists. The purpose of the phase I study is to determine the metabolism of the drug in humans and a safe dosage range, and to search for any extremely common toxic effects that were not detected in the prior animal studies.

Phase II studies are conducted on patients who have the target disease, normally no fewer than 100–200 individuals. These studies are also generally performed by clinical pharmacologists. The purpose of the phase II study is to gather additional information on the pharmacokinetics and possible toxic effects of the drug, and preliminary information on the efficacy of the drug. The dosage regimen that eventually will be tested in phase III is also determined in this phase.

Phase III consists of clinical trials conducted on a large number of patients, ranging from several hundred to several thousand. These studies are performed by clinical researchers. Phase III verifies phase I and phase II studies, ensuring and proving that the drug is effective in this larger group. However, phase III does not normally show that the new drug is more effective than previously available drugs. Even though a large number of patients are included in this phase, major limitations still exist

in the information it provides, as discussed above. Once all three phases are passed, the new drug application (NDA) can be submitted to the FDA for evaluation and review.

Phase IV studies, or post-marketing surveillance, may be conducted once the drug is approved in order to gather previously unknown information. These studies include testing products by quality control laboratories, testing marketed products at random and investigating adverse reaction reports, or long-term outcomes. Such post-approval research might be required by the FDA as a condition for approval. However, phase IV-type work also might be carried out without an FDA requirement. It is in phase IV that pharmacoepidemiology plays a most important role. Contributions of phase IV studies include supplementing the information available prior to marketing by giving better quantitation of the incidence of known adverse and beneficial effects such as in patients not studied prior to marketing; modifying effects of other drugs or diseases, or relative to other drugs used for the same indication; providing new types of information not available from premarketing studies such as particularly uncommon effects, delayed effects, patterns of utilization, effects of overdoses, or economic implications of drug use; and providing reassurance that a drug is safe or simply fulfilling medical, ethical, or legal obligations.

For developing countries, there have been emerging challenges and opportunities in drug registration and approval in recent years, in particular a rapid increase in laws, regulations, and guidelines for reporting and evaluating the data on safety, quality, and efficacy of new medicinal products. However, in developing countries the drug approval process as required by the US FDA is ignored to some degree. This has largely to do with the limited resources, particularly the highly specialized scientific skills required to carry out such studies, including pharmaceutical chemistry, toxicology, statistics, and clinical development. For example, many developing countries approve the marketing of new drugs based on data from foreign studies and are not concerned with gender differences or even the quality of the studies. Western standards as benchmarks for the design of trials may not be applicable when local remedies or herbal medicines are involved, although there is a clear trend in that direction. Western pharmaceutical corporations are typically not interested in drug development for local use, in which case the development and testing must be based on the manpower and infrastructure of the developing country. A good example is the effort to develop dihydroartemisinin, an antimalarial, by joint efforts of local authorities and the World Health Organization. This program has embarked on developing a new drug with international standards in which technology has been transferred through the Special Programme for Research and Training in Tropical Diseases (TDR/WHO) to the Thailand Tropical Diseases Research Programme (T2). This program, established in 1997, represents an organization that promotes research into new product (drugs, vaccines, and diagnostics) development and screening. TDR partners in this venture are the Thailand Research Fund (TRF) and the National Center for Genetic Engineering and Biotechnology/National Science and Technology Development Agency of Thailand (BIOTEC/NSTDA).

Another important factor promoting drug development and approval in developing countries is the outsourcing to those countries of clinical drug development by the pharmaceutical industry and contract research organizations (CROs). Recently, the number of clinical studies conducted in Asia, Latin America, and Central and Eastern Europe has been steadily rising. Conditions in these areas have become favorable due to the implementation of Good Clinical Practices (GCP) by an established local regulatory environment, and improved infrastructure under the initiation of the International Committee on Harmonization (ICH). The ICH, begun in 1990, is a joint initiative involving both regulators and industry from the European Union (EU), Japan, and the US to discuss scientific and technical aspects of product registration. The International Federation of Pharmaceutical Manufacturers Association (IFPMA) acts as a buffer between the ICH and its member countries. WHO connects to the ICH by acting as observers and plays an important role in linking this activity to other non-ICH countries. The purpose is to maintain a forum for dialogue among all parties and to make recommendations to achieve greater harmonization. A number of guidelines pertain directly to the field of pharmacoepidemiology, such as the extent of population exposure to assess the clinical safety of drugs intended for long-term treatment of non-life threatening conditions, clinical safety data management (definitions and standards for expedited reporting), and pharmacovigilance planning.

IV. STUDY DESIGNS AND DATA SOURCES AVAILABLE FOR PHARMACOEPIDEMIOLOGY STUDIES

Pharmacoepidemiology applies the methods of epidemiology to the content area of clinical pharmacology. Understanding the basic principles of epidemiology is a prerequisite, then, to understanding the issues particular to pharmacoepidemiology. There are basically six study designs available for pharmacoepidemiology, ranging from randomized clinical trials (experimental studies), to case-control studies, to case reports. Each of the study designs has its own advantages and disadvantages but all of them play an important role. Each is explained briefly below.

Hypotheses can be generated by reviewing *case reports*, the simplest form of study design. Case reports are, in fact, simply reports of the experience of individual patients. In pharmacoepidemiology, a case report describes a single patient who was exposed to a drug and experienced a particular, usually adverse, outcome. A good example is a published case report about a young patient who was taking an antihistamine and developed a serious cardiac arrhythmia. Case reports are useful for generating hypotheses about drug effects but cannot generally be used to test a hypothesis. This task requires a separate control group and a more appropriate study design. With very few exceptions, it is impossible to make a statement about causation based solely on case reports. Exceptions are when the outcome is so rare and so unique that it is unlikely to have other causes. The case of clear cell vaginal adenocarcinoma occurring in offspring of mothers exposed to diethylstilbestrol during pregnancy is a good example. Otherwise, it generally cannot be known if the reported patient is typical of those with the exposure or typical of those with the disease. The WHO Programme for International Drug Monitoring, which is a global drug surveillance program, is a good example of a data source for case reports. This initiative was started by no more than 10 countries in the early 1960s after the discovery of the thalidomide disaster. Currently, case reports of suspected ADRs are collected submitted by national pharmacovigilance centers, with 73 countries participating in this program as full members and an additional 12 as associate members. About 200,000 ADR reports are submitted annually to the WHO database; about three million case reports have been collected to date.

Another study design is *case series*, defined as a collection of patients with a single exposure whose clinical outcomes are evaluated and described. Alternatively, a case series can be defined as a collection of patients with a single outcome; previous exposure is then examined. Case series are useful after drug marketing for quantifying the incidence of an adverse reaction, and for ensuring that any particular adverse effect of concern does not occur in a population larger than that studied prior to drug marketing. A good example is represented by the post-marketing studies of the 'first-dose effect' of prazosin when the drug was first marketed (Joint Commission on Prescription Drug Use 1980). Case series, like case reports, normally cannot be used for hypothesis testing, as it also lacks a control group. Case series also cannot be used to determine causation; rather, it provides useful clinical descriptions of a disease or of patients who were exposed.

Another study design is *analysis of secular trends*, which examines trends over a period of time or across geographic boundaries. This approach is used to investigate whether trends in an exposure, which is a presumed cause, and trends in the incidence of a disease, which is a presumed effect, coincide. As an example, one might consider sales figures for a particular bronchodilator, comparing these data to death rates from bronchial asthma. If the mortality rates from bronchial asthma tend to increase in proportion to increasing sales of the bronchodilator, this is suggestive evidence of the toxicity of the drug. This kind of study can provide quick support for or against a hypothesis but can only be used for groups, not individuals, and therefore cannot be used to control for confounding variables. As such, it might not be the toxicity of the drug that increases mortality; rather, mortality might be rising because more severely ill patients may be receiving the drug. A good example is the study to demonstrate correlation between the introduction of isoprenaline forte and fenoterol inhalers and the incidence of death from asthma in New Zealand. Data sources available for this study design include drug utilization data by IMS HEALTH, a private company database that tracks the sales of pharmaceuticals worldwide; the Slone Survey, a telephone random survey of drug utilization of the non-institutionalized population in the US; and Sweden's Apoteksbolaget, the National Corporation of Swedish Pharmacies that provides pharmacy services for the entire country.

A *case-control study* is a study that compares cases with a disease to controls without the disease, looking for differences in prior exposures. For example, a case-control study of the risk of gastrointestinal bleeding from non-steroidal anti-inflammatory drugs (NSAIDs) compares cases of patients with gastrointestinal bleeding to controls without the bleeding. Prior exposure to NSAIDs is then determined. Using this design, it has been shown that there is a strong association between the use of NSAIDs and gastrointestinal bleeding. Several advantages of case-control studies deserve attention. First, it is feasible to study multiple possible causes for a single disease. Also, relatively rare diseases can be studied, as the design guarantees a sufficient number of cases with the disease. Most importantly, given a good source of exposure data, case-control studies can be very efficient, taking the shortest time to find an answer about the cause of an adverse drug reaction. The classic study of diethylstilbestrol and clear cell vaginal adenocarcinoma would have required more than 15 years, had it been performed on a prospective basis. A well-designed case-control study generally can be confirmed by a subsequent cohort study or randomized clinical trial, if performed. Some important disadvantages exist, though. A case-control study often has problems in control selection; selecting the wrong non-diseased subjects may result in a wrong answer. In addition, since the exposure data are obtained retrospectively, it is often a concern that the exposure data will be biased. Data sources available for this type of pharmacoepidemiology study design include ad hoc sources such as Case-Control Surveillance (CCS) and automated databases such as the Group Health Cooperative, Kaiser Permanente Medical Care Program, Health Services Databases in Saskatchewan, and Medicaid Databases.

A *cohort study* is a study that identifies an exposed group and a comparison group and follows them over time, looking for differences in their outcomes. Comparison can be between exposed and unexposed patients or between one exposure and another. A cohort study allows the study of multiple outcomes in relation to a single exposure, which can be uncommon. A good example is the comparison among different contraceptive methods, looking for the differences in the rate of venous thromboembolism. This design is very useful in post-marketing drug surveillance studies, which evaluate the effects of new drugs. The major disadvantage of this design is the fact that relatively large sample sizes are required to study relatively uncommon outcomes and that a long time period is necessary when studying delayed drug effects. The possibility of biased outcome data is another disadvantage, since the exposure is known at the time of measuring outcome. Cohort studies are also typically more costly than the previously described study designs. Data sources for cohort studies include pharmacy-based post-marketing surveillance studies and traditional post-marketing drug surveillance conducted by pharmaceutical companies.

The most convincing design is that of the *randomized clinical trial*, or experimental study. The key feature of this design is the random allocation of patients to receive the treatment of interest, thereby making the study groups as comparable as possible. Due to the nature of this design, a randomized trial can be difficult ethically or logistically but it can be used for supplementary pharmacoepidemiology studies. Conventional phase III clinical trials seeking drug approval are a good example of data sources for this study design.

V. SELECTED APPLICATIONS OF PHARMACOEPIDEMIOLOGY IN REGARD TO DRUG EVALUATION: FOCUS ON DEVELOPING COUNTRIES

As the ultimate goal of pharmacoepidemiology is to improve the rational use of drugs, the applications of the field to achieve that goal are quite broad. Here, we divide the applications into four major areas for improving the rational use of drugs: efficacy, safety, cost-effectiveness, and drug utilization.

Although there are no multinational drug companies headquartered in developing countries, some pharmacoepidemiology studies performed for regulatory purposes, and even for new drug applications, are moving to developing countries (as mentioned above). In addition, efficacy studies are being performed in developing countries that duplicate those conducted in other countries, with the intention of confirming the applicability of the results to those populations. The ICH guidelines are now proving that they provide a firm platform for clinical research in developing countries, bringing clinical trials to the good clinical practice (GCP) level. As it is well known that the costs of conducting clinical trials in developing countries are far lower than in

developed countries, the quality of the trials is good, and turnaround time is rapid, it is likely that the moving of clinical trials to developing countries will continue. Interestingly, two major developing countries that play significant roles in the global pharmaceutical industry in terms of the supply of raw materials, China and India, are now key players in the clinical trial industry. In addition, current global economic and social forces have pushed many countries to rely more on their own resources, including manufacturing their own medications. Interest in the use of both generic and herbal medicines has risen greatly in governments, local industries, and consumers, compared to the recent past. These factors have already brought more efficacy studies into many developing countries.

Without the sophisticated automated databases that exist in many developed countries, especially the US and the UK, studies of drug safety in developing countries have mostly consisted of case reports or case series, based on the spontaneous adverse drug reaction reporting systems initiated by the WHO-sponsored international drug monitoring project. During the last several years, pharmacovigilance programs have been established in many developing countries from which little information has been available in the past. The cumulative number of reports in the WHO database has increased substantially, from up to 2 million from the years 1968–2000 to more than 3 million by 2004. With the implementation of hospital quality assurance programs in many countries, there is a clear motive for physicians to complete the ADR reporting forms. In fact, in most countries, the monitoring center is part of the drug regulatory authority, with varying degrees of collaboration with academic institutions and decentralized systems to facilitate report gathering and signal detection.

Striving to fund the cost of treatment with new drugs or biotechnology products, which tend to be far more effective yet far more expensive than conventional ones, continues to drive policymakers and clinicians to evaluate the economic effects of new drugs. As the cost of drugs contributes significantly to total health care costs, economic data about the cost of medical care in general and drugs in particular have been generated. The economic evaluation of pharmaceuticals, or pharmacoeconomics, discussed in more detail in another chapter, is one of the major applications of pharmacoepidemiology; the field has grown rapidly as decisions about funding drug therapy are being made in an era of increasingly constrained health care resources. Examples of studies in this field are studies of the effectiveness of different dosing techniques in the treatment of pulmonary tuberculosis, which compared self-administered treatment with directly observed therapy.

It is well known that the drug approval process conducted by governments in developing countries tends to be far less sophisticated than in developed countries. Further, as mentioned earlier, many prescription drugs, including antibiotics, anxiolytics, etc., can be purchased from any drug store in developing countries with virtually no restraints. Advanced health care facilities have been more or less confined to urban areas, leaving the rural disadvantaged without access to proper care and relying on self-medication with local remedies. With so many drugs available in the market, it is quite astounding to find that in many places in the world, particularly in less developed countries, the scarcity of medicines makes access to basic and simple drugs hardly possible. Over one-third of the world's population still lacks access to essential drugs (World Health Organization, 1988). In the poorest parts of Africa and Asia, more than 50% of the population lacks access to essential drugs; 50–90% of drugs in developing and transitional economies are paid for out-of-pocket. In 1978, the Alma-Ata Conference recognized that being able to get essential drugs is important in preventing and treating diseases. Therefore, in 1981, the United Nations Action Programme on Essential Drugs was conceived, to assist countries in developing national drug policies and promoting the rational use of drugs. The major goal of the Essential Drugs Programme was to ensure that patients around the world would be able to obtain the drugs they need at an economical price and that these drugs would be safe, effective, and of high quality. The first Model List of Essential Drugs in 1977 included 208 individual drugs, which together could provide safe and effective treatment for the majority of communicable and non-communicable diseases. Thirty years later, the 15th Model List of Essential Drugs, prepared by a WHO expert committee in 2007, included well over 300 individual drugs. Essential drugs are one of the most cost-effective elements in modern health care and their potential health impact is remarkable. An example of the epidemiologic approach employed in this program is

the practical manual on Estimating Drug Requirements. Researchers are trained to conduct studies on various aspects of drug supply such as selection, procurement, distribution, and use. The studies are mostly descriptive in nature, but provide very important information on the drug use and needs of each particular country, which is essential for forming the basis for further action toward improving drug use. It is interesting to note, however, that despite the potential health impact of essential drugs and the substantial spending on drugs, lack of access to essential drugs, irrational use of drugs, and poor drug quality remain serious global public health problems.

The marketing, distribution, prescription, and use of drugs in developing countries are very complex as many 'prescribed drugs', such as anxiolytics or antibiotics, can be purchased 'over-the-counter'. In this circumstance, drug utilization in a developing country presents its own set of problems not relevant to developed countries; arguably, the applications of pharmacoepidemiology that are most prevalent in developing countries are those related to drug utilization studies. Drug utilization was defined by WHO as the 'marketing, distribution, prescription, and use of drugs in a society, with special emphasis on the resulting medical, social, and economic consequences'. Here, the studies can be divided further into those addressing the quantitative use of drugs, the qualitative use of drugs, also known as drug utilization review (DUR) or drug use review, and studies to evaluate and improve physician prescribing. The drug use indicator developed by the INRUD group is a good example of the studies based on this application. Indicators such as number of drugs used per case by age group or diagnosis, percentage of patients receiving antibiotics, average consulting time, average dispensing time, percentage of patients who know their drug dose, or percentage of patients receiving injections, are useful for evaluating current prescribing, as well as changes after interventions. For example, the percentage of patients receiving antibiotics ranges from around 20% in Guatemala to more than 60% in Sudan.

Strategies to improve prescribing are another area of relatively great interest in developing countries. Topics of research in this area include the impact of improved monitoring and/or supervision on the use of medicines in primary care settings; the effectiveness of group processes or opinion leaders for improving use of medicines in primary care; strategies for improving compliance with treatment guidelines; the impact of a hospital formulary and therapeutics committee on the use of medicines; and strategies for reducing the unnecessary use of expensive antibiotics in hospitals.

Still other examples show that pharmacoepidemiology has gained significantly more recognition and now plays a significant role in promoting the rational use of drugs in developing countries. Pharmacoepidemiology concepts have been disseminated to decision makers in health care settings, such as hospital directors, deans, regulatory authorities, and clinician, by organizations such as WHO, the International Clinical Epidemiology Network (INCLEN), INRUD, and the International Society for Pharmacoepidemiology (ISPE). The principles of pharmacoepidemiology have been integrated into the teaching of clinical pharmacology, transforming awareness of this area and increasing its application in recent years.

Besides the impact of those activities mentioned above in evaluating and promoting better drug use for patients, a number of initiatives in developed countries have gradually become recognized by developing countries. Perhaps two of the most outstanding initiatives are the widespread use of treatment guidelines in clinical practice and the strong interest by health authorities in implementing hospital quality assurance programs. It may sound counterintuitive since variation in treatment of diseases was long viewed as acceptable and the rule, not the exception, but such variability invariably led to unnecessary spending and, more importantly, inferior quality of care – someone is doing it incorrectly, even if we do not know who. The treatment guideline initiative has been introduced recently in several countries. For the quality assurance program, the picture is quite similar to the initiatives of the US Joint Commission on Accreditation of Healthcare Organization (JCAHO) whereby the use of adverse drug reaction monitoring programs and drug usage evaluation (DUE) programs in hospitals has been well recognized. Clearly, the drug use component is one of the major areas in the hospital-wide quality assurance program, and pharmacoepidemiology has been used as a tool in this exercise.

Payment by third-party payers, especially by the national health insurance programs or social security funds, has expanded dramatically during the last several years and the program to promote rational use of drugs is soon expected to make significant contributions. A good example is a program such as

the US CERTs (Centers for Education and Research on Therapeutics), which is a program administered by the Agency for Healthcare Research and Quality (AHRQ), in consultation with the FDA, to conduct research and provide education that will advance the optimal use of drugs, medical devices, and biological products. CERT goals are to develop knowledge about therapies and how to use them, to manage the risk, to improve the practice, and to inform policy makers about the state of clinical science and the effects of current and proposed policies.

VI. SUMMARY

In summary, although pharmacoepidemiology has made significant progress in developing countries, there are still monumental tasks ahead. As new, sophisticated, and expensive drugs continue to enter the market, the need to balance risks and benefits of these new products will become more and more challenging. Pharmacoepidemiology seems to have a promising future in improving the rational use of drugs in developing countries, as has already been shown in developed ones. As interest in pharmacoepidemiology in developing countries continues to grow in both education and research, one can anticipate the improvement in drug evaluation, quality, and utilization, with eventual improvement in the quality of patient care. The field has a sterling opportunity to enhance the quality of life of any individual in any country, by improving the use of medications by the society as a whole. One can say that pharmacoepidemiology in developing countries has come of age.

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Chapter 4

Economic Evaluation of Pharmaceuticals and Clinical Practice

Kevin A. Schulman, Henry A. Glick, Daniel Polsky, K.R. John

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I. INTRODUCTION

Conventional evaluation of new medical technologies such as pharmaceutical products includes consideration of efficacy, effectiveness, and safety. The methodology for such analyses is well developed, and studies of safety and efficacy often are required prior to drug marketing. Health care researchers from a variety of disciplines have developed new techniques for the evaluation of the economic effects of clinical care and new medical technologies. Clinicians, pharmacists, economists, epidemiologists, operations researchers, and others have contributed to the field of 'clinical economics', an evolving discipline dedicated to the study of how different approaches to patient care and treatment influence the resources consumed in clinical medicine.

The growth of clinical economics has proceeded rapidly as health policymakers have faced a series of decisions about funding new clinical therapies in an era of increasingly constrained health care resources. Assessments of new therapies include an accounting of the resources required for the new therapy, the extent of the substitution of the new resources for existing resources, if any, and the health outcomes that result from therapeutic intervention. Thus, clinical economics includes not only an assessment of the cost of a new therapy, but an assessment of its overall economic and clinical effect.

This chapter discusses the need for applying economic concepts to the study of pharmaceuticals, introduces the concepts of clinical economics and the application of these concepts to pharmaceutical research, reviews some of the methodologic issues addressed by investigators studying the economics of pharmaceuticals, and finally offers examples of this type of research.

II. METHODOLOGIC PROBLEMS TO BE SOLVED BY PHARMACOECONOMIC RESEARCH

II.a. Techniques of Clinical Economics

Economists emphasize that costs are more than just transactions of currency. Cost represents the con-

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sumption of a resource that could otherwise be used for another purpose. The value of the resource is that of its next best use, which no longer is possible once the resource has been used. This value is called the resource's 'opportunity cost'. For example, the time it takes to read this chapter is a cost for the reader, because it is time that cannot be used again; the opportunity to use it for another purpose has been foregone. Good investments are made when the benefits of the investment (e.g., what you learn) are greater than or equal to the value of the opportunities you have forgone (e.g., what you would be doing were you not reading this chapter).

In addition to the fact that not all costs involve a transaction of money, it is important to remember that, at least from the perspective of society as a whole, not all transactions of money should be considered costs. For example, monetary transactions that do not represent the consumption of resources (e.g., social security payments, disability payments, or other retirement benefits) are not costs by this definition. They simply transfer the right to consume the resources represented by the money from one individual to another.

In considering economic analysis of medical care, there are three dimensions of analysis (represented by the three axes of the cube in Fig. 1) with which readers should become familiar. Along the *X* axis are three types of economic analysis – cost–identification, cost–effectiveness, and cost–benefit. Along the *Y* axis are four points of view, or perspectives, that one may take in carrying out an analysis. One may take the point of view of society in assessing the costs and benefits of a new medical therapy. Alternatively, one may take the point of view of the patient, the payer, or the provider. Along the third axis, the *Z* axis, are the types of costs and benefits that can be included in economic analysis of medical care. These costs and benefits, defined below, include direct costs and benefits, productivity costs and benefits, and intangible costs and benefits.

II.b. Types of Analysis

II.b.1. Cost–Benefit Analysis

Cost–benefit analysis of medical care compares the cost of an intervention to its benefit. Both costs and benefits are measured in the same (usually monetary) units (e.g., dollars). These measurements are used to determine either the ratio of dollars spent to dollars saved or the net saving (if benefits are greater than costs) or net cost. All else equal, an investment should be undertaken when its benefits exceed its costs.

The methods of cost–benefit analysis may be applied to evaluate the total costs and benefits of interventions that are being compared by analyzing their cost–benefit ratios or their net benefits. Furthermore, the additional or 'incremental' cost of an intervention (i.e., the difference in cost between a new

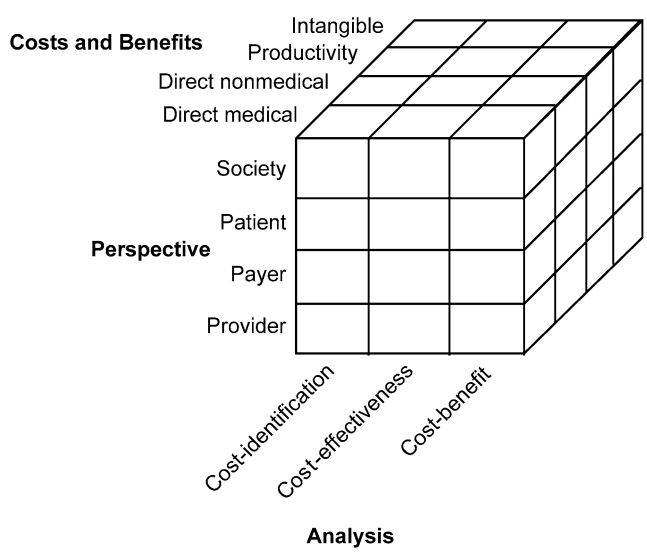


Fig. 1. The three dimensions of economic evaluation of clinical care (from Bombardier and Eisenberg, 1985, with permission).

therapy and conventional medical care) may be compared with its additional or 'incremental' benefit. Incremental analysis is generally preferred to comparisons of totals because it allows the analyst to focus on the differences between any two treatment modalities.

One potential difficulty of cost–benefit analysis is that it requires researchers to express an intervention's costs and outcomes in the same units. Thus, monetary values must be associated with years of life lost and morbidity due to disease and with years of life gained and morbidity avoided due to intervention. Expressing costs in this way is obviously difficult in health care analyses. Outcomes (treatment benefits) may be difficult to measure in units of currency. Translating disease and treatment outcomes into monetary measures may be more difficult than translating them into clinical outcome measures, such as years of life saved or years of life saved adjusted for quality.

II.b.2. Cost–Effectiveness Analysis

Cost–effectiveness analysis provides an approach to the dilemma of assessing the monetary value of health outcomes as part of the evaluation. While cost generally is still calculated only in terms of dollars spent, effectiveness is determined independently and may be measured only in clinical terms, using any meaningful clinical unit. For example, one might measure clinical outcomes in terms of number of lives saved, complications prevented, or diseases cured. Alternatively, health outcomes can be reported in terms of a change in an intermediate clinical outcome, such as cost per percent change in blood cholesterol level. Such results generally are reported as a ratio of costs to clinical benefits, with costs measured in monetary terms and benefits measured in the units of the relevant outcome measure (for example, dollars per year of life saved).

When several outcomes result from a medical intervention (e.g., the prevention of both death and disability), cost–effectiveness analysis may consider the outcomes together only if a common measure of outcome can be developed. Frequently, analysts combine different categories of clinical outcomes according to their desirability, assigning a weighted utility, or value, to the overall treatment outcome. A utility weight is a measure of the patient's preferences for his or her health state or for the outcome of an intervention. The comparison of costs and utilities sometimes is referred to as cost–utility analysis, with the denominator expressed as quality-adjusted life-years (QALYs).

As with cost–benefit analysis, cost–effectiveness analysis can compare a treatment's total costs and total effectiveness, or it can assess only the treatment's incremental costs and incremental effectiveness. In the former, the cost–effectiveness ratio of each intervention is calculated and the two ratios are compared (e.g., the cost per life saved using each intervention). In the latter approach, which assesses incremental costs and benefits, the incremental cost of the intervention is calculated, as is the incremental effectiveness, and the analyst can calculate the treatment dollar spent per additional effect (e.g., lives saved). Programs that cost less and demonstrate improved or equivalent treatment outcomes are said to be dominant and should always be adopted. Programs that cost more and are more effective should be adopted if both their cost–effectiveness and incremental cost–effectiveness ratios fall within an acceptable range and the budget for the program is acceptable. Programs that cost more and have worse clinical outcomes are said to be dominated and should never be adopted. Programs that cost less and have reduced clinical outcomes may be adopted depending upon the magnitude of the changes in cost and outcome.

As with the translation of clinical outcomes into monetary measures, there also are difficulties associated with combining different outcomes into a common measure in cost–effectiveness analysis. However, it generally is considered more difficult to translate all health benefits into monetary units for the purposes of cost–benefit analysis than to combine clinical outcome measures. Thus, cost–effectiveness analysis is used more frequently than cost–benefit analysis in the medical care literature.

II.b.3. Cost–Identification Analysis

An even less complex approach than cost–benefit or cost–effectiveness analysis would be simply to enumerate the costs involved in medical care and to ignore the outcomes that result from that care. This approach is known as cost–identification analysis. By performing cost–identification analysis, the researcher can determine alternative ways of providing a service. The analysis might be expressed in terms of the cost per unit of service provided. For example, a cost–identification study might measure the cost of a course of antibiotic treatment, but it would not calculate the clinical outcomes (cost–effectiveness

analysis) or the value of the outcomes in units of currency (cost–benefit analysis). Cost–identification studies, which include comparisons among different treatments based upon their costs alone, are appropriate only if treatment outcomes or benefits are equivalent for the therapies being evaluated.

II.b.4. Sensitivity Analysis

Most cost–benefit and cost–effectiveness studies require large amounts of data that may vary in reliability, validity, or the effect on the overall results of the study. This is especially the case when models are developed for the economic analysis using secondary data sources, when data collection is performed retrospectively, or when critical data elements are unmeasured or unknown. Sensitivity analysis is a set of procedures in which the results of a study are recalculated using alternate values for some of the study's variables in order to test the sensitivity of the conclusions to these altered specifications. Such an analysis can yield several important results by demonstrating the independence or dependence of a result on particular assumptions, establishing the minimum or maximum values of a variable that would be required to affect a recommendation to adopt or reject a program, and identifying clinical or economic uncertainties that require additional research. In general, sensitivity analyses are performed on variables that have a significant effect on the study's conclusions but for which values are uncertain.

III. TYPES OF COSTS

Another dimension of economic analysis of clinical practice illustrated by Fig. 1 is the evaluation of costs of a therapy. Economists consider three types of costs – direct, productivity, and intangible.

III.a. The Direct Medical Costs

The direct medical costs of care usually are associated with monetary transactions and represent costs that are incurred during the provision of care. Examples of direct medical costs include payments for purchasing a pharmaceutical product, payments for physicians' fees, salaries of allied health professionals, or purchases of diagnostic tests. Because the charge for medical care may not accurately reflect the resources consumed, accounting or statistical techniques may be needed to determine direct costs.

III.b. Direct Nonmedical Costs

Monetary transactions undertaken as a result of illness or health care to detect, prevent, or treat disease are not limited to direct medical costs. There is another type of cost that often is overlooked – direct nonmedical costs. These costs are incurred because of illness or the need to seek medical care. They include the cost of transportation to the hospital or physician's office, the cost of special clothing needed because of the illness, the cost of accommodations for receiving medical treatment at a distant medical facility, and the cost of special housing (e.g., the cost of modification of a home to accommodate an ill individual). Direct nonmedical costs, which are generally paid out of pocket by patients and their families, are just as much direct medical costs as are expenses that are more usually covered by third-party insurance plans.

Direct medical costs can be further classified to help determine the potential effect of a therapy in terms of the ability to change patterns of resource consumption by patients. If these costs increase with increasing volume of activity, they are described as variable costs. However, if the same costs are incurred regardless of the volume of activity, they are described as fixed costs. For example, the paper used in an electrocardiogram machine is a variable cost, since a strip of paper is used for every tracing. However, the machine itself is a fixed cost since it must be purchased whether one tracing is needed or many are performed. Of course, fixed costs are fixed only within certain bounds. A very large increase in activity will require the purchase of another piece of equipment. Even the fixed cost of a hospital's building is fixed only within certain limits of activity and a certain time frame. If enough increase in activity occurs, a new building might be needed. Alternatively, if patient care is transferred from an inpatient to an outpatient setting, a part of the building may be closed and the staff size decreased. Still, for the purposes of most decisions in clinical practice, costs can be considered to be fixed or variable.

III.c. Productivity Costs

In contrast to direct costs, productivity costs do not stem from transactions for goods or services. Instead, they represent the cost of morbidity (e.g., time lost from work) or mortality (e.g., premature death leading to removal from the workforce). They are costs because they represent the loss of opportunities to use a valuable resource, a life, in alternative

ways. A variety of techniques are used to estimate productivity costs of illness or health care. Sometimes, as with patients infected with human immunodeficiency virus, the productivity costs of an illness are substantially greater than the direct costs of the illness.

III.d. Intangible Costs

Intangible costs are those of pain, suffering, and grief. These costs result from medical illness itself and from the services used to treat illness. They are difficult to measure as part of a pharmacoeconomic study, though they are clearly considered by clinicians and patients in considering potential alternative treatments. Although investigators are developing ways to measure intangible costs – such as willingness-to-pay analysis whereby patients are asked to place monetary values on intangible costs – at present these costs often are omitted in clinical economics research.

IV. PERSPECTIVE OF ANALYSIS

The third axis in Fig. 1 is that of the perspective of an economic analysis of medical care. Costs and benefits can be calculated with respect to society's, the patient's, the payer's, and the provider's points of view. A study's perspective determines how costs and benefits are measured, and the economist's strict definition of costs (the consumption of a resource that could otherwise be used for another purpose) may no longer be appropriate when perspectives different from that of society as a whole are used. For example, a hospital's cost of providing a service may be less than its charge. From the hospital's perspective, then, the charge could be an overstatement of the resources consumed for some services. However, if the patient has to pay the full charge, it is an accurate reflection of the cost of the service to the patient. Alternatively, if the hospital decreases its costs by discharging patients early, the hospital's costs may decrease, but patients' costs may increase because of the need for increased outpatient expenses that are not covered by their health insurance plan.

Because costs will differ depending on the perspective, the economic impact of an intervention will be different from different perspectives. To make comparisons of the economic impact across different interventions, it is important for all economic analyses to adopt a similar perspective. The cost to society is the opportunity cost, the value of the opportunities foregone because of the resource having been consumed. Society's perspective usually is taken by measuring the consumption of real resources, including the loss of potentially productive human lives. As already noted, this cost does not count transfer payments, such as social welfare benefits. (From the government's point of view, however, such payments would be a cost, because the perspective of the government is not the perspective of society.) If an intervention is not a good value for money from the societal perspective, it would not be a worthwhile intervention for society, even if the intervention may have economic advantages for other stakeholders.

Nevertheless, conducting economic analysis from other perspectives, in addition to the societal perspective, is important. This is because the costs of medical care may not be borne solely by the same parties who stand to benefit from it. Economic analysis of medical care often raises vexing ethical problems related to equity, distribution of resources, and responsibility for the health of society's members. Economic analysis from multiple perspectives shed light on the equity issues associated with new interventions.

In summary, economic analysis of medical technology or medical care evaluates a medical service by comparing its monetary cost with its monetary benefit (cost–benefit), by measuring its monetary cost in relation to its outcomes (cost–effectiveness), or simply by tabulating the costs involved (cost–identification). Direct costs are generated as services are provided. In addition, productivity costs should be considered, especially in determining the benefit of a service that decreases morbidity or mortality. Finally, the perspective of the study determines the costs and benefits that will be quantified in the analysis, and sensitivity analyses test the effects of changes in variable specifications for estimated measures on the results of the study.

V. METHODOLOGIC ISSUES IN THE PHARMACOECONOMIC ASSESSMENT OF THERAPIES

The basic approach for performing economic assessments of pharmaceutical products, as discussed above, has been adapted from the general methodology for cost–effectiveness and cost–benefit analysis.

These methods have been well developed in medical technology assessment as well as in other fields of economic research. However, there remain a number of methodological issues that confront investigators in economic evaluations of pharmaceutical therapies. This section reviews some of these issues as they arise in the design, analysis, and interpretation of pharmacoeconomic evaluations.

V.a. The Problem

Clinical trials are useful for determining the efficacy of therapeutic agents. However, their focus on efficacy rather than effectiveness and their use of protocols for testing and treating patients poses problems for cost–effectiveness analysis. One difficulty in assessing the economic effect of a drug as an endpoint in a clinical trial is the performance of routine testing to determine the presence or absence of a study outcome. For example, in a study of prophylaxis against thromboembolic events, the protocol may specify testing of all patients for deep vein thromboses (e.g., fibrinogen scanning, venograms, or Doppler testing), whether or not the patients show clinical signs of these events. While this diagnostic strategy may be appropriate, it is not necessarily common practice. Yet, it can have wide-ranging effects on the calculated costs and outcomes of care.

First, the protocol may induce the detection of extra cases – cases that would have gone undetected if no protocol were used in the usual care of patients. These cases may be detected earlier than they would have been in usual care. In the prophylaxis example above, repeated testing of all patients is likely to increase the number of deep vein thromboses that are detected, especially if, in usual care, patients are only tested when they develop clinical signs of deep vein thromboses. This extra or early detection may also reduce the average costs for each case detected, because subclinical cases or those detected early may be less costly to treat than clinically detected cases. However, because these two potential biases – more cases, each of which may cost less – work in opposite directions, the total costs of care for patients in the trial may or may not exceed those that would occur in usual care.

Second, protocol-induced testing may lead to the detection of adverse drug effects that would otherwise have gone undetected. As above, the average costs of each may be less because the adverse effects would be milder. However, their frequency would obviously be higher, and they could result in additional testing and treatment.

Third, protocol-induced testing also may lead to the occurrence of fewer adverse events from the pharmaceutical product than would occur in usual care. The extra tests conducted in compliance with the protocol may provide information that otherwise would not have been available to clinicians, allowing them to take steps to prevent adverse events and their resulting costs. For example, an antibiotic protocol may call for more frequent testing of creatinine levels than would be conducted in usual care. These tests may warn physicians of impending renal problems, allowing them to change the drug dosage or the antibiotic. Thus, cases of nephrotoxicity that would have occurred in usual care may be avoided. This potential bias of reducing the costs of side effects and adverse events would tend to lower the overall costs of care observed in the trial compared to usual care.

Fourth, due to ethical obligations that arise when patients are enrolled in trials, outcomes detected in trials may be treated more aggressively than they would be in usual care. In trials, it is likely that physicians will treat all detected treatable clinical outcomes. In usual care, physicians may treat only those outcomes that in their judgment are clinically relevant. This potential bias would tend to increase the costs of care observed in the trial compared to usual care.

Fifth, protocol-induced testing to determine the efficacy of a product or to monitor the occurrence of all side effects, whether clinically detectable or not, generally will increase the costs of diagnostic testing in the trial, because many of these tests likely would be omitted in usual care. Alternatively, the protocol may reduce these costs in environments where there is overuse of testing. In teaching settings, for example, some residents may normally order more tests than are needed, and this excess testing may be limited by the protocol's testing prescriptions.

Sixth, clinical protocols may offer patients additional resources that are not routinely available in clinical practice. These additional resources may provide health benefits to patients. For example, protocols offering extensive home care services may affect the observed benefits of a therapy if the nursing intervention improves the management of the patient's illness. This could result in a bias in the study design if there are differences in the amount of home care services provided to patients in the treatment and control arms of a trial, or may result in additional health benefits to all study patients.

Seventh, patients in trials often are carefully selected. If a study sample has a mean patient age of 45 years, the result of the trial may not be readily generalizable to substantially older or younger populations. Similarly, exclusion criteria in clinical protocols may rule out patients with specific clinical syndromes (e.g., diabetes mellitus), women of childbearing potential, or patients of advanced age. These patients may require additional resources or may receive less benefit from therapy because their life span is shorter. These exclusions further limit the generalizability of the findings of efficacy studies.

A related issue in pharmacoeconomics trials is the generalizability of the health care delivery system of the patients in the study. A pharmacoeconomic study conducted through health a maintenance organization using its members as subjects may observe less referrals to specialist physicians than would the same clinical study in a different practice setting. This effect may be even more pronounced in multinational clinical trials, in which health care systems, physician education, and patients' expectations for treatment differ by country.

Eighth, when medications are introduced to the market, they often carry a premium related to patent protection for the product. In the small-molecule market, prices of medications often are greatly reduced after the patent expiration and the introduction of generic versions of the molecule. (In countries without strong intellectual property protections, the prices may reflect generic prices more quickly.) Large molecules, or biologics, may have a very different trajectory of costs. In many markets, biologics carry strong intellectual property protections and high prices, reflecting the relatively smaller market for these products compared to small-molecule drugs. Manufacturing of biologics is more complex, and the regulatory scheme (at least in the United States and the European Union) is distinct from that for small-molecules drugs. At present, there are no 'generic' versions of biologics in the United States, and a regulatory framework for follow-on biologics has only recently been introduced in the European Union. It is likely that the cost of even follow-on biologics will more closely reflect the costs of products with patent protection than the costs of generic versions of small-molecule drugs.

Other difficulties in projecting the results of clinical trials to usual care arise because the patients in clinical trials generally comply more completely with their treatment than do patients in usual care; they receive prescribed patterns of care; and because the potential existence a placebo effect may tend to understate the effectiveness the agent will have when it is utilized in usual care.

Routinely appending economic evaluations to clinical trials will likely yield 'cost–efficacy' analyses, the results of which may be substantially different from the result of cost–effectiveness analyses conducted in the usual care setting. The problem of generalizability is similar to that found in clinical epidemiology research. However, clinical economics explicitly recognizes the added complexity of having different resource-induced costs and benefits derived from clinical protocols and from observing patients in different health care systems in multicenter clinical trials. Commitment to publication of the results is crucial to the integrity of this work.

V.b. Possible Solutions

One possible solution to this problem is the inclusion of a 'usual care' arm appended as a third arm of a clinical trial. In such a three-arm study, patients randomized to the usual care arm of the study would be treated as they would be outside of the trial, rather than as mandated by the study protocol, and economic and outcomes data from usual care could thus be collected. These data would make it possible to quantify the number of outcomes that likely would be detected in usual care and the costs of these outcomes.

One drawback to this method is that physicians in the trial may treat all patients similarly, whether they are in the protocol-driven arm or the usual care arm of the study. This contamination can be partially overcome by randomizing physicians to the protocol or usual care arms, and can be overcome more completely by randomizing the sites of care (e.g., different hospitals for different arms of the study). However, these options require large numbers of physicians and/or sites of care and, thus, are costly to implement. Moreover, such a strategy may result in nonrandom assignment of patients to treatment arms.

A second method that has been used to overcome these problems is to collect data retrospectively from patients who are not in the trial but who would have met its entry criteria, using these data to estimate the likely costs and outcomes in usual care. These patients could have received their care prior to the trial (historical comparison group) or concurrent with it

(concurrent comparison group). In either case, some of the data available in the trial may not be available for patients in the comparison groups. Thus, investigators must ensure comparability between the data for usual care and trial patients.

Two problems arise when using a concurrent comparison group to project the results of a trial to usual care. First, as with the randomization scheme above, the use of a protocol in the trial may affect the care delivered to patients who are not in the trial. If so, usual care patients may not receive the same care they would have received if the trial had not been performed. Thus, the results of the trial may lose generalizability to other settings. Second, the trial may enroll a particular type of patient (e.g., investigators may 'cream-skim' by enrolling the healthiest patients with the least complications), possibly leaving a biased sample (e.g., of sicker and more complicated patients) for inclusion in the concurrent comparison group. This potential bias would tend to affect the estimate of the treatment costs that would be experienced in usual care.

Adoption of a historical comparison group would offset the issue of contamination. Because the trial was not ongoing when these patients received their care, it could not affect how they were treated. A historical comparison group would also tend to offset the selection bias: the subset of patients who would have been included in the trial if it had been carried out in the historic period will be candidates for the comparison group. However, use of a historic comparison group is unlikely to offset this bias entirely. Because this group is identified retrospectively, its attributes likely will reflect those of the average patients eligible for the trial, rather than those of the subset of patients who would have been enrolled in the trial (e.g., if cream-skimming had occurred).

However, differences between the care provided to patients in the trial and that provided to patients in this group may be due as much to secular trends in the provision of medical care as they are to the adoption of a study protocol. For example, length of stay in the United States has decreased since the early 1980s, due in part to the implementation of the Medicare Prospective Payment System. Thus, historical cohorts from earlier periods may have had longer lengths of stay as inpatients than is currently seen in clinical practice. These data may suggest a protocol-induced decrease in length of stay when one actually does not exist.

To avoid these difficulties, the usual care comparison group may include both historic and concurrent comparison groups. In this case, multivariable methods such as multiple regression analysis or other analytic techniques must be used to control for differences among the historic and concurrent comparison groups as well as between the comparison groups and the patients in the trial. For example, in a regression analysis of length of stay in the trial and in usual care, variables representing each of the groups will indicate the magnitude of the secular trends, the selection bias, and the protocol effects of the trial.

A number of methods currently are being investigated to help overcome the potential biases of resource-induced costs and benefits in clinical trials. These approaches include the development of "large and simple clinical trials", increased attention to the generalizability of patient selection criteria in study design, and conducting the trial in different health systems simultaneously to assess the impact of the therapy in different delivery settings (e.g., using a large health maintenance organization as a clinical testing site).

V.c. Issues in the Design of Prospective Pharmacoeconomic Studies

We have already addressed some of the general issues in the design and interpretation of pharmacoeconomic studies. Yet, prospective pharmacoeconomic studies, especially within phase III clinical trials, are often our only opportunity to collect and analyze information on new therapeutic products before decisions are made concerning reimbursement and formulary inclusion for these agents. We now address issues that arise in the design of these studies.

V.c.1. Sample Size

The size required of the sample to identify a meaningful economic difference is frequently problematic. Often those setting up clinical trials focus on the primary clinical question when developing sample-size estimates. They fail to consider the fact that the sample required to address the economic questions posed in the trial may differ from that needed for the primary clinical question. In some cases the sample size required for the economic analysis is smaller than that required to address the clinical question. More often, however, the opposite is true, in that the variances in cost and patient preference data are larger than those for clinical data. Then one needs to confront the question of whether it is either ethical

or practical to prolong the study for longer need be to establish the drug's clinical effects. Furthermore, in many cases the variances for the pharmacoeconomic data are unknown. Power calculations can be performed, however, to determine the detectable differences between the arms of the study given a fixed patient population and various standard deviations around cost and patient preference data (Table 1). Methods for calculating sample size in economic evaluations have been described elsewhere.

Table 1. Study differences detectable given a fixed sample size. Values represent minimum detectable differences between trial arms given the standard deviation reported for the row in the table, and a fixed sample size for each arm of the trial

Standard deviation (length of stay/US$)	Detectable difference R^2 for covariables			
	0.0	0.1	0.2	0.3
$n = 150$/group				
5	2	2	1	1
10	3	3	3	3
20	6	6	6	6
30	10	9	9	8
40	13	12	12	11
50	16	15	14	14
100	32	31	29	27
500	162	153	145	135
1000	324	307	289	271
2500	809	767	723	677
5000	1618	1535	1447	1354
$n = 300$/group				
5	1	1	1	1
10	2	2	2	2
20	4	4	4	4
30	7	7	6	6
40	9	9	8	8
50	11	11	10	10
100	23	22	20	19
500	114	109	102	96
1000	229	217	205	191
2500	572	543	512	479
5000	1144	1085	1024	957
$n = 450$/group				
5	1	1	1	1
10	2	2	2	2
20	4	4	3	3
30	6	5	5	5
40	7	7	7	6
50	9	9	8	8
100	19	18	17	16
500	93	89	84	78
1000	187	177	167	156
2500	467	443	418	391
5000	934	886	836	782

V.c.2. Participation of Patients

Those planning phase III clinical trials usually are more focused on the clinical results of the trial than they are on the economic results; they would usually like to keep the number of centers needed to complete the trial to a minimum; and they would rather finish the trial sooner than later. Thus, they have a concern that patients might agree to participate in the clinical trial, but not be willing to participate in the economic portion of the trial. In such a case, the investigators often argue that patients should be allowed to participate in the clinical portion of the trial but be excluded from the economic portion of the trial. While self-selection always poses difficulties for trials, it should be clear that this suggestion is particularly worrisome. The economic assessment would end up comparing an estimate of effects from the entire sample with an estimate of costs from a nonrandom subset of the entire sample, thus allowing substantial bias to enter the analysis. Protocols should allow prospective collection of resource consumption and patient preference data, while sometimes incorporating a second consent to allow access to patients' financial information. This second consent would be important if the primary concern was the possibility of patient selection bias in the analysis of clinical endpoints. However, given the low rates of refusal to the release of financial information, a single consent form should be considered for all trial data. The single consent would avoid the possibility of selection bias in the economic endpoints relative to the clinical endpoints.

V.c.3. Data Collection

In many cases, by the time clinical investigators think to include economic assessments in their trials, they generally have asked for the collection of so much clinical data that it is nearly impossible to ask the data collectors to collect any economic data. Collection of resource consumption data from primary or secondary sources is essential for a prospective economic evaluation of a pharmaceutical therapy. Some data elements, such as patient preference assessments, can only be collected on a prospective basis. Other data elements, such as outpatient

physician treatment records for a linked inpatient and outpatient economic evaluation of a therapy, or patient resource consumption information for hospitals without centralized billing systems, must be collected prospectively to simplify the data collection process for the study.

While some prospective data collection is required for almost all pharmacoeconomic studies, the amount of data to be collected for the pharmacoeconomic evaluation is still the subject of much debate. There is no definitive means of addressing this issue at present. Phase II studies can be used to develop data that will help determine which resource consumption items are essential for the economic evaluation. Without this opportunity for prior data collection, however, we must rely upon expert opinion to suggest major resource consumption items that should be monitored within the study. Duplicate data collection strategies (prospective evaluation of resource consumption within the study's case report form with retrospective assessment of resource consumption from hospital bills) can be used to ensure that data collection strategies do not miss critical data elements.

Resources are divided into specific categories for assessment for prospective data collection: inpatient resource use, outpatient resource use, and non–acute-care resource use. Within each of these categories, data can be subdivided into several categories: professional services (physicians, nurses, allied health professionals), hospital setting (intensive care unit, step-down unit, general medical floor), major diagnostic tests (radiologic tests, laboratory tests), major surgical procedures (operations and non-operating room procedures), and medications. Issues related to data collection for economic studies have been reviewed elsewhere.

V.c.4. Appropriate Comparators

Selection of appropriate treatment alternatives in a clinical study is essential for a useful economic evaluation of a pharmaceutical therapy. This issue is both a clinical and an economic one. Comparators can be the most common alternative therapies for a condition or the lowest possible cost alternatives, even when not frequently used. However, in pharmacoeconomic studies, treatment comparators may be inappropriately selected as much for their relatively high price as for their likely effectiveness. Phase III studies have special limitations in this regard, because agents will be compared against the placebo to assess efficacy rather than against alternative treatments to assess the relative effectiveness of the agent.

V.c.5. Multicenter Evaluations

The primary results of economic evaluations usually is a comparison of average, or pooled, differences in costs and differences in effects among patients who received the therapies under study. It is an open question, however, whether pooled results are representative of the results that would be observed in the individual centers or countries that participated in the study. In some, the therapy may provide good value for the costs, whereas in others it may provide poor value. Three reasons commonly cited for these differences are differences in practice patterns (i.e., medical service use), differences in absolute and relative prices for medical service use (i.e., unit costs), and differences in underlying morbidity/mortality patterns in different centers and countries.

There is a growing literature that addresses the transferability of a study's pooled results to subgroups. Approaches include evaluation of the homogeneity of different centers' and countries' results; use of random effects models to borrow information from the pooled results when deriving center-specific or country-specific estimates; direct statistical inference by use of net monetary benefit regression; and use of decision analysis.

VI. FACTORS AFFECTING RESOURCE CONSUMPTION

Pharmacoeconomic research holds as a basic assumption the proposition that clinical severity of disease is the sole determinant of resource use by patients. Studies of regional variation, such as those by Wennberg and colleagues, highlight the shortcomings of this assumption. This creates a significant challenge for health services research, and for pharmacoeconomics in particular. For example, when a new therapy is introduced to reduce severity of disease as a substitute for physician services that similarly reduce the severity of disease, if physicians either continue to provide the service to maintain their clinical practice or change the characteristics of the patients to whom they provide services (i.e., operate on less severely ill patients), we will not achieve the potential economic advantage afforded by the new therapy.

VI.a. Economic Data

Analysts generally have access to resource utilization data such as length of stay, monitoring tests performed, and pharmaceutical agents received. When evaluating a therapy from a perspective that requires cost data rather than charge data, however, it may be difficult to translate these resources into costs. For example, does a technology that frees up nursing time reduce costs, or are nursing costs fixed in the sense that the technology is likely to have little or no effect on the hospital payroll? Economists taking the social perspective would argue that real resource consumption has decreased and thus nursing is a variable cost. Accountants or others taking the hospital perspective might argue that, unless the change affects overall staffing or the need for overtime, it is not a saving. This issue depends in part on the temporal perspective taken by the analyst. In the short term, it is unlikely that nursing savings are recouped; in the long term, however, there probably will be a redirection of services. This analysis may also be confounded by the potential increase in the quality of care that nurses with more time may be able to provide to their patients. In countries that have a shortage of hospital beds, hospital administrators often do not recognize staffing savings from early-discharge programs, because the bed will be occupied by a new patient as soon as the old patient is discharged.

VI.b. Perspective

When perspectives other than the societal perspective are adopted, it is unclear what benefits or outcomes should be counted in the analysis. For example, if a governmental agency's perspective is adopted, in which transfer payments such as pensions are counted as costs, quick deaths at age 65 may be valued more than long, costly deaths at age 75. Independent of whether we should condone this perspective, we must determine whether health status is an independent goal to be included in the analysis.

In summary, due to their focus on efficacy and their use of clinical protocols, economic assessments of pharmaceutical products based upon phase III clinical trials are not without their problems. However, these issues can be developed in pharmacoeconomic analysis plans or through supplemental data collection activities conducted concurrently with the clinical trial.

VII. MEASUREMENT AND MODELING IN CLINICAL TRIALS

The types of data available at the end of a clinical trial will depend upon the trial's sample size, duration, and clinical endpoint. There are two categories of clinical endpoints considered in pharmacoeconomic analysis: intermediate endpoints and final endpoints. An intermediate endpoint is a clinical parameter, such as systolic blood pressure, which varies as a result of therapy. A final endpoint is an outcome variable, such as change in survival, or quality-adjusted survival, that is common to several economic trials, which allows for comparisons of economic data across clinical studies and is of relevance to policy makers.

The use of intermediate endpoints to demonstrate clinical efficacy is common in clinical trials, because it reduces both the cost of the clinical development process and the time needed to demonstrate the efficacy of the therapy. Intermediate endpoints are most appropriate in clinical research if they have been shown to be related to the clinical outcome of interest, as in the following:

- the use of changes in blood cholesterol levels to demonstrate the efficacy of new lipid lowering agents (intermediate endpoint: changes in low-density and high-density lipoprotein levels; final endpoint: changes in myocardial infarction rate and survival; demonstration of the relationship between intermediate and final endpoints: Framingham Heart Study);
- the use of change in blood pressure to demonstrate the efficacy of new antihypertensive agents (intermediate endpoint: changes in systolic and diastolic blood pressure; final endpoint: changes in stroke rates and survival; demonstration of the relationship between intermediate and final endpoints: Framingham Heart Study); and
- the use of change in molecular response to demonstrate the efficacy of a new antineoplastic agent (intermediate endpoint: molecular response; final endpoint: survival; demonstration of relationship between intermediate and final endpoints: epidemiological study).

Ideally, a clinical trial would be designed to follow patients throughout their lives, assessing both clinical and economic variables, to allow an incremental assessment of the full impact of the therapy on patients over their lifetimes. Of course, this type of study is almost never performed. Instead, most

clinical trials assess patients over a relatively short period of time. Thus, some pharmacoeconomic assessments must utilize data collected from within the clinical trial in combination with an epidemiologic model to project the clinical and economic trial results over an appropriate period of a patient's lifetime.

The importance of this effort is illustrated in the following hypothetical example. A new therapy is under development that reduces the absolute risk of dying from a chronic disease by 50% as measured in a one-year trial. However, this therapy is not curative. A four-year trial was initiated at the same time as the one-year trial. The first-year results were the same in both the four-year trial and the one-year trial. However, there was an increased risk of death for treatment patients in the second and third year of the four-year trial, and by the end of the third year of the trial the survival rate was identical in the treatment and control arms of the four-year trial. While there was a clear benefit to the new therapy in terms of postponing events from the first year of treatment to later years, the economic assessment of the therapy would suggest a greatly reduced treatment benefit from the four-year trial as compared with the one-year trial.

In projecting results of short-term trials over patients' lifetimes, it is typical to present at least two of the many potential projections of lifetime treatment benefit. A one-time effect model assumes that the clinical benefit observed in the trial is the only clinical benefit received by patients. Under this model, after the trial has ended, the conditional probability of disease progression for patients is the same in both arms of the trial. Given that it is unlikely that a therapy will lose all benefits as soon as one stops measuring them, this projection method generally is pessimistic compared to the actual outcome. A continuous-benefit effect model assumes that the clinical benefit observed in the trial is continued throughout the patients' lifetimes. Under this model, the conditional probability of disease progression for treatment and control patients continues at the same rate as that measured in the clinical trial. In contrast to the one-time model, this projection of treatment benefit most likely is optimistic compared to the treatment outcome.

While we and others have developed models as secondary analyses of new therapies, a number of clinical trials have included collection of primary economic data. This change has resulted from an increasing awareness of the need for reliable economic data about new therapies at the time when the therapies are being introduced to the market. This impetus has also resulted from issues related to the complexity and cost of developing appropriate economic data for a secondary analysis of a new therapy, and issues related to the potential for bias in the design of economic studies conducted from analysis of secondary data sources. However, as illustrated above, even primary data collection in clinical trials does not eliminate the need for treatment models in the economic analysis of new therapies.

VIII. ANALYSIS PLAN FOR COST DATA

Analysis of cost data shares many features with analysis of clinical data. One of the most important is the need to develop an analysis plan prior to performing the analysis. Table 2 identifies a set of tasks that should be addressed in such a plan. The analysis plan should describe the study design (e.g., report on whether the trial is randomized and double-blind; identify the randomization groups; outline the recruitment strategy; describe the criteria for patient evaluation) and any implications the design has for the analysis of costs (e.g., how one will account for recruiting strategies such as rolling admission and a fixed stopping date).

The analysis plan should also specify the hypothesis and objectives of the study, define the primary and secondary endpoints, and describe how the endpoints will be constructed (e.g., multiplying resource counts measured in the trial times a set of unit costs measured outside the trial). In addition, the analysis plan should identify the potential covariables that will be used in the analysis and specify the time periods of interest (e.g., costs and clinical outcomes at

Table 2. Steps in an economic analysis plan

1.	Study design/summary
2.	Study hypothesis/objectives
3.	Definition of endpoints
4.	Covariates
5.	Prespecification of time periods of interest
6.	Statistical methods
7.	Types of analyses
8.	Hypothesis tests
9.	Interim analyses
10.	Multiplicity issues
11.	Subgroup analysis
12.	Power/sample size calculations

6 months might be the primary outcome, while costs and clinical outcomes at 12 months might be a secondary outcome).

Also, the analysis plan should identify the statistical methods that will be used and how hypotheses will be tested (e.g., a p value cutoff or a confidence interval for the difference that excludes 0). And the plan should prespecify whether interim analyses are planned, indicate how issues of multiple testing will be addressed, and predefine any subgroup analyses that will be conducted. Finally, the analysis plan should include the results of power and sample size calculations.

If there are separate analysis plans for the clinical and economic evaluations, efforts should be made to make them as consistent as possible (e.g., shared use of an intention-to-treat analysis, shared use of statistical tests for variables used commonly by both analyses, etc.). At the same time, the outcomes of the clinical and economic studies can differ (e.g., the primary outcome of the clinical evaluation might focus on event-free survival, while the primary outcome of the economic evaluation might focus on quality-adjusted survival). Thus, the two plans need not be identical.

The analysis plan also should indicate the level of blinding that will be imposed on the analyst. Most, if not all, analytic decisions should be made while by an analyst who is blinded to the treatment groups (i.e., fully blinded rather than simply blinded to treatment A vs. treatment B). Blinding is particularly important when investigators have not precisely specified the models that will be estimated, but instead rely on the structure of the data to help make decisions about these issues.

VIII.a. Methods for Analysis of Costs

When one analyzes cost data derived from randomized trials, one should report means of costs for the groups under study as well as the difference in the means, measures of variability and precision, such as the standard deviation and quantiles of costs (particularly if the data are skewed), and an indication of whether the costs are likely to be meaningfully different from each other in economic terms.

Traditionally, the determination of a difference in costs between groups has been made using the Student's t-test or analysis of variance (ANOVA) (univariate analysis) and ordinary least-squares regression (multivariable analysis). The recent proposal of the generalized linear model promises to improve the predictive power of multivariable analyses.

VIII.a.1. Univariate Analysis

A basic assumption underlying t-tests and ANOVA (which are parametric tests) is that cost data are normally distributed. Given that the distribution of these data often violates this assumption, a number of analysts have begun using nonparametric tests, such as the Wilcoxon rank-sum test (a test of median costs) and the Kolmogorov–Smirnov test (a test for differences in cost distributions), which make no assumptions about the underlying distribution of costs. The principal problem with these nonparametric approaches is that statistical conclusions about the mean need not translate into statistical conclusions about the median (e.g., the means could differ yet the medians could be identical), nor do conclusions about the median necessarily translate into conclusions about the mean. Similar difficulties arise when – to avoid the problems of nonnormal distribution – one analyzes cost data that have been transformed to be more normal in their distribution (e.g., the log transformation of the square root of costs). The sample mean remains the estimator of choice for the analysis of cost data in economic evaluation. If one is concerned about nonnormal distribution, one should use statistical procedures that do not depend on the assumption of normal distribution of costs (e.g., nonparametric tests of means).

Table 3 shows the results of the univariate analysis of hospital costs measured among men receiving vehicle and an investigational medication for the

Table 3. Hospital costs of tirilazad mesylate for subarachnoid hemorrhage in men

Variable	Treatment groups	
	Vehicle	Tirilizad, 6 mg/kg per day
Cost, US$	20,287	25,185
Standard deviation	(22,542)	(22,619)
Distribution		
5%	4,506	10,490
25%	9,691	13,765
50%	13,773	18,834
75%	23,044	31,069
95%	53,728	51,771
Comparison of differences		
t-test	0.15	
t-test (log of costs)	0.02	
Wilcoxon rank-sum	0.001	
Kolmogorov–Smirnov	0.001	

treatment of aneurysmal subarachnoid hemorrhage. The mean cost for patients receiving vehicle was US$20,287 (standard deviation (SD), US$22,542); the mean cost for patients receiving the investigational medication was US$25,185 (SD, US$22,619). The distribution (as seen from the quantiles reported in Table 3, which shows the distribution of costs for the two groups) is skewed. For example, the difference between the 25th and 50th percentiles is approximately US$4,500 for the two treatment groups, but is approximately US$10,000 between the 50th and 75th percentiles. Of note, from the 5th to the 75th percentile, there was approximately a US$5,000 difference between the two treatment groups. By the 95th percentile, the costs in the two groups were similar. These distributions provide evidence that the costs differ between the two treatment groups.

The parametric and nonparametric statistical tests, however, yielded conflicting conclusions about whether the cost differences were statistically different from one another. The t-test comparing mean costs between the groups indicated a nonsignificant difference ($p = 0.15$), whereas the t-test comparing the mean log of costs and both of the nonparametric statistical tests indicated they differed ($p < 0.02$). In this case, one might conclude that the difference in the medians between groups is statistically significant, whereas the difference in the means between groups is not. Similarly conflicting conclusions about the statistical significance of observed differences in costs have been reported in other studies. Although each of these statistical tests is informative, given that the important outcome for the analysis of the value for the costs of the new therapy (e.g., the cost–effectiveness ratio) is the difference in mean costs, the statistical test of differences in means (e.g., t-test) should be used for inferences about this outcome. Measuring the correct parameter should take precedence over threats to the efficiency of the way that parameter is measured.

VIII.a.2. Multivariate Analysis

Regression analysis often is used to assess differences in costs, in part because the sample size needed to detect economic differences may be larger than the sample needed to detect clinical differences (i.e., to overcome power problems). Traditionally, ordinary least-squares regression has been used to predict costs (or their log) as a function of the treatment group while controlling for covariables such as disease severity, costs prior to randomization, etc. However, use of the log of costs as the outcome variable simply to avoid statistical problems posed by untransformed costs leaves one with the problem that we are not interested in this outcome itself; rather we are interested in the difference in untransformed costs. In addition, the retransformation of the predicted difference in the log of costs into an estimate of the predicted difference in costs is not trivial. A generalized linear model framework has been proposed to maintain the log distribution and overcome issues related to retransformation.

While univariate t-tests and ANOVAs assume the normal distribution of cost data, ordinary least-squares regression assumes that the error terms from the prediction of costs are normally distributed. Because of the potential violation of this assumption, however, a number of alternative multivariable methods have recently been proposed for analyzing costs. In addition to the generalized linear model mentioned above, these methods include nonparametric hazards models, parametric failure-time models, Cox semiparametric regression, and joint distributions of survival and cost. The relative merits of several of these methods have been compared by Lipscomb and colleagues and by Manning and Mullahy; however, there is little conclusive evidence regarding which model is best in a given analytic circumstance.

Table 4 shows selected results of an ordinary least-squares regression predicting hospital costs

Table 4. Selected coefficients and p values for the hospital cost regressions for men receiving tirilizad mesylate for subarachnoid hemorrhage

	Coefficient	p value
Intercept	1,747	0.90
Randomization group	*	0.05
6 mg/kg per day	6,058	
2 mg/kg per day	−100	
0.6 mg/kg per day	−247	
Neurograde of subarachnoid hemorrhage		0.0001
Grade 2	3,950	
Grade 3	3,904	
Grade 4	9,132	
Grade 5	5,406	

*6 mg/kg/day vs. vehicle, 2 mg/kg/day, and 0.6 mg/kg/day, $p =$ 0.03, 0.03, and 0.02, respectively; no other comparisons statistically significant.

measured among men receiving vehicle and the investigational medication for the treatment of aneurysmal subarachnoid hemorrhage. On average, costs among those receiving the investigational medication were US$6,058 higher than costs among patients receiving vehicle ($p = 0.03$). Increasing levels in the neurograde of subarachnoid hemorrhage upon entry to the study (grades of subarachnoid hemorrhage range from I to V, with V being the most severe) were generally associated with increasing costs; the reduction in costs among those in grade V was due principally to the large number of patients in this category who died in the hospital. Other predictors of hospital costs included the additional days between onset of subarachnoid hemorrhage and randomization into the trial (+); age (+), and country (+/−) (data not shown).

IX. UNCERTAINTY IN ECONOMIC ASSESSMENT

There are a number of sources of uncertainty surrounding the results of economic assessments. One source relates to sampling error (stochastic uncertainty). The point estimates are the result of a single sample from a population. If we ran the experiment many times, we would expect the point estimates to vary. One approach to addressing this uncertainty is to construct confidence intervals both for the separate estimates of costs and effects as well as for the resulting cost–effectiveness ratio. A substantial literature has developed related to construction of confidence intervals for cost–effectiveness ratios.

One of the most dependably accurate methods for deriving 95% confidence intervals for cost–effectiveness ratios is the nonparametric bootstrap method. In this method, one resamples from the study sample and computes cost–effectiveness ratios in each of the multiple samples. To do so requires one to (1) draw a sample of size n with replacement from the empiric distribution and use it to compute a cost–effectiveness ratio; (2) repeat this sampling and calculation of the ratio (by convention, at least 1000 times for confidence intervals); (3) order the repeated estimates of the ratio from lowest (best) to highest (worst); and (4) identify a 95% confidence interval from this rank-ordered distribution. The percentile method is one of the simplest means of identifying a confidence interval, but it may not be as accurate as other methods. When using 1,000 repeated estimates, the percentile method uses the 26th and 975th ranked cost–effectiveness ratios to define the confidence interval.

In the multivariable regression analysis above, we estimated that therapy with the investigational medication added US$6,058 to the cost of hospitalization (95% confidence interval, US$693 to US$11,423). The results of a logistic regression predicting death indicated that the investigational medication yielded a difference in the predicted probability of death of 0.225. The cost per death averted was US$26,924 (US$6,058/0.225). The results of the bootstrap analysis indicated that the 95% confidence interval for the cost–effectiveness ratio ranged from US$4,300 to US$54,600. Interpreting the results of the bootstrap in a Bayesian sense, evaluating stochastic uncertainty alone, there is a 96% chance that the ratio is below US$50,000 per death averted.

In addition to addressing stochastic uncertainty, one may want to address uncertainty related to parameters measured without variation (e.g., unit cost estimates, discount rates, etc.), whether or not the results are generalizable to settings other than those studied in the trial, and, for chronic therapies, whether the cost–effectiveness ratio observed within the trial is likely to be representative of the ratio that would have been observed if the trial had been conducted for a longer period. These sources of uncertainty are often addressed using sensitivity analysis.

IX.a. Cost–Effectiveness of Immunotherapy After Live-Donor Kidney Transplantation: An Example

A randomized clinical trial with block randomization was conducted in tertiary-care teaching hospitals in India to compare the immunotherapeutic effects of high-dose cyclosporin vs. low-dose cyclosporin regimens after kidney transplantation (data from Christian Medical College & Hospital, Vellore, Tamil Nadu, India). Adult nondiabetic patients with chronic renal failure who were receiving their first kidney transplantation were eligible for the study. Of 236 eligible patients, 221 (94%) were randomized into the two treatment arms (119 in the low-dose treatment arm, 117 in the high-dose treatment arm). Cost data were collected prospectively during the transplantation and posttransplantation periods. Baseline characteristics were similar between the two groups. Patients in the low-dose treatment group received a regimen of cyclosporin, azathioprine, and prednisolone. The high-dose group

received cyclosporin and prednisolone. After six months, patients who did not experience severe complications (i.e., death, redialysis) were considered to have been treated effectively.

Severe complications occurred in 5.6% of patients in the low-dose group and in 9.6% of patients in the high-dose group. The difference in the rate was 4% (c.i. – 9.6 to 2.7) with a p value of 0.26. Total societal cost of treatment after six months of follow-up was 217,747 rupees for the high-dose group and 229,539 rupees for the low-dose group. Incremental costs for the high-dose treatment were 11,792 rupees, with no additional benefit. Sensitivity and threshold analyses verified the robustness of the assumptions.

X. THE FUTURE

The emergence of cost as a criterion for the evaluation of pharmaceutical products requires the continued development and application of research methods to guide decision-makers. Patients, and physicians acting on their behalf, are principally concerned about the effectiveness and safety of drugs. However, as patients, payers, and society become more concerned about the cost of medical care, the clinical contribution of pharmaceutical agents will be weighed against their costs and compared with the next best alternative. As third-party payers increasingly cover drug costs, they will be concerned with their expenditures on pharmaceuticals and the value obtained for the money spent. Hospitals and other providers of care, operating under increasingly constrained budgets, will increase their assessments of pharmaceutical expenditures.

The naive decision-maker might weigh drugs according to their purchase price alone. This paradigm ignores two essential elements in choosing pharmaceuticals. First, in identifying a drug's cost, its purchase price is only part of its real economic impact. The costs of preparation and delivery, as well as the cost of monitoring for and treating adverse events and side effects, are unavoidable elements of the cost of treating patients.

Second, a full analysis should go beyond the identification of cost. Only if the safety and effectiveness of two pharmaceutical agents are equivalent will cost alone determine the choice of therapy. Cost–effectiveness analysis requires that cost be weighed against effectiveness and that when two or more alternatives are being compared, the additional cost per additional unit of effectiveness be measured. Beyond these considerations of cost–identification and cost–effectiveness, a full economic analysis will also assess the net value, or utility, of the drug's clinical contribution.

This is a challenging period for the field of clinical economics. Many of the earlier methodologic challenges of the field have been addressed, and researchers have gained experience in implementing economic evaluations in a multitude of settings. This experience has raised new questions for those interested in the development of new clinical therapies and in the application of economic data to the decision-making process.

With the increasing importance of multinational clinical trials in the clinical development process, many of the problems facing researchers today involve the conduct of economic evaluations in multinational settings. Foremost among these is the problem of generalizability. There is little consensus among experts as to whether the findings of multinational clinical trials are more generalizable than findings from trials conducted in single countries. This question is even more problematic for multinational economic evaluations, because the findings of economic evaluations reflect complex interactions between biology, epidemiology, practice patterns, and costs that differ from country to country.

As physicians are asked simultaneously to represent their patients' interests while being asked to deliver clinical services with parsimony, and as reimbursement for medical services becomes more centralized in many countries, decision-makers must turn for assistance to collaborative efforts of epidemiologists and economists in the assessment of new therapeutic agents. Through a merger of epidemiology and economics, better information can be provided to the greatest number of decision-makers, and limited resources can be used most effectively for the health of the public.

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Chapter 5

Clinical Pharmacology and Drug Policy

Marc Blockman, Peter I. Folb

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I. INTRODUCTION

The discipline of clinical pharmacology brings together clinical and scientific practice to support critical and independent appraisal of data pertaining to drugs and therapeutics, and the rational use of medicines. An understanding and knowledge of clinical pharmacology encourages and makes possible the cost-effective use of medicines and vaccines in prevention and treatment of disease at every level of health care and it assists in the making of policies that govern such use. It is important that there should be an educational infrastructure and career path for health professionals in clinical pharmacology.

In its modern form clinical pharmacology was developed in the 1960s, principally in response to public scares about the safety of medicines. The trigger was thalidomide, an incompletely tested drug administered to pregnant women that caused congenital malformations in more than 10,000 newborn infants. In 1961 it was found to be a cause of phocomelia (seal-like rudimentary upper and lower limbs) and other associated abnormalities in infants at birth. The medical world came to realise that the scientific discipline of pharmacology, until then preoccupied with drug action, receptors and laboratory experiments (as important as these are), needed to address more systematically issues of efficacy, safety and rational use of medicines in humans. It was a crucial development that logically followed the earlier contributions of Bradford Hill and others who had systematically developed a logical basis for the controlled clinical trial. The discipline was born of necessity and it held the promise of bringing together drug action, pathology, toxicology, immunology statistics and epidemiology in the interest of safe and effective use of medicines in the clinic and hospital.

Given the public health importance of clinical pharmacology and its potential to contribute to health policy, it is surprising that over the past 40 years it has not thrived, and that it is weakest in the developing world. This chapter reflects the personal experience of the authors, and their efforts to establish clinical pharmacology in a country with a developing economy. It is intended to serve as an affirmation of the need for science and clinical practice to come together in support of rational and cost-effective use of medicines, especially in resource-limited countries and situations. A large proportion of what is expended on medicines in many countries is lost through inefficient systems of procurement and distribution, irrational use, poor adherence, counterfeit and sub-standard medicines, and corruption. Renewed efforts are needed to stimulate clinical pharmacology and to attract inspired leadership. The public needs to have confidence in the medicines available to them, without which people even come to doubt the soundness and reliability of the

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health system itself. That is a central issue in national and international health policy.

II. THE MODERN CHALLENGE FOR CLINICAL PHARMACOLOGY

At the heart of the challenge for modern clinical pharmacology is the need to bring what is generally seen as an academic discipline to the service of policy. That requires, *inter alia*, political will and support, leadership, expertise, applying the academic to the practical without one sacrificing the other, finding a way to work with industry; in short, securing public confidence through excellence and integrity. Clinical pharmacology is a responsive discipline, identifying, seeking out and addressing the special needs of the community.

There are a number of critical elements in an efficient university clinical pharmacology department. They include teaching, analytical and experimental laboratory work, clinical service, drug information and critical appraisal, advisory support for the professions, drug safety research and evaluation, and pharmacovigilance.

II.a. Teaching

The medical graduate should have the following core skills in clinical pharmacology:

- Sound knowledge of the scientific basis of drug action, including pharmacokinetics, pharmacodynamics and toxicology.
- Ability to apply scientific principles in a clinical context.
- Basic understanding of research methodology, statistics and evaluation of data.
- Insight into the scientific basis of drug development.
- Familiarity with the concept of drug utilisation review.

Teaching clinical pharmacology to undergraduates can be especially rewarding. It reconciles scientific principles and clinical practice, simplifying each. It should take place at the bedside and in the clinic, concentrating on essential and "gold standard" drugs and on safety. It is possible to teach the entire curriculum to medical students on no more than 25–30 commonly-used medicines. Principles are taught in a way that allows for general application. They include the basis of drug action, pharmacokinetics and pharmacodynamics, the pathological and toxicological basis of drug injury and drug-induced diseases, prediction of drug safety, populations at special risk including neonates and the very young, the elderly, pregnant women, breastfeeding women and infants, and patients with associated diseases such as renal failure. This creates opportunities to introduce concepts of experimental medicine, clinical trial design, elementary statistics concepts, and pharmacoepidemiology. That is likely to foster an interest in research. Students are encouraged to develop their own formularies that might start up a lifetime of study, record keeping and problem solving. The methods of examination and evaluation should be faithful to this approach, protecting students from having to learn detail, emphasising rather concept and principle.

II.b. Analytical and Experimental Laboratory

Every modern clinical pharmacology department needs a competent analytical laboratory to function properly. Ideally, the laboratory should be accredited as meeting standards of good laboratory practice (GLP). A laboratory makes therapeutic drug monitoring (TDM) possible, facilitating individualised drug therapy by drawing on pharmacokinetic, pharmacodynamic and pharmacogenetic principles. Therapeutic drug monitoring reduces the risks of toxicity and for certain drugs it enhances the likelihood of achieving therapeutic effects. Interpretation of the drug concentration takes into account one or more of the following: dosing to sample time; route of administration, dosage, precision and validity of the analytical method, the relevance of the pharmacokinetic model, concomitant therapy, and any underlying disease. Since any of these influences might affect the usefulness of the result a systematic approach to TDM is necessary. TDM is particularly helpful in allowing for accurate dose adjustments to be made where drugs have narrow therapeutic ratios (the margin between efficacy and safety) or where the pharmacokinetics are inherently variable and unpredictable. In such cases, clinical interpretation of the laboratory result is paramount if the results are to be useful. Such interpretation takes into account patient co-morbidity and concomitant medication. Systems should be in place for quality assurance of the laboratory results. Controls should take into consideration linearity of the assay results, the coefficient of variation of the assay at low and high concentrations, minimum level of detection and the relevance

of that level to the clinical situation, and laboratory procedures ensuring stability and specificity. Validated methods, reference measurements and standard operating procedures form an integral part of the laboratory process. Good laboratory practice, linked with sound clinical interpretation of the results, is likely to improve patient outcome. A number of independent indicators reflect on the effectiveness of TDM. They include an increasing number of patients falling within the therapeutic range over time, a declining number of inappropriate serum drug concentrations, patient adherence to treatment, and a fall in drug expenditure due to reduced drug doses. TDM can also contribute to improvements in patient morbidity and mortality, fewer adverse events, and shortened hospital stays. Management of patients treated with cardiac glycosides, anti-epileptic agents, immunosuppressive agents and antibiotics such as the aminoglycosides is especially assisted by TDM. The laboratory makes blood screening of common poisons possible, in so doing often expediting diagnosis and management of drug overdosing and accidental poisoning. Finally, the clinical pharmacology service laboratory makes possible collaborative clinical research with other departments in the teaching hospital and beyond, with industry, and it serves as a resource for training in research methodology.

II.c. Clinical Service

At the heart of clinical pharmacology lies a strong clinical service. That includes consultation in complex medical, surgical, gynaecological and anaesthetic cases, leadership and informed input in research ethics, drug-safety and drug-induced diseases, complex therapeutic decision-making, and design and interpretation of clinical trials. The introduction of life-saving new drugs might be possible where otherwise they might be regarded as prohibitively toxic or otherwise problematic. The service creates a basis for training registrars (residents) through opportunities to take responsibility for optimal use of medicines. Drug studies conducted by others are supported and encouraged. Trainees in internal medicine, paediatrics and anaesthetics should be encouraged to rotate through the clinical pharmacology department.

The less money available for health care the more important is the role of clinical pharmacology. In hospitals providing specialised services, where constraints on the availability and affordability of complex medicines are often acutely felt, clinical pharmacology makes it possible to reduce substantially the drug budget.

Clinical pharmacology plays no less significant a role in primary health care. That includes emphasis on essential drugs, safe and rational use of essential medicines including their side effects and outcomes, drug data transmission and analysis, and training with emphasis on prevalent diseases. Interactions between orthodox and traditional (complementary) medicines are carefully considered. Cost–benefit analysis is made possible.

This is the infrastructure that makes it possible for the clinical pharmacologist is to advise government and to provide leadership in drug policy, clinical trials, ethics of clinical studies, pharmacoeconomics, pharmacoepidemiology, drug regulation, the scientific basis of drug development, traditional medicines, and complementary medicines.

II.d. Drug Information

All activities related to the use of medicines need the underpinning of independent drug information, managed by professionals using up-to-date information technology. From this is likely to flow support for a national drug formulary that supports an essential drugs programme and treatment protocols. A drug information service that is open to and readily accessed by pharmacists and general practitioners in community practice is likely also to function as a resource for government, drug regulators, hospital administrators and to others responsible for health policy. Patient groups might also engage with a drug information and knowledge transmission unit. The unit will progressively accumulate issues, queries and outputs that it has handled in a manner that builds on its relevance and significance. If there is at the same time access to epidemiological data, and to drug costs and expenditures, a powerful research capability is built. All this assumes that the professionals working in drug information centres are free of conflict of interest and that their decisions and recommendations are based on sound evidence and clinical principles alone.

III. DRUG SAFETY

Every country needs an authoritative, independent, competent and reliable system for evaluating adverse reactions to drugs and vaccines – a system that is linked with and provides support for the national drug regulatory authority (NRA) and for the national ministry of health. More than 80 countries

today have such a system; many do not. Some of the units responsible are directly linked with the NRA while others are based in an academic department. Increasingly, these units are providing the opportunity to conduct pharmacovigilance studies, expanding the scope of their operations into efficacy and cost–benefit analysis. Great opportunities exist in these arrangements for research. The system needs to be in place to enable the NRA and government to respond to urgent drug and vaccine safety issues, as they arise.

III.a. Pharmacovigilance

In 2003 the 55th World Health Assembly resolved (WHA resolution 55.18) as follows: Recognizing the need to promote patient safety as a fundamental principle of all health systems, [The WHO] urges Member States:

(i) To pay the closest possible attention to the problem of patient safety; and,
(ii) To establish and strengthen science-based systems necessary for improving patients' safety and the quality of health care, including the monitoring of drugs, medical equipment and technology.

The resolution has a significant bearing on the introduction of new medicines for neglected diseases and on the rational use of medicines that are already available. Pharmacovigilance, as the discipline has come to be known, is supported by the International Collaborating Centre of the WHO, based in Uppsala, Sweden (the Uppsala Monitoring Center, UMC), and a network of more than 83 countries that are now affiliated to the UMC as contributing and collaborating centres. Drug regulatory authorities have come to depend increasingly on their national pharmacovigilance centres (those countries that have one) for ongoing review of the safety of medicines that they approve at the time of licensing, and for support of rational use – particularly medicines used in the public sector. Pharmacovigilance underpins dedicated national programmes such as tuberculosis or malaria control and treatment, roll-out of anti-HIV medicines, schistosomiasis, human African trypanosomiasis and immunization coverage. It has the potential to support the introduction of new vaccines and medicines, and to provide the necessary infrastructure for essential drugs programmes. Health ministries, professionals and the public are reassured to know that there is a sound system ensuring the safety of medicines, especially at the time they are first introduced.

For a country to rely on its own pharmacovigilance programme a number of elements need to be in place:

(i) A dedicated pharmacovigilance centre, independently funded (usually by the State), and staffed by persons with expert knowledge of drug safety and evaluation of adverse drug event reports.
(ii) Links between the pharmacovigilance centre and the WHO, specifically UMC.
(iii) Close ties with the national drug regulatory authority that address the mutual needs of the NRA and the pharmacovigilance centre in monitoring drug safety.
(iv) Access to drug information.
(v) Clinical pharmacological expertise.

Pharmacovigilance is a necessary public health activity. To achieve its potential the national pharmacovigilance programme should have clinical underpinning, and support from the ministry of health. Outcomes measurement and analysis are necessary for its successful operation in the mainstream of public health, so that its impact on the national disease profile can be demonstrated. The special needs of the vulnerable should be addressed, including the very young, the elderly, pregnant women, and patients with other diseases such as renal, cardiac, hepatic, etc.). Pharmacovigilance is a vital component of public health programmes for malaria, tuberculosis, HIV/AIDS, schistosomiasis, national immunisation and family planning.

Technological advances in information capture, storage and retrieval, improved systems and resources for financing public health and drug safety initiatives, specialisation in drug safety, and a growing awareness of the importance to the public good of medicines that are safe and rationally used, in addition to their efficacy and good quality, should make these objectives realisable.[1]

[1] The future of pharmacovigilance, assuming that the resolution of the WHA referred to above is carried forward (Waller and Evans, 2003; Risk Management Public Workshop, 2003; Wilson et al., 2003; Verstraeten et al., 2003) is envisaged to include the following: (i) access to databases by practitioners, and linkage or integration of databases for the purpose; (ii) quality control of pharmacovigilance, ensuring its support by robust and independent drug information systems; (iii) use of a common technical language that is supportive of WHO programmes; (iv) integration of vaccines and medicines in a common system; (v) education

IV. RATIONAL DRUG USE

Rational use of medicines is defined by the World Health Organization (1985) as "Patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and their community". Much prescribing, world-wide, fails to meet expectations of rationality. This includes: polypharmacy; wrong dosing; inappropriate use of antimicrobials often in inadequate dosage, or for non-bacterial infections; administration of injections when oral formulations would suffice; prescription that is in conflict with agreed clinical guidelines; and inappropriate self-medication. Lack of access to essential medicines may result in serious morbidity and mortality, particularly with childhood infections and adult chronic diseases such as hypertension, diabetes, epilepsy and mental illness. Inappropriate and excessive use of medicines wastes precious resources and is harmful in terms of poor outcomes and adverse drug reactions. Indiscriminate use of antibiotics contributes to antimicrobial resistance. Stock outs result in inappropriate patient demand, reduced access, and unnecessary attendance at clinics. The result is likely to be loss of patient confidence in the health system.[2]

A multi-disciplinary approach is needed to develop, implement and evaluate interventions aimed at promoting rational drug use. A national body is needed to coordinate policy and strategy nationally, in the public and private sectors. Government, the health professions, academia, the national drug regulatory authority, pharmaceutical industry, consumer groups and non-governmental organizations involved in health care should be included.

Standard treatment guidelines serve as an essential platform for rational drug use. They are systematically developed statements aimed at enabling prescribers to make decisions on appropriate treatments for specific conditions. Evidence-based clinical guidelines are essential in promoting rational use of medicines. They provide a benchmark for diagnosis and treatment against which other treatments can be compared. They should be developed in a participatory manner that includes the users, easy to read, supported by training and wide dissemination; and reinforced by prescription audit and feedback. Guidelines should be developed according to level of care, prevalence of the conditions and skills of prescribers. Regular updating assures credibility and acceptance of the guidelines.

Essential medicines are those medicines and vaccines that satisfy the most common and important health care needs of the population. An essential medicines list (EML) makes medicine management easier in every respect – procurement, storage, distribution, prescribing and dispensing. The national EML should be determined by national treatment guidelines. Selection of essential medicines for the list is based on clear criteria of efficacy, safety, quality, cost and cost–effectiveness, and the list should be regularly updated.

V. DRUGS AND THERAPEUTICS COMMITTEES

A drugs and therapeutics committee (DTC), alternatively known as pharmacy and therapeutics committee, is aimed at ensuring safe and effective (rational) use of medicines in the facility or area under its jurisdiction. Hospital DTCs are common in industrialised countries and they are widely used to influence national decision-taking. Members of DTCs should represent the major specialties and the administration; they should be independent and be without any conflict of interest. Critical to the success of DTCs are a sound scientific and clinical basis for decision taking, clear objectives; a firm mandate, support by senior management, transparency in

in the universities, and advancement of the discipline by incorporating it into curricula with the scientific and clinical elements that underpin it – pathology, epidemiology, immunology, pharmacology, toxicology, and clinical practice; (vi) strong collaborative arrangements; and (vii) extending the systems and expertise of pharmacovigilance to the countries where presently they do not exist, especially to Africa.

[2] There are several established methods to measure the type and extent of irrational drug use. These include: (i) Medicine consumption data, used to identify expensive medicines of lesser efficacy, or to compare actual consumption against expected consumption. The Anatomical Therapeutic Classification (ATC)/Defined Daily Dose (DDD) can be used to compare drug consumption between institutions, regions and countries. (ii) WHO drug use indicators help characterise general prescribing and identify quality of care problems at primary health care facilities. (iii) Focused drug use evaluations or drug utilization reviews can identify problems concerning specific medicines or treatment of particular diseases, particularly in hospitals. (iv) Focus group discussion, in-depth interviews, structured observations and questionnaires can be used to investigate the reasons behind irrational use. The data collected can assist in the design of appropriate interventions and measure the impact of such interventions on medicine use.

its operations and conclusions, wide representation, in its membership, technical competence, multidisciplinary approach, and sufficient resources to implement decisions. The value of participation of clinical pharmacologists in DTCs is self-evident.

VI. THE IDEAL CLINICAL PHARMACOLOGIST

The ideal clinical pharmacologist would have a strong grounding in clinical medicine and s/he would have direct responsibility for patient care. They would have a scientific bent and experience in the conduct and directing of research, and an ongoing and close involvement in and understanding of research. S/he is well placed to advocate the practice of evidence-based medicine and therapeutics. The linking in one person of these attributes serves as a model to students and young practitioners who often seek assurance that it is possible and necessary to integrate science, clinical practice, research, and epidemiology and statistics in serving the care of patients.

National regulatory authorities (NRAs) depend on external experts to review data and provide independent reports in the registration of new medicines and vaccines, and in considering drug safety. If a national pricing review system exists in the public sector the input of clinical pharmacologists is advisable, indeed essential. Tendering for medicines, developing clinical guidelines, evaluating clinical trials, and discovering novel drugs for neglected diseases are other examples of activities eminently dependent on their input. The public needs to know that drug safety issues, vaccine scares, and the like are reviewed and advised upon by experts sufficiently separated from the advocacy role that government may have. Expertise is needed when medicines are not effective, or are unexpectedly toxic, and when the possibility of counterfeit is raised and must be explored. Medicines should be affordable and available, as well as safe, of good quality and effective. Whenever possible, the use of sound generic medicines is promoted. In all these functions the clinical pharmacologist has an essential role to play, and they are equally important in the developing world, or more so.

VII. PREQUALIFICATION OF MEDICINES AND VACCINES

The World Health Organization, through its Department of Vaccines and Biologicals (V&B), provides advice to UNICEF and other United Nations agencies on the acceptability, in principle, of vaccines considered for purchase by UN agencies (WHO, 2002). This has been extended in recent years to pharmaceuticals other than vaccines, in particular anti-tuberculosis, antiretrovirals and antimalarial agents (WHO, 2004). Prequalification has been effective in promoting confidence in the quality of the vaccines and other medicines shipped to countries through UN purchasing agencies. In recent years this WHO arrangement has been expanded to include vaccines in complex multivalent combinations and vaccines for outbreaks such as cholera and meningitis. The system also supports countries seeking guidance on reliable sources of vaccines and other medicines for purchase (WHO, 2002). Its purpose is to verify that vaccines and other critically required medicines meet the specifications of the relevant UN agency, based on scientific evidence.

The WHO prequalification assessment procedure follows a number of principles: (i) reliance on, and inclusion of, a fully functional national regulatory authority (NRA) in the country of manufacture; (ii) an understanding of the product and presentations offered, production process, quality control methods, technical information and specifications, and relevance of the clinical data for the target population; (iii) testing of final product characteristics and assessment of production consistency through compliance with GMP specifications; (iv) random testing to monitor compliance with tender specifications on a continual basis; and (v) monitoring of complaints from the field.[3] Thus, the prequalification process involves initial evaluation, reassessment and ongoing monitoring (WHO, 2002; WHO, 2004), and it depends on clinical pharmacological expertise for its success.[4]

[3] WHO can advise UNICEF and other UN agencies whether vaccines and other medicines included in the prequalification scheme effectively meet WHO-recommended requirements only if the national regulatory authority of the producing country exercises independent and appropriate oversight of the pharmaceuticals concerned, and if they have been adequately assessed by that authority (WHO, 2002).

[4] The review process at WHO differs in detail but not in principle between vaccines and medicines for HIV/AIDS, tuberculosis

VII.a. HIV/AIDS

There are, and will increasingly be, considerable additional strains put on clinical pharmacology by HIV/AIDS. This includes special requirements for the following:

(i) Development of rational and affordable outcomes-based drug protocols, produced jointly with other clinicians in related disciplines, including vaccines.
(ii) Drug safety monitoring and pharmacovigilance of antiretroviral agents.
(iii) Laboratory assays of antiretroviral drugs and other drugs for complicating and coincidental diseases.
(iv) Clinical trials support.
(v) Support for local drug development and regulatory approval, including vaccines.

This will require laboratory services and affiliated scientists, as for national and regional clinical pharmacology centres.

VIII. THE FUTURE OF CLINICAL PHARMACOLOGY

Clinical pharmacology is well placed to support and instruct in the evaluation of medicines, the claims made for them, and the assessment of outcomes as a result of treatment interventions. This will increasingly be based on evidence-based medicine, drug utilisation data, drug costs and epidemiological data relevant to the country.

Information technology is likely to expand considerably in the coming years, with the use of computers becoming universal in the practice of hospital and clinic-based medicine. Clinical pharmacology will advance greatly as a result. Public education will make enormous progress in the coming years. With its access to independent information, and capacity for dissemination of drug information, clinical pharmacology and therapeutics will play a central role in the process of professional and public education to a degree that will be unrecognisable from the present.

Drug and drug metabolite assays will become available for critically required medicines using analytical systems that do not depend on expensive commercial kits or large samples of blood or serum. Anti-HIV drugs, anti-tuberculosis drugs, anti-malarial agents, and toxicology testing will benefit from this. The safety and quality of traditional and complementary medicines will come increasingly under the spotlight, given their special and dominant role in the ordinary care of many patients. Databases, laboratories with sophisticated equipment, regulatory systems and general information systems will be required to support these developments.

No understanding of the future of clinical pharmacology would be complete without reading the gloomy prognosis of clinical pharmacology and therapeutics given by Maxwell and Webb (2006), supported by Breckenridge and others (2006). Referring particularly to the United Kingdom, they conclude that clinical pharmacology and therapeutics is in decline. The situation, they believe, would be worse in developing countries. They predict a future that will deteriorate further to the extent that the discipline might eventually wither. Several factors are thought to have contributed to the problem. They include the fact that clinical pharmacology (and therapeutics) has never moved far from its university base and so the links with public health services are weak. The move to integrated and problem-based learning at schools of medicine is seen to have detracted from the traditional course-based approach which made it possible to present the principles of the discipline together with its clinical application. In the merging of departments and research units the distinct entity of clinical pharmacology has been lost. Finally, clinical pharmacology has proven to be an attractive base for the appointment of individuals to national organisations such as regulatory agencies, pharmacovigilance and health technology assessment – a major internal brain drain. Clinical pharmacology looks weak as a specialty without a link to an organ or a disease, but based on optimising the development and use of tools applied by others. Paradoxically, all this has happened against the background of unprecedented public expectations of the medicines they take, and intolerance of prescribing errors, many of which are avoidable. Patients

and malaria. The evaluation process for medicines includes full assessment by NRA assessors, from both developed and developing countries, from which a report is generated that includes independent clinical and data verification and validation, and assessment of bioequivalence where appropriate. For prequalification of vaccines containing novel agents there would, in addition, need to be a plan for pharmacovigilance that allows for routine reporting of adverse events, reviewed by a competent authority (WHO, 2004).

expect to have access to reliable information regarding medicines so that they might take part in the decision-making process, and they are not satisfied.

The facts are that in most countries clinical pharmacologists (if they exist) are ideally prepared to support rational prescribing practices and to help balance medicines budgets through activities such as drug and therapeutics committees, formulary management, and reviews of drug use, even if these activities are not the sole preserve of clinical pharmacologists. The same assets are needed to teach rational therapeutics to medical students and other student health professionals, for management of drug overdose, and participating in the work of ethics committees. Progress towards a more individual approach to treatment will require substantial input from clinical pharmacologists. Knowledge about what medicines do in the body has expanded rapidly, providing opportunities to improve safe use of medicines and greater efficacy. That is true everywhere.

The prospects for clinical pharmacology in developing countries are particularly exciting. Expertise is necessary for development of therapeutic protocols, licensing of new medicines, liberalisation of the compassionate use of medicines, focus on drug costs, novel drug development for neglected diseases, enabling patient participation in decision taking regarding medicines and addressing litigation, reducing the emphasis on the current ultra-conservative approach to drug regulation by NRAs, ethics including the ethics of clinical trials, good standards of clinical practice, supporting and expediting prequalification of medicines and vaccines for UN agencies, broadening the scope of pharmacovigilance and developing the tools so that issues of safety, efficacy, costs and affordability are comprehensively addressed, working with the pharmaceutical industry, working with traditional healers and enabling development and promoting safety of their medicines, overseeing clinical trials, and broadening the science pertaining to the use of medicines in special risk groups.

These are challenges worth addressing.

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Chapter 6

Drug Regulation: History, Present and Future[1]

Lembit Rägo, Budiono Santoso

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I. HISTORY OF MEDICINES REGULATION

Medicines are perhaps as old as mankind and the concepts how their quality has to be ensured has evolved gradually over the time. For example, Mithridates VI (120 BC), King of Pontus, concocted a compound preparation called "Mithridatium" which included 41 individual components and was held as a panacea for almost all diseases until as late as 1780s. It took until 1540 when in England the manufacture of Mithridatium and other medicines was subjected to supervision under the Apothecaries Wares, Drugs and Stuffs Act. The Act was one of the earliest British statutes on the control of medicines and it established the appointment of four inspectors of "Apothecary Wares, Drugs and Stuffs". This could be seen as the start of pharmaceutical inspections. History of Pharmacopoeias, the official books of drug quality standards, probably dates back to one of the proclamations of the Salerno Medical Edict issued by Fredrick II of Sicily (1240), and ordered apothecaries to prepare remedies always in the same way – *forma curiae*. The first Pharmacopoeias as we know them today stared to appear in Europe from 16th century e.g. the first Spanish Pharmacopoeia was issued in 1581. The standards for the manufacture of Mithridatum were established in England in *The London Pharmacopoeia* only in 1618.

The modern medicines regulation started only after breakthrough progress in the 19th century life sciences, especially in chemistry, physiology and pharmacology, which laid a solid foundation for the modern drug research and development and started to flourish after the second World War.

Unfortunate events have catalysed the development of medicines regulation more than the evolution of a knowledge base. In 1937 over 100 people in the United States died of diethylene glycol poisoning following the use of a sulfanilamide elixir, which used the chemical as a solvent without any safety testing. This facilitated introduction of The Federal Food, Drug and Cosmetic Act with the premarket notification requirement for new drugs in 1938. However, in countries with poor regulatory environment even recently medicines contaminated with diethylene glycol have killed patients.

The second catastrophe that influenced the development of medicines regulation far more than any event in history was the thalidomide disaster. Thalidomide was a sedative and hypnotic that first went on sale in Western Germany in 1956. Between 1958 and 1960 it was introduced in 46 different countries worldwide resulting in an estimated 10,000 babies being born with phocomelia and other

[1] The views stated in this chapter reflect the views of the authors and not necessarily those of the World Health Organization.

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deformities. The role of this disaster in shaping the medicines regulatory systems is not hard to underestimate.

As a result the whole regulatory system was reshaped in the UK where a Committee on the Safety of Drugs (CSD) was started in 1963 followed by a voluntary adverse drug reaction reporting system (Yellow Card Scheme) in 1964. In the United States, The Drug Amendments Act of 1962 was passed by Congress requiring the FDA to approve all new drug applications (NDA) and, for the first time, demanded that a new drug should be proven to be effective and safe. Of equal importance, the FDA was also given the authority to require compliance with current Good Manufacturing Practices (GMP), to officially register drug establishments and implement other requirements. The EEC Directive 65/65/EEC on the approximation of provisions laid down by law, regulation and administrative action relating to medicinal products was also induced by the thalidomide disaster.

It took almost ten years for the European Community (EC), since Council Directive 65/65/EEC was introduced, to further develop harmonization in the Community. In 1975 two Council Directives were introduced, the first on approximation of the laws of Member States relating to analytical, pharmacotoxicological and clinical standards and protocols in respect of the testing of proprietary medicinal products (75/318/EEC), and the second on the approximation of provisions laid down by law, regulation and administrative action relating to medicinal products (75/319/EEC). The latter established an 'old' Committee on Proprietary Medicinal Products (CPMP) as an advisory committee to the EC and introduced the multistate procedure known now as the mutual recognition procedure. Directive 87/22/EEC introduced the concentration procedure which is now known as the centralized procedure. These directives, and following council regulation, were the landmarks for starting harmonization inside the European Union with the final longstanding aim of creating a 'common market' for medicines. The Council Regulation EEC/2309/93 established the European Medicines Evaluation Agency (EMEA) in 1993 and re-established the CPMP as a 'new' CPMP to formulate the opinion of the Agency on questions relating to the submission of applications and granting marketing authorizations in accordance with the centralized procedure. The details of European marketing authorization procedure are described in detail in other publications.

Somewhat parallel with the ongoing harmonization and movement towards creating a common market for medicines inside the EU, the need for wider harmonization was after preliminary contacts between officials from Japan, EU and US discussed during the International Conference of Drug Regulatory Authorities (ICDRA – organized by WHO every second year) in Paris in 1989. The preliminary informal discussions had revealed a need for the harmonization of requirements relating to the new innovative drugs and the green light given in Paris led to the establishment in 1990 of the International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH), a collaborative initiative between the EU, Japan and the United States with observers from WHO, EFTA and Canada. ICH harmonization focuses primarily on technical requirements for new, innovative medicines. However, countries with limited resources are mostly generic markets and may have difficulties of implementing numerous sophisticated ICH standards. Pharmaceutical regulatory harmonization facilitates the availability of safe, effective and good quality pharmaceuticals. World Health Organization (WHO)[2] supports harmonization on national, regional, inter-regional and international levels. International consensus on quality, safety and efficacy standards can accelerate the introduction of new medicines and increase availability of generic medicines through fair competition, thereby lowering prices.

II. WHY REGULATING DRUGS?

Drugs are not ordinary consumers' products. In most instances, consumers are not in a position to make decisions about when to use drugs, which drugs to use, how to use them and to weigh potential benefits against risks as no medicine is completely safe. Professional advise from either prescribers or dispensers are needed in making these decisions. However, even healthcare professionals (medical doctors, pharmacists) nowadays are not in capacity to

[2] WHO is the directing and coordinating technical agency for health within the United Nations system. It is responsible for providing leadership on global health matters, shaping the health research agenda, setting norms and standards, articulating evidence-based policy options, providing technical support to countries and monitoring and assessing health trends.

take informed decisions about all aspects of medicines without special training and access to necessary information. The production of medicines, their distribution and dispensing also requires special knowledge and expertise. Among medical disciplines clinical pharmacology could be considered as a discipline that covers most comprehensively clinical aspects of medicines safety and efficacy. Among medical specialists clinical pharmacologists have the most comprehensive training to understand all the complexities of the clinical use of medicines. Due to sophisticated scientific issues related to medicines just any medical training may not be enough to take fair judgments about their safety and efficacy. Also only basic training in pharmacy may not enable to take proper judgments about medicines quality.

The use of ineffective, poor quality, harmful medicines can result in therapeutic failure, exacerbation of disease, resistance to medicines and sometimes death. It also undermines confidence in health systems, health professionals, pharmaceutical manufacturers and distributors. Money spent on ineffective, unsafe and poor quality medicines is wasted – whether by patients/consumers or insurance schemes/governments. Governments have the responsibility to protect their citizens in the areas where the citizens themselves are not able to do so. Thus, Governments need to establish strong national regulatory authorities (NRAs), to ensure that the manufacture, trade and use of medicines are regulated effectively. In broad terms the mission of NRAs is to *protect and promote public health*. Medicines regulation demands the application of sound scientific (including but not limited to medical, pharmaceutical, biological and chemical) knowledge and specific technical skills, and operates within a legal framework. The basic elements of effective drug regulation have been laid down in several WHO documents.

III. WHAT IS MEDICINES REGULATION?

Medicines regulation incorporates several mutually reinforcing activities all aimed at promoting and protecting public health. These activities vary from country to country in scope and implementation, but generally include the functions listed in Table 1.

What makes medicines regulation effective? Medicines regulation demands the application of sound medical, scientific and technical knowledge and skills, and operates within a legal framework. Regulatory functions involve interactions with various stakeholders (e.g. manufacturers, traders, consumers, health professionals, researchers and governments) whose economic, social and political motives may differ, making implementation of regulation both politically and technically challenging. Medicines regulation has administrative part but far more important is the scientific basis for it. *All medicines must meet three criteria: be of good quality, safe and effective.* The judgments about medicines quality, safety and efficacy should be based on solid science. There are several general and specific factors contributing to effective regulation by NRAs. General factors include political will and commitment to regulation, adequate availability of medicines that are accessible (to avoid smuggling and illegal use), strong public support for drug regulation, effective cooperation between the NRA and other government institutions including those dealing with law enforcement (e.g. customs and police), and sufficient qualified and experienced pharmaceutical, medical and other professionals. Political environment favouring independent science based decision-making and control of import/export and distribution (including e-commerce) of medicines is essential. The specific factors for NRA include clear mission statement, adequate medicines legislation and regulation, appropriate organizational structure and facilities, clearly defined NRA roles and responsibilities, adequate and sustainable financial resources, including resources to retain and develop staff and appropriate tools, such as standards, guidelines and procedures. International collaboration with other NRAs

Table 1. Principal medicines regulatory functions

- Licensing of the manufacture, import, export, distribution, promotion and advertising of medicines
- Assessing the safety, efficacy and quality of medicines, and issuing marketing authorization for individual products
- Inspecting and surveillance of manufacturers, importers, wholesalers and dispensers of medicines
- Controlling and monitoring the quality of medicines on the market
- Controlling promotion and advertising of medicines
- Monitoring safety of marketed medicines including collecting and analysing adverse reaction reports
- Providing independent information on medicines to professionals and the public

Source: WHO Policy Perspectives on Medicines no 7, 2003.

Table 2. Minimum regulatory functions for a national regulatory authority (NRA)

As an absolute minimum NRAs should

- Ensure that all medicines manufacturing, importation, exportation, wholesale and distribution establishments are licensed. Activities and premises must comply with Good Manufacturing Practices (GMP) and Good Distribution Practice requirements
- Before medicines are marketed, assess their *safety, efficacy and quality*
- Monitor the quality and safety of medicines on the market to prevent harmful, substandard and counterfeit medicines from reaching the public
- Regularly inspect and control the informal market, including e-commerce, to prevent illegal trade of medicines
- Monitor advertising and promotion of medicines, and provide independent information on their rational use to the public and professionals
- Participate in sub-regional and regional regulatory networks and international meetings of drug regulatory authorities to discuss issues of mutual interest and concern, facilitate timely exchange of information and promote collaboration
- Monitor and evaluate performance to assess if perceived regulatory objectives have been met, to identify weaknesses and take corrective action

Source: WHO Policy Perspectives on Medicines no 7, 2003.

(for example, in the EU national regulators are required to collaborate in line with respective Community regulations) and internal collaboration with all stakeholders, transparency (making transparent how and based on which information decisions are made) and accountability combined with good management and effective internal quality system contribute to the success of a regulatory authority. Minimum functions that a NRA should be able to carry out are laid down in Table 2.

Excessive promotion of pharmaceuticals has been associated in many countries with serious problems of irrational drug use. Unethical medicines promotion activities often convey misleading information about drugs to the different target audiences. Misinformation can be in the form of an expansion of indications or an exaggeration of efficacy but can also present itself as downplaying the seriousness or the incidence of adverse reactions. Such misleading information will create a wrong perception of the efficacy and safety of medicinals among prescribers and consumers and it will lead to a significant increased demand for drugs. In many countries, relevant provisions regarding such control measures have been stipulated in legislation. For example, only product information approved during the registration process can be included in the package inserts, leaflets or promotional materials. Regulatory or legal provisions with respect to drugs usually appreciate the right of patients or consumers on proper information about the drugs they take. WHO has developed guidelines on Ethical Criteria for Medicinal Drug Promotion. These guidelines in line with European regulations and regulations in many other countries do not allow direct to patient advertising of prescription only medicines (in US it is allowed and has increased sales of several medicines dramatically). These guidelines remain also useful today and provide ethical criteria for different promotional activities and cover, among others, advertisements to prescribers and to the general public, the availability of free samples of prescription drugs for prescribers or of non-prescription drugs to the general public, medical symposia and other scientific meetings, activities of medical representatives, packaging and labeling and the information for patients in the package inserts.

There are few in depth comparative studies of regulatory systems in different countries globally. The study by Ratanwijitrasin and Wondemagegnehu (2002) revealed that in spite of similarities there are still substantial differences existing in how regulatory systems in different countries carry out minimum functions required for effective medicines regulation. A huge variety in national regulatory capacity does exist and not all national regulators can effectively implement even minimum regulatory oversight of pharmaceutical market in their jurisdiction. Substandard and counterfeit medicines are still common in many parts of the world.

IV. DRUG REGISTRATION

Registration of drugs, also known as *product licensing* or *marketing authorization*, is an essential element of drug regulation. All drugs that are marketed,

distributed and used in the country should be registered by the national competent regulatory authority. Only the inspection of manufacturing plants and laboratory quality control analysis certainly does not guarantee product quality and safety. Drug regulation should therefore include the scientific evaluation of products before registration, to ensure that all marketed pharmaceutical products meet the criteria of *safety, efficacy* and *quality*. Although these criteria are applicable to all medicines including biological products (including vaccines, blood products, monoclonal antibodies, cell and tissue therapies) and herbal medicines (also other traditional and complementary medicines) there are substantial differences in the regulatory requirements for some groups of medicines. There should also be clear distinctions between medicines which can be dispensed without prescription (over the counter or OTC medicines) and those for which a prescription is needed. Usually new medicines are introduced as prescription only medicines and only after obtaining knowledge and experience about their safe use they may be considered being used as OTC for self-medication. This is valid only in case patients are expected to be able for adequate self-diagnosis as well. WHO has issued Guidelines for the Regulatory Assessment of Medicinal Products for Use in Self-Medication. In regulatory practice active pharmaceutical ingredients used in medicines are expressed using International Nonproprietary Names (INNs). INNs are assigned upon request to a molecular entity responsible for the pharmacological action by WHO. The INN system as it exists today was initiated in 1950 by a World Health Assembly resolution WHA3.11 and began operating in 1953. Chemical names and entire formulas are often difficult to remember and may be incomprehensible for a non specialist (for example, perhaps few medical doctors know that 4′-hydroxyacetanilide or *N*-(4-hydroxyphenyl) acetamide is paracetamol). The cumulative list of INN now stands at some 7500 plus names designated since that time, and this number is growing every year by some 120–150 new INN (INNs are proposed also for biological medicines such as monoclonal antibodies and gene therapy products). INNs are also widely used in scientific literature and in teaching basic and clinical pharmacology. The lists of International Nonproprietary Names are published in regular manner. Use of INNs in product labeling and information is nowadays in most countries compulsory. As important as assessment of quality, safety and efficacy is ensuring appropriateness, accuracy and availability of approved by regulators product information. When marketing authorization is granted for medicines a set of clinical information including indications are approved. The use of medicines for indications that have not been approved by a regulator is called 'off-label' use. This means that the safety and efficacy of medicines for these indications has not been assessed and approved by a regulator. One of the most common off-label use areas is pediatric medicine.

In the next section we are concentrating on giving general overview of registration requirements for two major groups of medicines: *innovative* (originator) and *multisource* (generic) medicines.

IV.a. Innovative Medicines

Innovative medicines (originator products) are new medicines that have not been used in humans earlier and contain new active ingredients (usually expressed using INN system). Nowadays these medicines are usually first approved by regulators in well resourced countries using regulatory requirements harmonized in the framework of International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH – see also web site: www.ich.org). The terms of reference for ICH include to maintain a forum for constructive dialogue between regulatory authorities and the pharmaceutical industry on the real and perceived differences in the technical requirements in the EU, USA and Japan in order to ensure a more timely introduction of new medicinal products, and their availability to patients, to monitor and update harmonized technical requirements leading to a greater mutual acceptance of research and development data and to contribute to the protection of public health from international perspective.

The ICH technical Topics are divided into four major categories and specific ICH Topic Codes (such as Q1, E6, S1 and M4) are assigned according to these categories. Q means '*Quality*' *Topics* i.e., those relating to chemical and pharmaceutical Quality Assurance (examples: Q1 Stability Testing, Q3 Impurity Testing). S means '*Safety*' *Topics*, i.e., those relating to *in vitro* and *in vivo* preclinical studies (examples: S1 Carcinogenicity Testing, S2 Genotoxicity Testing). E means '*Efficacy*'

Topics, i.e., those relating to clinical studies in human subject (examples: E4 Dose Response Studies, Carcinogenicity Testing, E6 Good Clinical Practices; Clinical Safety Data Management is also classified as an 'Efficacy' Topic – E2). M designates '*Multidisciplinary*' *Topics*, i.e., cross-cutting Topics which do not fit uniquely into one of the above categories (examples here are M1 Medical Terminology – MedDRA, M2 Electronic Standards for Transmission of Regulatory Information – ESTRI, M3 Timing of Pre-clinical Studies in Relation to Clinical Trials, M4 The Common Technical Document – CTD and M5 Data Elements and Standards for Drug Dictionaries). ICH guidelines are not mandatory for anybody per se but the strength of ICH process lies in the commitment for implementation by the ICH 'regions' (EU, USA and Japan) using appropriate national/regional tools. For example, in the EU all ICH guidelines are submitted to the Committee for Human Medicinal Products (CHMP) associated to European Medicines Agency (EMEA, see web site: http://www.emea.europa.eu/) for endorsement once they have reached certain maturity phase ICH process. The CHMP, in consultation with the European Commission decides on the duration for consultation with interested parties (up to 6 months). The European Medicines Agency (EMEA) publishes and distributes the *Step 2* guidelines for comments. At *Step 4* the guidelines are endorsed by the CHMP and a time frame for implementation is established (usually 6 months). The guidelines are subsequently published by the European Commission in the Rules Governing Medicinal Products in the European Union (http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/index.htm). *Step 2* and *Step 4* guidelines are also available from the EMEA site on the Internet (http://www.emea.europa.eu).

As more than 95% of new medicines are worked out in the ICH "regions" the technical requirements for the safety, efficacy and quality of new medicines is determined at large by ICH technical guidelines. The application format for registration (marketing authorization) of new medicines in ICH and associated countries (such as Canada, Switzerland and Australia) has to follow The Common Technical Document (CTD) which provides harmonized structure and format for new product applications. This Common Technical Document is divided into four separate sections and 5 modules (see Fig. 1). The four sections address the application organization (M4: Organization), the Quality section (M4Q), the Safety section (M4S) and the Efficacy section (M4E) of the harmonized application. Module 1 contains ICH region specific administrative data and prescribing information and is not part of CTD. Module 2 contains CTD summaries, Module 3 is dedicated to quality, Module 4 for non-clinical study reports and Module 5 on clinical study reports. The structure of Common Technical Document (CTD) is given in the Fig. 1. The content for CTD has to be compiled taking into consideration technical requirements in more than 56 ICH guidelines for Quality, Safety and Efficacy plus 5 multidisciplinary (M) topics. Registration of new medicines by less resourced regulatory agencies is often based on first approval either by US FDA or EMEA from EU. Indirectly ICH guidelines used by these regulatory agencies have major impact on approval of new medicines beyond ICH regions. Many ICH guidelines, especially those concerning preclinical and clinical research, are of interest to the research community and can serve also as educational tools.

Clinical pharmacologists should be familiar with available ICH guidelines concerning medicines efficacy and safety. Those involved in clinical research have to know in depth Good Clinical Practice (GCP – ICH E6) guidelines as well the guidelines concerning the research ethics. WHO has its own GCP guidelines which do not contradict ICH guideline but which in addition describe the role of regulatory authorities. In addition, WHO has developed a tool for implementation of GCP which provides practical advice on the principles of GCP and has an interactive CD which incorporates many texts related to GCP and research ethics. In research ethics the fundamental principle that "*no one shall be subjected without his free consent to medical or scientific experimentation*" has found further interpretation in a set of principles laid down in the World Medical Association (WMA) *Declaration of Helsinki* (first edition 1964, current version from 2004 under revision). In case of research ethics and medicines safety the work of the Council for International Organizations of Medical Sciences (CIOMS) should be referred to. CIOMS was founded under the auspices of the World Health Organization (WHO) and the United Nations Educational, Scientific and Cultural and Organization (UNESCO) in 1949. In the late 1970s, CIOMS set out, in cooperation with WHO, to prepare guidelines "to indicate how the ethical principles that should guide the conduct of biomedical research involving human subjects, as set forth in the *Declaration of Helsinki*,

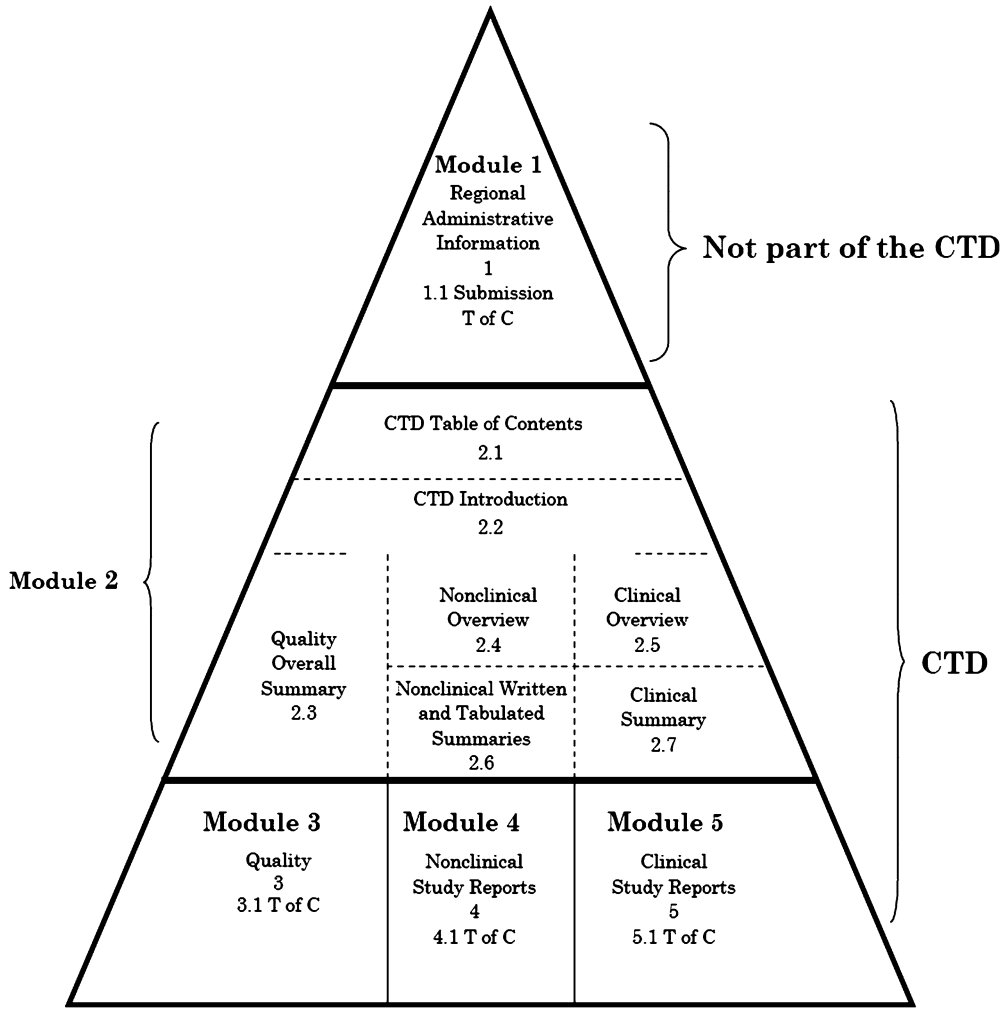


Fig. 1. Diagrammatic representation of the organization of the ICH Common Technical Document (CTD).

could be effectively applied, particularly in developing countries". In 1991, CIOMS published the International Guidelines for Ethical Review of Epidemiological Studies; and, in 1993, International Ethical Guidelines for Biomedical Research Involving Human Subjects. This guideline was updated and published in 2002 and is designed to be of use, particularly to low-resource countries, in defining the ethics of biomedical research, applying ethical standards in local circumstances, and establishing or redefining adequate mechanisms for ethical review of research involving human subjects. In addition, WHO has created several guidance documents how to establish and run Ethics Committees dealing with clinical research. Several CIOMS guidelines have also influenced regulatory approach to medicines safety. Most important of them are International Reporting of Adverse Drug Reactions, which has been basis for ICH guideline E2A (pre-approval reporting) and ICH E2B (electronic case submission of individual case safety reports – ICSRs). CIOMS International Reporting of Periodic Drug-Safety Update Summaries has been basis for ICH E2C (periodic safety update report – PSUR). The latest CIOMS working group resulted in publishing The Development Safety Update Report (DSUR): Harmonizing the Format and Content for Periodic Safety Reporting During Clinical Trials. CIOMS has also been involved in discussing issues related to pharmacogenetics with regulators, industries and academia which resulted in publishing Pharmacogenetics: Towards Improving Treatment with Medicines.

IV.b. Multisource (Generic) Medicines

Multisource (generic) medicines are formulated when patent and other exclusivity rights expire. These medicines have an important role to play in public health as they are well known to medical community and usually more affordable due to competition. The key for generic medicines is their therapeutic interchangeability with originator products. To ensure the therapeutic interchangeability generic products must be pharmaceutically interchangeable (contain the same amount of active ingredient and have the same dosage form) and bioequivalent to the originator product. Bioequivalence is usually established using comparative *in vivo* pharmacokinetic studies with originator products. The detailed description how it is carried out is described in respective WHO document and national regulatory guidelines. Well resourced regulatory authorities require that a multisource (generic) medicine must meet certain regulatory criteria. These are presented in Table 3.

WHO has developed comprehensive set of guidelines for generic drug registration which are useful for drug authorities in developing countries: *Marketing Authorization of Pharmaceutical Products with Special Reference to Multisource (Generic) Products – A Manual for Drug Regulatory Authorities* (first edition 1999, updated version to be published in 2008).

In the context of generic medicines it is appropriate to ask what is a "pharmacopoeia" (word is derived from Greek *pharmako-poios* "drug-maker") and how it fits in nowadays regulatory systems? The answer to this question may seem obvious, but the term "pharmacopoeia" is used in a varied way in different contexts. In the pharmaceutical sense, the pharmacopoeia is an official (legally binding) publication containing recommended quality specifications for the analysis and determinations of drug substances, specific dosage forms, excipients and finished drug products. A quality specification is composed of a set of appropriate tests which will confirm the identity and adequate purity of the product, ascertain the strength (or amount) of the active substance and, when possible, certain its performance characteristics. General requirements are also given in the pharmacopoeia on important subjects related to drug quality, such as microbiological purity, dissolution testing and stability.

Table 3. Regulatory requirements for multisource (generic) medicines

A generic medicines must:	
(1)	contain the same active ingredients as the innovator drug
(2)	be identical in strength, dosage form, and route of administration
(3)	have the same use indications
(4)	be bioequivalent (as a marker for therapeutic interchangeability)
(5)	meet the same batch requirements for identity, strength, purity and quality
(6)	be manufactured under the same strict standards of GMP required for innovator products

The underlying principles of a pharmacopoeia are that pharmaceutical substances and products intended for human use should be manufactured in sites that are adequately equipped, dispose of appropriate professional and technical knowledge and that are operated by qualified staff. General rules of appropriate pharmaceutical manufacture are contained in the Good Manufacturing Practices (GMP) requirements recommended by WHO and/or those laid down by the competent national (or regional, such as European Commission) regulatory authority. In regulatory terms GMP could belong to ABC of regulatory requirements for medicines and compliance with it is vital for products quality. GMP is applicable for both innovator and generic products. It is applicable for manufacture of active pharmaceutical ingredients and finished dosage forms. Even manufacture of investigational drugs should follow GMP. Without GMP consistency of manufacture clinical performance of medicines cannot be assured.

There is a practical distinction between pharmacopoeial standards and manufacturers' release specifications, although both comprise sets of tests to which a given product should conform. Release specifications are applied at the time of manufacture of a pharmaceutical product to confirm its appropriate quality but they also need to have a predictive value, to support the notion that the manufacturer is responsible for the product during its entire shelf-life. In many cases pharmacopoeial monographs are based on the specifications developed by the manufacturers of innovator (originator) products.

In order to launch innovator products pharmacopoeial specifications are not necessary as the manufacturers quality specifications have to pass rigor scientific assessment by the competent regulatory authorities in conjunction with pre-clinical and clinical safety and efficacy data. It is important to notice

that the focus in regulatory environment has been shifting from finished dosage form quality control to the control of the whole complex of processes and procedures involved in the manufacture of both active pharmaceutical ingredients (APIs) and finished dosage forms. The objective of a nowadays regulatory approval is to ensure that the manufacturer has built quality into the product from A to Z.

In case of multisource (generic) medicines (which are formulated after the patents and other exclusivity rights expire) pharmacopoeial monographs are more important as they enable manufacturers not to elaborate their own specifications but rather develop the products to meet the requirements of pharmacopoeial standards (both for APIs and finished dosage forms). It should be noted that not all pharmacopoeias present monographs (quality standards) for finished dosage forms. Pharmacopoeial standards have also certain limitations. For example, testing using pharmacopoeial methods is not necessarily identifying all possible dangerous impurities.

Pharmacopoeial methods are usually designed to catch the impurities that are likely to occur during the route of synthesis that has been utilized by the originator. In case of different route of synthesis or accidental contamination with other chemicals it may not necessarily pick up the impurities even if they pose danger to the health. This is why nowadays well resourced regulatory authorities never base their marketing authorizations of multisource (generic) products only on quality control testing based on pharmacopoeial monographs. In fact, the pre-marketing quality control testing has diminished constantly and more accent is put on market surveillance after the product is put on the market.

Pharmacopoeial monographs help to verify the quality and in case of multisource (generic) medicines they may indicate also on pharmaceutical interchangeability with the originator product. However, pharmacopoeial monographs even for finished dosage forms may have limitations in proving therapeutic interchangeability which is very important for clinical use of medicines (Box 1).

WHO hosts *The International Pharmacopoeia*. This pharmacopoeia is based on specifications validated internationally, through an independent international scientific process.

Unlike national (such as *British Pharmacopoeia*, *Indian Pharmacopoeia* or *US Pharmacopoeia*) and regional (such as *European Pharmacopoeia*) pharmacopoeias, *The International Pharmacopoeia* has, *a priori*, no determined legal status, but WHO Member States are free to adopt it and to incorporate it into national legislation, either in part or in whole. The first edition was published in two volumes (1951 and 1955). The latest fourth edition of *The International Pharmacopoeia* was published in 2006 and an update is to be published in 2008.

Most importantly, a new series of monographs has been added for antiretrovirals. These monographs have been developed as part of the WHO strategy to make quality antiretroviral medicines more widely available to HIV-positive patients. Such specifications support the joint United Nations – WHO Prequalification project, managed by WHO (web site: http://mednet3.who.int/prequal/). International Chemical Reference Substances (ICRS) are primary chemical reference standards used in conjunction with *International Pharmacopoeia* monographs. They are supplied primarily for use in physical and chemical tests and assays described in the specifications for quality control of drugs published in *The International Pharmacopoeia* or proposed in draft monographs.

WHO gives advice on the establishment and management of national quality control laboratories, prepares guidelines on their functioning, publishes guidance and gives advice on Good Manufacturing Practices (GMP) and other regulatory issues, following the underlying principle that *quality must be built into a product from the very beginning of the manufacturing process*. The whole area of work is overseen by the WHO Expert Committee on Specifications for Pharmaceutical Preparations. The WHO Expert Committee on Specifications for Pharmaceutical Preparations is the highest level advisory body

Box 1. Pharmacopoeial standards

Pharmacopoeial standards should be used in the framework of *all regulatory measures* such as Good Manufacturing Practice (GMP) inspection of active pharmaceutical ingredient and finished dosage form manufacturing, scientific assessment of all quality specifications, interchangeability data and labeling information provided by the manufacturer. The most of their value is in post-marketing surveillance of the quality of multisource (generic) medicine.

to WHO's Director-General and its Member States in the area of quality assurance. The advice and recommendations provided by this Expert Committee are intended to help national and regional authorities (in particular drug regulatory authorities), procurement agencies, as well as major international bodies and institutions to combat problems of substandard and counterfeit medicines.

The importance and role of WHO in the field of quality assurance of medicines, especially for those countries that have no or little means to develop their own quality control specifications, persists. WHO has numerous activities to support member states such as creating necessary nomenclatures, guidelines and guidance (WHO GMP being a good example) but also delivering training courses and workshops on various topics of regulatory sciences dedicated to assessment of safety, efficacy and quality of medicines in order to build national capacity to regulate medicines.

V. ROLE OF WHO IN DRUG REGULATION

WHO is the directing and coordinating authority for health within the United Nations system (see more on web site: http://www.who.int/en/). It is responsible for providing leadership on global health matters, shaping the health research agenda, setting norms and standards, articulating evidence-based policy options, providing technical support to countries and monitoring and assessing health trends. In the 21st century, health is a shared responsibility, involving equitable access to essential care and collective defence against transnational health threats.

WHO's role in drug regulation is fourfold. First, issuing necessary norms and standards (see examples above) through its Expert Committees (such as WHO Expert Committee on Specifications for Pharmaceutical Preparations and WHO Expert Committee on Biological Standardization) and Expert Committee like bodies (such as International Nonproprietary Names Expert Group and International Working Group for Drug Statistics Methodology – issuing Anatomical, Therapeutic and Chemical or ATC codes and Daily Defined Doses or DDDs for drug utilization research). Second, supporting regulatory capacity building leading to implementation of drug regulation on national level and its harmonization on regional and Global level. This activity involves assessment of regulatory activities on country level and various technical training courses (such as GMP and GCP, how to assess generic medicines, bioequivalence, safety monitoring and pharmacovigilance, quality assurance and quality control) and customized technical assistance (in cooperation with numerous WHO collaborating centers and other partners) to the countries. Third, in selected areas of essential products, ensuring the quality, safety and efficacy of limited high public health value essential medicines (such as antiretrovoirals to treat HIV/AIDS, or medicines to treat malaria) and vaccines (used in national vaccination programs) through "prequalification". *De facto* prequalification, although primarily meant for UN procurement and international donors, is a regulatory activity mimicking medicines registration (marketing authorization) in its all elements to ensure that products prequalified meet all international standards for quality, safety and efficacy. Prequalification program has also a very strong capacity building element built into it. Fourth, WHO plays a very important role in facilitating exchange of regulatory information for which it has developed a number of tools. Since 1980 WHO convenes every second year International Conference of Drug Regulatory Authorities (ICDRA) and publishes their proceedings. These conferences provide drug regulatory authorities of WHO Member States with a forum to meet and discuss ways to strengthen collaboration. The ICDRAs have been instrumental in guiding through its recommendations regulatory authorities, WHO and interested stakeholders and in determining priorities for action in national and international regulation of medicines, vaccines, biomedicines and herbals.

WHO manages also a system for regular exchange of information between Member States on the safety and efficacy of pharmaceutical products, using a network of designated national drug information officers. WHO ensures the prompt transmission to national health authorities of new information on serious adverse effects of pharmaceutical products and it also responds to individual requests for information. These goals are achieved by the regular publication of regulatory information in the *WHO Pharmaceuticals Newsletter* (http://www.who.int/medicines/publications/newsletter/en/index.html) and by the dissemination of one-page *Drug Alerts* on an *ad hoc* basis. Relevant restrictive regulatory decisions are ultimately compiled in the United

Nations Consolidated List of Products Whose Consumption and/or Sale Have Been Banned, Withdrawn, Severely Restricted or not Approved by Governments. WHO publishes updates to this list: Pharmaceuticals: Restrictions in use and availability. WHO publishes also quarterly *WHO Drug Information* (http://www.who.int/druginformation/) journal which provides an overview of topics of current relevance relating to drug development, safety and regulation. Latest lists of proposed and recommended International Nonproprietary Names (INN) for Pharmaceutical Substances are also published in this journal.

WHO cooperates very actively with national regulatory authorities of all of its Member States. It tries to facilitate spreading best practices and experience. Through its observer role in the international Conference of Harmonization (ICH) WHO is liaising between ICH and non-ICH countries trying to ensure that information exchange between highly industrialized and less resourced countries is taking place.

VI. FUTURE OF MEDICINES REGULATION

Medicines regulation has been developing together with the sciences involved in developing new drugs. Also developments in health delivery systems have plaid role as those involved in health service delivery are interested in safe and effective treatments which would be cost effective and affordable. Both costs of research and development and regulatory assessment of products is increasing. There is likely no alternative for more harmonization (international, regional and sub-regional) of regulatory requirements and work sharing (together with information sharing) between different national regulatory authorities. The cost of full regulatory assessment of a new drug is increasingly becoming not affordable (both in terms of financial and human resources) for less resourced smaller regulatory agencies. What are the new areas of development beyond better harmonization, information exchange and gradual building of trust in each others decisions leading to recognition instead of duplication?

Although even quality issues are still a problem (poor quality of starting materials including active pharmaceutical ingredients, quality problems with finished dosage forms, spreading of counterfeit medicines) it is likely that new technologies and new products will create new regulatory challenges. For example, how will increasing public attention and expectations on medicines safety shape the regulations? How using new technologies such as nanotechnologies change the medicines regulation? Issues relating to the understanding of how the nanoparticles are presented to organs, cells and organelles are of the highest importance when trying to understand the different mechanisms for intracellular trafficking and use their full therapeutic potential. Those aspects cannot be established without improving appropriate basic knowledge of cell and molecular biology at the intracellular level. However, at the same time important quality problems can rise. In order to assure quality physical and chemical properties of nanopharmaceuticals, including residual solvents, processing variables, impurities and excipients, should all be well known. There will be a need for well-established standard tools to be used in the characterization of nanopharmaceuticals, including availability of validated assays to detect and quantify nanoparticles in tissues, medicinal products and processing equipment. Toxicological aspects of nanomedicines have been highlighted with focus on long-term toxicity. Carbon nanotubes, quantum dots and other nonbiodegradable and potentially harmful materials should be given closer attention weather associated with medicines or diagnostics. A special set of standards must be gradually established in the global regulatory environment. In fact, some elements already do exist. In Europe Directive 2004/27/EEC on medicines addresses directly the need for the study of environmental impact of medicines which will have major impact for new nanomaterails to be used in medicines. To examine and predict environment impact is a new task for regulators.

Using genetic information to create safe and effective medicines offers potential for more individualized therapies and patient benefits but will also have an impact on the use of healthcare resources. Pharmacogenetics has been viewed as something for the future, but real clinical examples now exist. Some pharmacogenetic tests, such as the thiopurine methyltransferase (TPMT) test that aims to predict the risk of severe neutropenia for the purine drugs azathioprine and 6-mercaptopurine, have already relatively low unit costs (approximately 50$ US). However, even low unit cost tests may have a significant cost impact if they have a high volume of uptake in a healthcare system. There may be added value associated with introducing a pharmacogenetic test to

guide a prescribing decision, in terms of improved health-related quality of life resulting from fewer severe side effects and improved treatment response in the patient population taking the medicine. Pharmacogenetic tests broadly fall into one of two categories, those provided through clinical laboratories, such as the TPMT test, and those for which a product license has been granted in a similar way to new medicines, such as Third Wave Technologies' (WI, USA) Invader® UGT1A1 Molecular Assay, which was approved by the US FDA in 2005. The last option means that regulators are directly involved. Regulators are starting to regulate pharmacogenetics and some guidance already exists in Canada, EU and US. Recently also ICH started to deal with pharmacogenomics and pharmacogenetics. The E15 guideline Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories has been finalized.

Another area of challenges includes biological medicines including 'generic' biological medicines. New product groups are emerging and even with known product groups there are challenges ahead, especially from the point of view of safety. Other important areas for drug regulators remain pharmocovigilance, pediatric medicines, orphan medicines and medicines for diseases outside ICH regions. There are few financial incentives to create medicines for tropical and neglected diseases but recently due to public private partnerships for drug development and creation of specific regulatory pathways such EU Article 58 procedure that enables European Medicines Agency to assess these products and provide scientific advise for WHO has improved the situation. There are even calls for 'complete rethink' of the regulatory systems in order to prepare for the next 20–30 year.

The present short overview of medicines regulation is clearly not comprehensive but rather an attempt to give idea about the complexities of this important area of work that has many direct links with clinical pharmacology. Clinical pharmacologists as medical specialists equipped with unique knowledge about medicines have a role and responsibility to develop and contribute to medicines regulation.

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Chapter 7

Medicines in Developing Countries

Budiono Santoso, Kathleen Holloway, Hans V. Hogerzeil, Valerio Reggi

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I. INTRODUCTION

Major causes of morbidity and mortality in many developing countries such as malaria, tuberculosis, pneumonia, acute diarrheas, maternal diseases can be treated with simple essential medicines (Box 1). But, essential medicines will save lives and improve health, only if they are available, affordable and of good quality, and properly utilized.

In developed countries, the discovery of new medicines and their introduction in the existing health care system during the second part of the last century has dramatically improved health, reducing mortality and morbidity from many common diseases. The society in general have benefited from these advances through the regular access to the needed medicines in their health care system. However, in many developing countries the needed essential medicines are not always available, accessible and affordable to those in need.

The discovery of new medicines and their introduction into the market will not optimally have positive impacts on health if the needed essential medicines are not available and affordable, if they are not of good quality and if they are not properly utilized by the health care providers and consumers. This chapter will highlight the issues related to commonly occurring problems in the area of medicines in developing countries, and relevant policies and programme to deal with them. In particular, the chapter will highlight the problems of access to the needed medicines, the problems irrational use by providers and consumers and the problems of counterfeit medicines. The sections on equitable access to essential medicines and on promoting rational use are taken from WHO Policy Perspectives on Medicines (WHO, 2004; WHO, 2002) reflecting the positions advocated by WHO on these issues.

II. EQUITABLE ACCESS TO ESSENTIAL MEDICINES

Essential medicines save lives and improve health when they are available, affordable, of assured quality and properly used. Still, lack of access to essential medicines remains one of the most serious global public health problems. Although considerable progress in terms of access to essential medicines has been made in the last twenty-five years since the introduction of the essential medicines concept, not all people have benefited equally from improvements in the provision of health care services, nor from low cost, effective treatments with essential medicines (Table 1). Through a combination of public and private health systems, nearly two-thirds of the world's population are estimated to have access to full and effective treatments with the medicines they need, leaving one-thirds without regular access. It is estimated that by improving access to existing essential medicines and vaccines, about 10 million lives per year could be saved.

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Box 1. Definition of essential medicines

Essential medicines are those that satisfy the priority health care needs of the population. They are selected with due regard to public health relevance, evidence on efficacy and safety, and comparative cost effectiveness. Essential medicines are intended to be available within the context of functioning health systems at all times in adequate amounts, in the appropriate dosage forms, with assured quality and adequate information, and at a price the individual and the community can afford. The implementation of the concept of essential medicines is intended to be flexible and adaptable to many different situations; exactly which medicines are regarded as essential remain a national responsibility

Table 1. Key points for policy makers: Access to medicines supported by the principles of the essential medicines concepts

- Common health problems for the majority of the population can be treated with a small number of carefully selected medicines
- Individual health professionals normally use fewer than 50 different medicines, the WHO Model List of Essential Medicines contains about 300 active substances
- Training and clinical experience should focus on the proper use of these few medicines
- Procurement, distribution and other supply activities can be carried out most efficiently for a limited number of pharmaceutical products
- Patients can be better informed about the effective use of medicines by health professionals

Essential medicines are only one element in the continuum of health care provision but they are a vital element. The major access challenges which can be obstacles for health improvement are:

- *Inequitable access.* About 30% of the world population lacks regular access to essential medicines. In the poorest parts of Africa and Asia the figure rises to over 50%.
- *Health reforms.* In many low-income and middle-income countries, health sector reforms have led to insufficient public funding for health.
- *Medicines financing.* In many high-income countries, over 70% of medicines are publicly funded, whereas in low- and middle-income countries public medicines expenditures does not cover the basic medicines needs of the majority of the population. In these countries, 50–90% of medicines are paid for by patients themselves.
- *Treatment cost.* High cost of treatments with new essential medicines for tuberculosis, HIV/AIDS, bacterial infections and malaria will be unaffordable for many low- and middle-income countries.
- *Globalization.* Global trade agreements can have a negative impact on access to newer essential medicines in low- and middle-income countries.

Access to health care and therefore to essential medicines is part of the fulfillments the fundamental right to health. All countries have to work towards the fulfillments of equitable access to health services and commodities, including essential medicines necessary for the prevention and treatment of prevalent diseases. Appropriate policies and action plans need to be put in place to achieve this aim (Table 2).

II.a. The Access Framework

Improving access to essential medicines is perhaps the most complex challenges to all actors in the public, private and NGO (non-government organization) sectors involved in the field of medicines supply. They must all combine their efforts and expertise, and work jointly towards the solutions. Many factors define the level of access, such as financing, prices, distribution systems, appropriate dispensing and use of essential medicines.

WHO has formulated a four part framework to guide and coordinate collective action on access to essential medicines, namely,

- Rational selection and use of essential medicines,
- Affordable prices,
- Sustainable financing, and
- Reliable supply system.

II.a.1. Rational Selection and Use of Essential Medicines

No health system in the world have unlimited access to all medicines. Rational selection of essential medicines is one of the core principles of national medicines policy. It focuses on therapeutic decisions, professional training, public information, financing, supply and quality assurance efforts on

Table 2. Key actions: Check list for policy makers

Rational selection and use of essential medicines
- Develop national treatment guidelines based on the best available evidence concerning efficacy, safety, quality and cost effectiveness
- Develop a national list of essential medicines based on national treatment guidelines
- Use of national list of essential medicines for procurement, reimbursement, training, donations and supervision

Affordable prices
- Use available and impartial price information
- Allow price competition in the local market
- Promote bulk procurement
- Implement generic policies
- Negotiate equitable pricing for newer essential medicines for priority diseases
- Undertake price negotiation for newly registered essential medicines
- Eliminate duties, tariffs and taxes on essential medicines
- Reduce mark-ups through more efficient distribution and dispensing system
- Encourage local production of essential medicines of assured quality when appropriate and feasible
- Include WTO/TRIPS compatible safeguards into national legislation and apply

Sustainable financing
- Increase public funding for health, including for essential medicines
- Reduce out-of-pocket spending, especially by the poor
- Expand health insurance through national, local and employer schemes
- Target external funding – grants, loans, donations – at specific diseases with high public health impact
- Explore other financial mechanisms, such as debt relief and solidarity funds

Reliable supply system
- Integrate medicines in health sector development
- Create efficient public–private–NGO mix approaches in supply delivery
- Assure quality of medicines through regulatory control
- Explore various purchasing schemes: procurement cooperatives

those medicines which all have their greatest impact in a given healthcare setting. It is a global concept which can be applied in any country, in both public and private sectors and at different levels of the healthcare system. Rational selection and use can be pursued through various tools.

National treatment guidelines are defined by WHO as systematically developed evidence-based statements which assist providers, patients and other stakeholders to make informed decisions about health interventions. Guidelines have mostly been used to advise practitioners on which interventions to use in their interactions with patients.

National lists of essential medicines should be developed for different levels of care and on the basis of treatment guidelines for common diseases and conditions that should be treated at each level. Careful selection of essential medicines is the first step in ensuring access.

Rational use of essential medicines is one of the core activities of health workers and patients. Trained and motivated health staff, and the necessary diagnostic equipment, are needed to ensure the safe and effective treatments, minimizing the risks and waste linked to irrational prescribing and use of medicines.

II.a.2. Affordable Prices

With the potential cost saving of providing a full range of treatments for prevailing common diseases, medicines prices and financing are inescapable factors in access to essential medicines (Box 2). Affordable prices can be pursued through the following mechanism.

Price information is fundamental in obtaining the best price. Several international and regional price information services are made available for WHO Member States (Table 3). Price information helps price negotiations, in locating new supply sources, and in assessing the efficiency of local procurement.

Price competition through tendering of generic products and therapeutic competition are powerful price reduction tools, as evidenced by experiences from large producing countries such as Brazil and India. Through generic competition price reductions at 75–95% were achieved over the initial brand prices (Fig. 1). In addition, price reductions were also obtained through therapeutic competition – between several branded products belonging to the same therapeutic class.

Bulk procurement encompasses that medicines orders are pooled together, that the focus is on the list of priority medicines and that duplication within therapeutic categories is avoided as much as possible. This will result in larger procurement volume and will increase purchasing power. Bulk procurement can be through cooperation of facilities in a country, but positive experience has also been reported from arrangements between states.

Box 2. Inequities on financing

The inequities are striking. In developed countries, a course of antibiotics to cure pneumonia can be bought for the equivalent of 2 or 3 hours wages. One year's treatment of HIV/AIDS infection consumes the equivalent of 4–6 moths' salary. And the majority of costs are reimbursed. In developing countries, a full course of antibiotics to cure a common pneumonia may cost one's month wages. In many countries, one-year's HIV/AIDS treatment, if it were purchased, would consume 30 years' income. And the majority of households must buy their medicines with money from their own pocket

Table 3. WHO medicines price information services

WHO works with several partners to make price information easily accessible to governments, non-governmental organizations, donor agencies and any institution involved in medicines procurement.

- *International Drug Price Indicator Guide*. Details of 350 active ingredients in 750 dosage forms from 17 sources. Indicative price of generic products on the international market and selected tender prices. Produced by Management Sciences for Health and WHO.
- *Sources and Prices of Selected Medicines and Diagnostics for People Living with HIV/AIDS*. Details of 59 active ingredients in 100 dosage forms. Issued by UNICEF, UNAIDS, Medicines San Frontiere and WHO. Covers antiretroviral (ARV) medicines, HIV/AIDS test kits for diagnosis and ongoing monitoring, and medicines treating opportunistic infections, for pain relief, for use in palliative care, for the treatment of HIV/AIDS-related cancers, and for managing drug dependence.
- *Pharmaceutical Starting Materials/Essential Drugs Report*. Details over 273 active ingredients. Issued by WHO and the International Trade Centre, a joint WTO-UNCTAD Centre.
- *AFRO Essential Drugs Price Indicator.* Nearly 300 essential medicines and dosage forms are listed. Details are provided by Member States and low cost essential drugs suppliers. Published by the Regional Office for Africa and the WHO Collaborating Centre for the Quality Assurance of Medicines, University Potchefstroom, South Africa.
- *AMRO: AIDS and STI – Average Prices for One Year Treatment with Antiretrovirals in Countries of Latin America and the Caribbean*: survey by Pan American Health Organization of ARV Therapy in Latin American countries.

Source: http: www.who.int/medicines/organization/par/ipc/drugpriceinfo.shtml

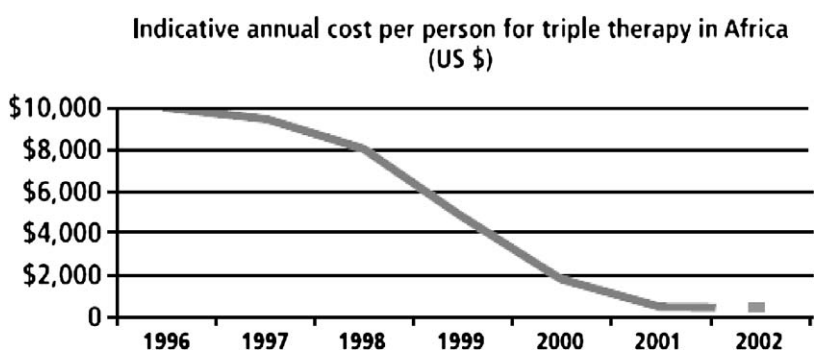


Fig. 1. Advocacy, corporate responsiveness and competition have reduced antiretroviral prices by 95% in 3 years.

Generic policies are effective instruments when a patent expires. In the United States of America the average whole sale price falls to 60% of the price of the branded medicines when one generic competitor enters the market, and to 29% when 10 competitors. To introduce and expand the use of generic medicine products, it is important that (1) supportive regulations exist, (2) reliable quality assurance is in place, (3) professional and public acceptance is obtained, and (4) financial incentives are in place.

Equitable pricing is especially important for newer essential medicines that are still protected by patents or other instruments that provide market exclusivity. Equitable pricing is explained as the adaptation of prices which are charged by the manufacturer or seller to countries with different purchasing

power. Wide spread equitable pricing is economically feasible provided that low-income countries do not leak back to high-income countries.

Sustainable financing for essential medicines must be viewed in the context of overall health care financing. Most low- and-middle income countries rely on a diverse set of health and medicines financing mechanisms which can contribute in the payment of medicines. Nevertheless there are still opportunities in many low and middle income countries for both better and more public funding on health and essential medicines.

Reduction or elimination of duties and taxes for both generic and patented essential medicines contribute to price reduction. In developing countries, the final price of a medicines may be two five times the producer or importer price. This reflects the effects of multiple middlemen, taxes of over 20% in some countries, pharmaceutical import duties up to 65%, high distribution costs, and pharmacy and drug seller charges.

Local production of assured quality when economically feasible and where it follows good manufacturing practices (GMP) can result in lower medicines prices. This can be facilitated by transfer of technology, GMP inspections, and other arrangements. Generic companies in India, Brazil and Thailand have offered their help to low- and middle-income countries to produce antiretrovirals locally through technology transfer through South–South collaboration.

The WTO/TRIPS Agreement defines minimum requirements for intellectual property rights that are applicable to all WTO (World Trade Organization) members. Significantly higher prices are anticipated with full implementation of TRIPS (Trade Related Aspects of Intellectual Property Rights) requirements in low and middle income countries. National patent and related legislation should include standards of patentability that take health into account, promote generic competition, incorporate provisions for TRIPS compatible safeguards such as compulsory licensing and parallel import.

II.a.3. Sustainable Financing

Sustainable financing for essential medicines must be viewed in the context of overall health care financing. Most low- and middle-income countries rely on a diverse set of health and drug financing mechanisms which can contribute in the payment of medicines. Nevertheless there are still opportunities in many low- and middle-income countries for both better and more public spending on health and essential medicines.

Increased public funding for health and medicines is important for high public health impact and strong potential for equity and solidarity, and for support to the disadvantaged. It does not mean that low- and middle-income countries should reallocate funds from prevention or other health priorities, but that additional new public funding should be brought to the health sector. One example is the Global Funds to fight AIDS, Tuberculosis and malaria that offers an opportunity of additional new public funding to those countries where public funding is increasing very slowly or not at all.

Out of pocket spending is a result of failure by the government to allocate sufficient financial resources for medicines supplies essential for treating prevailing diseases for the majority of the population. Patients therefore have to buy all medicines they need from the private sector.

Cost sharing with patients should be seen only as a transitional measure towards long term aims, such as universal health insurance. User charges or co-payment for medicines in public health services do not always lead to increased supply of medicines and may result in decreased utilization of public health services. In addition they can further impoverish already disadvantaged populations. User's charges should complement rather than replace government allocations for curative health services and essential medicines provision.

While virtually 100% of the population has *health insurance* of some forms in most high-income countries, median coverage is 35% in Latin America, 10% in Asia, and less than 8% in Africa. Additionally the inclusion of medicine reimbursement in health insurance varies greatly. Coverage of newer and high-cost essential medicines through well-developed social security schemes is necessary. Advantages of prepayment are that the healthy part of the population subsidizes the sick, and through income related premiums, the wealthy citizens can subsidize the poor. It reflects the solidarity principles that health care should be provided according to need and financed according the ability to pay.

Donor assistance and development loans such as bilateral aid and development loan/grants from development banks continue to provide for many countries sources of health sector financing, which can include funding for essential medicines, such

Table 4. Four types of medicines supply strategies in addition to central medical stores

Central Medical Stores	Centralized, fully public management, warehousing and delivery system
(Semi)autonomous supply agency	Centralized, (semi)private management and warehousing system
Direct delivery system	Centralized decision making but decentralized, private direct delivery system
Prime distributor	Centralized decision making but decentralized, private warehousing and delivery system
Fully private supply	Decentralized decision making, fully private wholesalers and pharmacies system

as HIV/AIDs-related therapies or combination treatment for medicine resistant malaria. Yet it is debatable whether development loans should be used for consumables such as medicines.

Donor funding for and donations of medicines can have an impact on health in low- and middle-income countries in the short term. In the medium term these donations should be targeted at specific diseases and planned as additional supplies integrated into the national medicines supply system. But in the long term, self-sufficiency is the only viable means to tackle increasing disease burdens.

Other financing mechanisms which are being pursued include targeted use of debt relief funds, tax incentives in high-income countries, in kind funding in the form of medicines donations, and solidarity funds.

II.a.4. Reliable Health and Supply Systems

Rapid assessment of health care and supply systems is essential for identifying major weaknesses and initiating corrective actions. Among the many elements of an effective health care system, those most important in supporting access to essential medicines are as follows.

Health sector development is a vital government obligation. In a national health system, proper use of well known and newer essential medicines for priority health problems depends on certain minimal level of medical and pharmaceutical services. This includes inexpensive diagnostic test to confirm diagnosis, and well-informed trained clinicians, pharmacists, nurses and other health staff to help patients, especially those with chronic illnesses, to adhere to their treatments. An overall capacity strengthening of the health and supply systems is a pre-requisite to respond adequately to the increased medical and pharmaceutical needs of populations.

Public–private–NGO (non-governmental organization) *mix* approaches are being pursued to ensure timely availability of medicine supplies of assured quality in the health care system. These vary considerably with respect to the role of the government, the role of the private sector (non-profit and for profit), and the incentives for efficiency. Many countries struggle with the unfortunate combination of an inefficient public medicines supply system meant for the entire country and various private supply systems serving mostly urban areas. Increasingly, an effective medicines supply system is seen to depend on an appropriate mix of public, private and NGO procurement, storages and distribution services (Table 4).

Regulatory control is shared responsibility of the national regulatory authorities, pharmaceutical producers, distributors and other actors active in medicines management. Effective medicines regulation is public service necessary to ensure the quality of pharmaceutical product, that producers fully implement good manufacturing practices to combat sub standard and counterfeit medicines, and to contain drug resistance resulting from uncontrolled supply and use of antibiotics and other essential medicines for both public and private sectors.

Procurement cooperatives increases efficiency. Regional and sub-regional procurement schemes can become a credible option for ensuring medicines supplies. The Gulf Cooperation Council (GCC) and the Organization of Eastern Caribbean States Procurement Services (OECS/PPS) successfully organize pooled procurement for six and eight countries respectively.

III. PROMOTING RATIONAL USE OF MEDICINES

III.a. The Problem of Irrational Use

Irrational or non-rational use is the use of medicines in a way that is not compliant with rational use as defined in Box 3. World-wide more than 50% of all medicines are prescribed, dispensed, or sold inappropriately. Conversely, about one-third of the

Box 3. Definition of rational use of medicines (WHO, 1985)

> Patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and their community

world's population lacks access to essential medicines and 50% of patients fail to take them correctly. Common types of irrational medicine use are:

- the use of too many medicines per patient (polypharmacy);
- inappropriate use of antimicrobials, often in inadequate dosage, for non-bacterial infections;
- over-use of injections when oral formulations would be more appropriate;
- failure to prescribe in accordance with clinical guidelines;
- inappropriate self-medication, often of prescription-only medicines.

Lack of access to medicines and inappropriate doses result in serious morbidity and mortality, particularly for childhood infections and chronic diseases, such as hypertension, diabetes, epilepsy and mental disorders. Inappropriate use and over-use of medicines waste resources – often out-of-pocket payments by patients – and result in significant patient harm in terms of poor patient outcomes and adverse drug reactions. Furthermore, over-use of antimicrobials is leading to increased antimicrobial resistance and non-sterile injections to the transmission of hepatitis, HIV/AIDS and other blood-borne diseases. Finally, irrational over-use of medicines can stimulate inappropriate patient demand, and lead to reduced access and attendance rates due to medicine stock-outs and loss of patient confidence in the health system.

III.a.1. Assessing the Problem of Irrational Use

To address irrational use of medicines, prescribing, dispensing and patient use should be regularly monitored in terms of:

- *the types* of irrational use, so that strategies can be targeted towards changing specific problems;
- *the amount* of irrational use, so that the size of the problem is known and the impact of the strategies can be monitored;
- *the reasons* why medicines are used irrationally, so that appropriate, effective and feasible strategies can be chosen. People often have very rational reasons for using medicines irrationally (Box 4). Causes of irrational use include lack of knowledge, skills or independent information, unrestricted availability of medicines, overwork of health personnel, inappropriate promotion of medicines and profit motives from selling medicines.

There are several well-established methods to measure the type and degree of irrational use. Aggregate medicine (drug) consumption data can be used to identify expensive medicines of lower efficacy or to compare actual consumption versus expected consumption (from morbidity data). Anatomical Therapeutic Classification (ATC)/Defined Daily Dose (DDD) methodology can be used to compare drug consumption among institutions, regions and countries. WHO drug use indicators (Table 5) can be used to identify general prescribing and quality of care problems at primary health care facilities.

Focused drug use evaluation (drug utilization review) can be done to identify problems concerning the use of specific medicines or the treatment of specific diseases, particularly in hospitals. The qualitative methods employed in social science (e.g. focus group discussion, in-depth interviews, structured observation and structured questionnaires), can be used to investigate the motives underlying irrational use. All data collected should be used to design interventions and to measure the impact of those interventions on medicine use.

III.b. Working towards Rational Use of Medicines

A major step towards rational use of medicines was taken in 1977, when WHO established the 1st Model List of Essential Medicines to assist countries in formulating their own national lists. In 1985, the present definition of rational use was agreed at an international conference in Kenya. In 1989, the International Network for the Rational Use of Drugs (INRUD) was formed to conduct multi-disciplinary intervention research projects to promote more rational use of medicines (e-mail: inrud@msh.org, web site: http://www.msh.org/inrud). Following this,

Box 4. Monitoring of medicine use

Monitoring medicine use and using the collected information to develop, implement and evaluate strategies to change inappropriate medicine use behaviour are fundamental to any national programme to promote rational use of medicines. A mandated multi-disciplinary national body to coordinate all activities and sufficient government funding are critical to success

Table 5. Selected WHO/INRUD drug use indicators for primary health care facilities (WHO, 1993)

Prescribing indicators:
Average number of medicines prescribed per patient encounter
% medicines prescribed by generic name
% encounters with an antibiotic prescribed
% encounters with an injection prescribed
% medicines prescribed from essential medicines list or formulary
Patient care indicators:
Average consultation time
Average dispensing time
% medicines actually dispensed
% medicines adequately labelled
% patients with knowledge of correct doses
Facility indicators:
Availability of essential medicines list or formulary to practitioners
Availability of clinical guidelines
% key medicines available
Complementary drug use indicators:
Average medicine cost per encounter
% prescriptions in accordance with clinical guidelines

Source: International Network for Rational Use of Drugs.

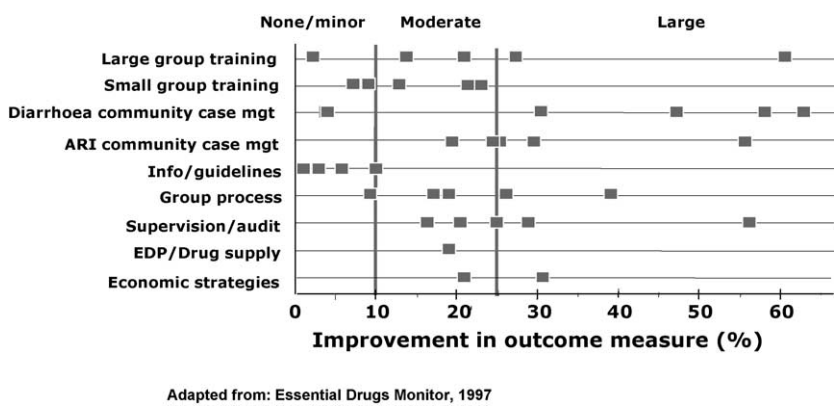


Fig. 2. Review of 30 studies in developing countries. Size of drug use improvements with different interventions.

the WHO/INRUD indicators to investigate drug use in primary health care facilities were developed and many intervention studies conducted. A review of all the published intervention studies with adequate study design was presented at the 1st International Conference for Improving the Use of Medicines (ICIUM) in Thailand in 1997. Figure 2 shows a summary of the magnitude of prescribing improvement by type of intervention. The effect varied with intervention type, printed materials alone having little impact compared to the greater effects associated with supervision, audit, group process and commu-

nity case management. Furthermore, the effects of training were variable and often un-sustained, possibly due to differences in training quality and the presence or absence of follow-up and supervision.

Further evidence was presented at the second international conferences for improving the use of medicines held in Chiang Mai, Thailand in 2004 respectively (URL: http://www.icium.org). On the basis of this evidence the second conference issued a major recommendation for countries to have national programmes to promote rational use of medicines. The conference further recommended that such programmes should be based on coordinated implementation of sustainable multi-faceted interventions, scaled up to the national level and with inbuilt systems for monitoring medicines use in order to evaluate progress.

III.b.1. Core Policies to Promote More Rational Use of Medicines

Although many gaps remain in our knowledge, a summary of what is known concerning core policies, strategies and interventions to promote more rational use of medicines is presented in the following sections and summarized in Table 6.

III.b.1.1. Mandated multi-disciplinary national body to coordinate medicine use policies. Many societal and health system factors, as well as professionals and many others, contribute to how medicines are used. Therefore, a multi-disciplinary approach is needed to develop, implement and evaluate interventions to promote more rational use of medicines. A national regulatory authority (RA) is the agency that develops and implements most of the legislation and regulation on pharmaceuticals. Ensuring rational use will require many additional activities which will need coordination with many stakeholders. Thus a national body is needed to coordinate policy and strategies at national level, in both the public and private sectors. The form this body takes may vary with the country, but in all cases it should involve government (ministry of health), the health professions, academia, the RA, pharmaceutical industry, consumer groups and non-governmental organizations involved in health care. The impact on medicine use is better if many interventions are implemented together in a coordinated way, single interventions often having little impact.

III.b.1.2. Clinical guidelines. Clinical guidelines (standard treatment guidelines, prescribing policies) consist of systematically developed statements to help prescribers make decisions about appropriate treatments for specific clinical conditions. Evidence-based clinical guidelines are critical to promoting rational use of medicines. Firstly, they provide a benchmark of satisfactory diagnosis and treatment against which comparison of actual treatments can be made. Secondly, they are a proven way to promote more rational use of medicines provided they are: (1) developed in a participatory way involving end-users; (2) easy to read; (3) introduced with an official launch, training and wide dissemination; and (4) reinforced by prescription audit and feedback. Guidelines should be developed for each level of care (ranging from paramedical staff in primary health care clinics to specialist doctors in tertiary referral hospitals), based on prevalent clinical conditions and the skills of available prescribers. Evidence-based treatment recommendations and regular updating help to ensure credibil-

Table 6. Twelve core interventions to promote more rational use of medicines

1.	A mandated multi-disciplinary national body to coordinate medicine use policies
2.	Clinical guidelines
3.	Essential medicines lists based on treatments of choice
4.	Drugs and therapeutics committees in districts and hospitals
5.	Problem-based pharmacotherapy training in undergraduate curricula
6.	Continuing in-service medical education as a licensure requirement
7.	Supervision, audit and feedback
8.	Independent information on medicines
9.	Public education about medicines
10.	Avoidance of perverse financial incentives
11.	Appropriate and enforced regulation
12.	Sufficient government expenditure to ensure availability of medicines and staff

ity and acceptance of the guidelines by practitioners. Sufficient resources are needed to reimburse all those who contribute to the guidelines, and to cover the costs of printing, dissemination and training.

III.b.1.3. Essential medicines list based on treatments of choice. Essential medicines are those that satisfy the priority health care needs of the population. Using an essential medicines list (EML) makes medicine management easier in all respects; procurement, storage and distribution are easier with fewer items, and prescribing and dispensing are easier for professionals if they have to know about fewer items. A national EML should be based upon national clinical guidelines. Medicine selection should be done by a central committee with an agreed membership and using explicit, previously agreed criteria, based on efficacy, safety, quality, cost (which will vary locally) and cost–effectiveness. EMLs should be regularly updated and their introduction accompanied by an official launch, training and dissemination. Public sector procurement and distribution of medicines should be limited primarily to those medicines on the EML and it must be ensured that only those health workers approved to use certain medicines are actually supplied with them. Government activities in the pharmaceutical sector, e.g. quality assurance, insurance reimbursement policies and training, should focus on the EML. The WHO Model List of Essential Medicines can provide a starting point for countries to develop their own national EML.

III.b.1.4. Drugs and therapeutics committees in districts and hospitals. A drugs and therapeutics committee (DTC), also called a pharmacy and therapeutics committee, is a committee designated to ensure the safe and effective use of medicines in the facility or area under its jurisdiction. Such committees are well-established in industrial countries as a successful way of promoting more rational, cost-effective use of medicines in hospitals (Table 7). Governments may encourage hospitals to have DTCs by making it an accreditation requirement to various professional societies. DTC members should represent all the major specialities and the administration; they should also be independent and declare any conflict of interest. A senior doctor would usually be the chairperson and the chief pharmacist, the secretary.

Table 7. Responsibilities of a drugs and therapeutics committee

- Developing, adapting, or adopting clinical guidelines for the health institution or district
- Selecting cost-effective and safe medicines (hospital/district drug formulary)
- Implementing and evaluating strategies to improve medicine use (including drug use evaluation, and liaison with antibiotic and infection control committees)
- Providing on-going staff education (training and printed materials)
- Controlling access to staff by the pharmaceutical industry with its promotional activities
- Monitoring and taking action to prevent adverse drug reactions and medication errors
- Providing advice about other drug management issues, such as quality and expenditure

Factors critical to success include: clear objectives; a firm mandate; support by the senior hospital management; transparency; wide representation; technical competence; a multi-disciplinary approach; and sufficient resources to implement the DTC's decisions.

III.b.1.5. Problem-based training in pharmacotherapy in undergraduate curricula. The quality of basic training in pharmacotherapy for undergraduate medical and paramedical students can significantly influence future prescribing. Rational pharmacotherapy training, linked to clinical guidelines and essential medicines lists, can help to establish good prescribing habits. Training is more successful if it is problem-based, concentrates on common clinical conditions, takes into account students' knowledge, attitudes and skills, and is targeted to the students' future prescribing requirements. The *Guide to Good Prescribing* describes the problem-based approach, which has been adopted in a number of medical schools.

III.b.1.6. Continuing in-service medical education as a licensure requirement. Continuing in-service medical education (CME) is a requirement for licensure of health professionals in many industrialized countries. In many developing countries opportunities for CME are limited and there is also no incentive since it is not required for continued licensure. CME is likely to be more effective if it is

problem-based, targeted, involves professional societies, universities and the ministry of health, and is face-to-face. Printed materials that are unaccompanied by face-to-face interventions, have been found to be ineffective in changing prescribing behavior. CME need not be limited only to professional medical or paramedical personnel, but may also include people in the informal sector such as medicine retailers. Often CME activities are heavily dependent on the support of pharmaceutical companies, as public funds are insufficient. This type of CME may not be unbiased. Governments should therefore support efforts by university departments and national professional associations to give independent CME.

III.b.1.7. Supervision, audit and feedback. Supervision is essential to ensure good quality of care. Supervision that is supportive, educational and face-to-face, will be more effective and better accepted by prescribers than simple inspection and punishment. Effective forms of supervision include prescription audit and feedback, peer review and group processes. Prescription audit and feedback consists of analysing prescription appropriateness and then giving feedback. Prescribers may be told how their prescribing compares with accepted guidelines or with that of their peers. Involving peers in audit and feedback (peer review) is particularly effective. In hospitals, such audit and feedback is known as drug use evaluation. Group process approaches amongst prescribers consist of health professionals themselves identifying a medicine use problem and developing, implementing and evaluating a strategy to correct the problem. This process needs facilitation by a moderator or supervisor. Community case management is a special type of supervised group process involving community members in treating patients.

III.b.1.8. Independent medicine information. Often, the only information about medicines that practitioners receive is provided by the pharmaceutical industry and may be biased. Provision of independent (unbiased) information is therefore essential. Drug information centres (DICs) and drug bulletins are two useful ways to disseminate such information. Both may be run by government or a university teaching hospital or a non-governmental organization, under the supervision of a trained health professional. Whoever runs the DIC or bulletin must (1) be independent of outside influences and disclose any financial or other conflict of interest; and (2) use evidence-based medicine and transparent deduction for all recommendations made. The *WHO Model Formulary* provides independent information on all medicines in the WHO Model Essential Medicines List.

III.b.1.9. Public education about medicines. Without sufficient knowledge about the risks and benefits of using medicines and when and how to use them, people will often not get the expected clinical outcomes and may suffer adverse effects. This is true for prescribed medicines, as well as medicines used without the advice of health professionals. Governments have a responsibility to ensure both the quality of medicines and the quality of the information about medicines available to consumers. This will require:

- Ensuring that over-the-counter medicines are sold with adequate labelling and instructions that are accurate, legible and easily understood by laypersons. The information should include the medicine name, indications, contra-indications, dosages, drug interactions, and warnings concerning unsafe use or storage.
- Monitoring and regulating advertising, which may adversely influence consumers as well as prescribers and which may occur through television, radio, newspapers and the internet.
- Running targeted public education campaigns, which take into account cultural beliefs and the influence of social factors. Education about the use of medicines may be introduced into the health education component of school curricula or into adult education programmes, such as literacy courses.

III.b.1.10. Avoidance of perverse financial incentives. Financial incentives may strongly promote rational or irrational use. Examples include:

- Prescribers who earn money from the sale of medicines (e.g. dispensing doctors), prescribe more medicines, and more expensive medicines, than prescribers who do not; therefore the health system should be organized so that prescribers do not dispense or sell medicines.
- Flat prescription fees, covering all medicines in whatever quantities within one prescription, lead to over-prescription; therefore user charges should be made per medicine, not per prescription.
- Dispensing fees, calculated as a percentage of the cost of the medicines, encourage the sale of

Table 8. Regulatory measures to support rational use

- Registration of medicines to ensure that only safe efficacious medicines of good quality are available in the market and that unsafe non-efficacious medicines are banned
- Limiting prescription of medicines by level of prescriber; this includes limiting certain medicines to being available only with a prescription and not available over-the-counter
- Setting educational standards for health professionals and developing and enforcing codes of conduct; this requires the cooperation of the professional societies and universities
- Licensing of health professionals – doctors, nurses, paramedics – to ensure that all practitioners have the necessary competence with regard to diagnosis, prescribing and dispensing
- Licensing of medicine outlets – retail shops, wholesalers – to ensure that all supply outlets maintain the necessary stocking and dispensing standards
- Monitoring and regulating medicine promotion to ensure that it is ethical and unbiased. All promotional claims should be reliable, accurate, truthful, informative, balanced, up-to-date, capable of substantiation and in good taste. WHO's ethical guidelines (1988) may be used as a basis for developing control measures

more expensive medicines; therefore a flat dispensing fee irrespective of the price of the medicine is preferable. Although it may lead to price increases for cheaper medicines, it lowers the price of higher cost medicines.

- Patients prefer medicines that are free or reimbursed. If only essential medicines are provided free by government or reimbursed through insurance, patients will pressure prescribers to prescribe only essential medicines. If medicines are only reimbursed when the prescription conforms to clinical guidelines, there may be an even stronger pressure on prescribers to prescribe rationally.

III.b.1.11. Appropriate and enforced regulation. Regulation of the activities of all actors involved in the use of medicines is critical to ensuring rational use (Table 8). If regulations are to have any effect, they must be enforced, and the regulatory authority must be sufficiently funded and backed up by the judiciary.

III.b.1.12. Sufficient government expenditure to ensure availability of medicines and staff. Lack of essential medicines leads to the use of non-essential medicines, and lack of appropriately trained personnel leads to irrational prescribing by untrained personnel. Furthermore, without sufficient competent personnel and finances, it is impossible to carry out any of the core components of a national programme to promote rational use of medicines. Poor clinical outcome, needless suffering and economic waste are sufficient reasons for large government investment.

Governments are responsible for investing the necessary funds to ensure that all public health facilities have sufficient, appropriately trained health professionals and enough essential medicines at affordable prices for all the population, with specific provisions for the poor and disadvantaged. Achieving these will require limiting government procurement and supply to essential medicines only, and investing in adequate training, supervision and health staff salaries.

IV. COMBATING COUNTERFEIT MEDICINES

IV.a. Silent Murderer

Medicines including vaccines save lives and prevent diseases and epidemics only when they are efficacious, safe, of good quality and rationally used. Unfortunately in recent years there has been an alarming increase in the distribution and sales of counterfeit medicines in many countries. The problems of counterfeit medicines have become rapidly expanding trans national criminal activities, which pose serious threat to the health and safety of the people throughout the world, especially in countries where regulation and law enforcement are weak (Cokcburn et al., 2005; UNICRI, 2006). When patients take counterfeit medicines, whose packaging look like the genuine ones, they are unaware that they have taken useless or dangerous products containing none, insufficient, or even wrong ingredients. Counterfeit medicines resemble a silent murderer when they are used to treat life threatening conditions (Newton et al., 2002; Aldous, 2005), and people of lower-income segment who are attracted by the lower price of counterfeit medicines are at

greater risk of purchasing and consuming unsafe counterfeit products.

IV.a.1. What Are Counterfeit Medicines?

The below definition needs some explanatory words (Box 5). A first aspect to consider is that counterfeiting implies the intention to cheat those who receive the medicine – either in the distribution chain or as patients. This is important because it permits to make necessary distinction between counterfeit medicines and sub-standard medicines. Counterfeit medicines are sub-standard because they are manufactured and distributed out of control and their composition is unpredictable. On the other hand, not all sub-standard medicines are counterfeits. Sub-standard products are genuine products, manufactured by officially licensed manufacturers, which do not meet quality specification set for them. All sub-standard products are manufactured without compliance with Good Manufacturing Practices (GMP) and other regulatory requirements established by the competent national regulatory authorities in order to ensure that efficacy and safety of medicines is not affected by quality problems.

Another aspect to consider is that experiences have shown that there are so many different kinds of counterfeit medicines. Counterfeiters have targeted well known branded as well as unbranded products, expensive as well as inexpensive products, that they have even produced counterfeit medicines that do not refer to any existing brand or manufacturer.

IV.a.2. What Are the Consequences of Counterfeit Medicines

Medicines counterfeiting can involve any kind of medicines, but when it involves medicines for life threatening condition such as malaria, infections, diabetes, cardiovascular diseases, their impact on health outcomes can be formidable. For example, a high incidence of counterfeit new antimalarials, containing no active ingredient, has been reported in Greater Mekong countries in South East Asia. The prevalence of counterfeit antimalarial medicines in the samples collected in this area has been rising rapidly in recent years and ad hoc studies have found that over fifty percent of artesunate and over ninety per cent of mefloquine products did not contain any active ingredient (Dondorp et al., 2004; Newton et al., 2003). In such situations the outcome of malaria treatment can be severely jeopardized and even fatal.

The consequences a patient can experience if s/he is given no medicine, the wrong medicine, the wrong dose, or a toxic mixture of chemicals can be very serious (see Box 6). It is not surprising that many cases

Box 5. Definition of counterfeit medicines

WHO defines counterfeit medicine as one which is deliberately and fraudulently mislabeled with respect to identity and/or source. Counterfeiting can apply to both branded and generic products, and may include products with:

- Correct ingredients
- Wrong ingredients
- Incorrect amount of active ingredients
- Without active ingredients
- Fake packaging

Source: WHO, 1999.

Box 6. The human cost

Verónica Díaz lived in Viedma, a modern city in Argentina. She was 22 and healthy, except for a mild ferropenic anaemia (insufficient iron in her blood) for which she was receiving injections of an iron preparation. After the 7th of a 10-injection treatment, she became very sick and was hospitalized on 18 December 2004. She died of liver failure on 23 December 2004. While hospitalized samples of the medicine she was taking were collected and tested. On the day she died, the medicines authority of Argentina (ANMAT) ascertained that she had been given a highly toxic counterfeit. ANMAT ordered the immediate recall of the product, established a 24-hour hotline to receive and provide information, and started a comprehensive investigation. By 27 December ANMAT had traced the source of the counterfeit product to a distributor. Investigations and laboratory tests continued in January 2005 and led to tracking and recovering of most of the counterfeit product and to the prosecution of four persons. Yet, the highly fragmented distribution system was not fully responsive to the recall. In May 2005, a 22-year old pregnant woman was injected with the same counterfeit iron preparation. She survived, but gave birth to a 26-week premature baby weighing only 1300 grams

of counterfeiting have been uncovered while investigating therapeutic failure or adverse events observed in patients treated, unknowingly, with fake medicines. Counterfeit medicines usually contain a lower levels or no active ingredient at all, thus failing to cure the patient. However, several cases have been found that counterfeit medicines also contain poisonous substances, such as diethylene glycol, therefore even more dangerous to patient health. For example, the use of counterfeit glycerin containing high percentage of diethylene glycol (which is extremely toxic) in the manufacture of cough syrups has been reported to cause hundreds of fatalities in Panama and in China in 2006 (UNICRI, 2006).

There are however other consequences that is essential to remember. One is that the presence of counterfeits challenges people's confidence in the entire health care delivery system, hitting manufacturers, pharmacists, doctors, and private and government institutions alike.

IV.a.3. Where Counterfeit Medicines Can be Found?

Counterfeit medicines can be found everywhere. Although with different frequency, and no country of the world can say to have never known the problem. In developing countries, medicines are often sold in street-market stalls, in unlicensed outlets, without proper packaging, and in many other uncontrolled situations. It is certainly easier to sell counterfeit medicines in these situations than in countries that can count on more effective control on manufacturing and distribution as well as on more effective law enforcement. Yet, counterfeit medicines are increasingly detected in those European and North-American countries which are considered reference models in medicine regulation and enforcement. Counterfeit cases have involved widely-used drugs such as atorvastatin or paracetamol, limited-use drugs such as growth hormone, paclitaxel or filgrastim, as well as other kinds of drugs such as sildenafil and tadalafil. This means that counterfeit medicines can surface in community pharmacies and the hospital alike.

Nobody knows the precise dimensions of the counterfeit medicines problem. Counterfeits are difficult to detect, investigate, quantify. Rough estimates, mainly based on unpublished reports and studies focused on specific medicines or geographical areas, suggest that up to 10% of the medicines circulating in the world could be counterfeit. This estimate shadows broad differences among different countries and areas within a country. It is very likely that this estimate is not a realistic description of the situation of the best regulated countries of the world. Yet, a few dozen cases in a year mean many thousands of tablets and ampoules and therefore many thousands of patients at risk!

In some Sub-Saharan African countries, a WHO study (WHO, 2003) shows a high failure rate in quality control testing on chloroquine tablets. Only 58% of the medicines tested had an acceptable levels of chloroquine content and only 25% had the correct dissolution rate (which is an indicator of the fact that the active substance is dissolved in the intestine and therefore can be absorbed by the body) (Figure 3). Treating patients with poor quality medicines may result in providing insufficient dosages, so promoting the development of resistance.

IV.a.4. Who Are the Counterfeiters

Organized crime has extended its criminal activities to counterfeiting medicines. Yet, it is important to realize that counterfeiting requires the cooperation of people who have had professional experience in pharmaceutical manufacturing and distribution. This should not lead to distrust an entire profession, but rather to consider how all health professionals could help pharmacists to protect their reputation. In addition to organized crime, there are small-scale counterfeiting activities as well as individuals acting alone. The most emblematic case is Robert Courtney's, a Kansas City pharmacist who, in ten years, accumulated at least US$ 19 million by diluting injections, often prepared for patients he personally knew. He got a 30-year sentence.

A few elements may explain why criminals engage in counterfeiting medicines:

- It is relatively easy to hide and smuggle medicines. No country can count on customs controls specialized in combating counterfeit medicines. Customs control is not helped by liberalization of international commerce and the growing number of 'natural products', 'nutritional supplements' and other products non-classified as pharmaceuticals that use packaging and forms more and more similar to those of medicines.
- Demand for medicines does not dwindle and most users are not able to distinguish between real and counterfeit.
- Manufacturing bad quality medicines does not require huge investment and the equipment is easy to move.

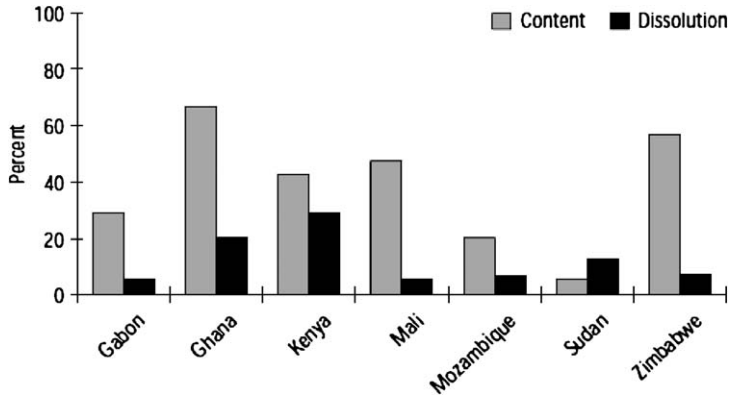


Fig. 3. Percentage failures in ingredient content and dissolution in quality control tests on chloroquine tablets in seven Sub-Saharan African countries. *Source*: WHO, 2003.

- In many countries, regulatory and control systems, especially oversight on distribution channels, are ineffective. In addition, in most countries, punishment is not sufficiently harsh to deter criminals.

IV.a.5. What Factors Make Circulation of Counterfeit Medicines Possible?

Criminality does not explain everything. Many factors favour the development of counterfeiting and trade of counterfeit medicines. We shall mention some of these factors with the understanding that their importance varies considerably among the different countries.

A first factor is governments' willingness to recognize or deny the existence or the gravity of the problem. Denying the problem entails that no adequate measures are taken. This is the basis for other factors that favour counterfeiters:

- inadequate legal framework and ineffective punishment: counterfeiting medicines is not properly defined and is dealt with in the same way as all other types of counterfeiting,
- weak administrative and coordination measures, not focused on fighting counterfeit medicines,
- ineffective control on pharmaceutical manufacturing, importation and distribution.

In addition to the ubiquitous factor of corruption, there is a number of socio-economic factors, many of which are specific to some countries or specific areas inside a country:

- national drug policies that prioritize economic over public health aspects of medicine manufacturing: in these situations exportation takes priority over respect of good manufacturing practices and patients' interests;
- ineffective collaboration among authorities and institutions involved in regulation, control, investigation and prosecution, such as health authorities, police, customs, judiciary;
- extremely fragmented distribution channels involving an unnecessarily large number of transactions, which increases the opportunities for counterfeiters to infiltrate the normal distribution system;
- existence of 'extraterritorial' zones which are substantially out of regulatory oversight and control and where it is possible to manipulate goods and the documentation that accompanies them;
- inadequate access to health services and reliable pharmaceutical supply, absence or insufficient coverage of social security systems: these problems, far too common in rural areas of developing countries, create opportunities for 'informal operators' who can settle and try to meet, in their informal way, populations' real needs;
- extremely wide price gaps or extremely high prices in countries that do not regulate prices: in these cases patients who are not covered by a security system screen markets in search of better prices, this leads to fierce competition among vendors and opens opportunities for counterfeiters who can offer unbeatable prices;
- illiteracy and poverty: in these situations patients are at a particular disadvantage and are not able to know and claim their rights;
- excessive promotion (direct and indirect) of certain medicines creating unexpected demand as

well as 'alternative' supply circuits: the most obvious examples are drugs such as sildenafil or anabolic steroids;
- Internet trade, which makes it easy to hide the actual origin of the medicines;
- third-party manufacturing, which, if not properly and carefully organized, may lead to the unauthorized use of manufacturing techniques and packaging materials.

IV.a.6. How to Protect Public Health?

Combating counterfeit medicines requires the collaboration, at national, regional and international level, among several institutions and several groups representing the civil society. Each has a role to play, but it is necessary that collaboration be based on free circulation of information and frank discussion of problems.

The first issue to address is to sensitize and obtain the commitment of law-makers in order to introduce adequate legislative measures, in particular:
- that counterfeiting medicines be clearly defined and recognized as a crime that is different and more serious than counterfeiting other kinds of goods because its effects go far beyond the economic sphere and hit, sometimes very dramatically, people's health;
- that effective coordination mechanisms be put in place to ensure collaboration among the different institutions that have a role to play in combating counterfeit medicines; these institutions must be able to act in a synergic, rapid and effective way under the guidance of a single unit in charge of coordination and able to avoid that competency disagreements or unnecessary bureaucratic complications delay action creating in this way opportunities for counterfeiters;
- that effective measures be put in place to adequately control exportation and distribution systems on the basis of the principle that, without unnecessarily hindering free movement of goods, protection of public health should be given priority over commercial interests.

In order to sensitize decision-makers it is necessary to develop initiatives that involve all stakeholders of the public sector and the civil society through organizations representing health professionals, patients, manufacturers, distributors, as well as communication professionals and the media.

It is also necessary to take into account the international dimensions of counterfeiting. It has already been said that liberalization and intensification of international trade offer opportunities, albeit undesired, for trading in medicines of unclear origin, including counterfeits. It appears therefore necessary that national authorities improve border control and develop appropriate international collaboration and exchange of information. In this connection, international organizations have an important role to play by facilitating communication among national authorities and developing internationally agreed legal and administrative instruments. Essential players are Interpol, Organization for Economic Cooperation and Development, World Customs Organization, World Intellectual Property Organization, World Trade Organization, and, needless to say, the World Health Organization.

Pharmaceutical manufacturers and their associations are also key players in combating counterfeit medicines. It is industry that most frequently detects cases. In the past, many companies have kept quiet on the cases they had detected, probably for fear of negative commercial consequences of cases becoming widely known. However, this attitude has now changed as many have come to the conclusion that industry's image would be much more negatively affected if the public opinion found out that, for commercial reasons, patients are deliberately left exposed to counterfeit medicines. Industry has many roles to play, but the key ones are: providing information that help detecting and investigating cases, and developing and adopting technologies that make it more difficult to counterfeit medicines and make it easier to detect counterfeits.

Pharmaceutical distributors, wholesalers, importers, exporters, all those involved in the distribution chain are key players that, maybe more than others, should improve their capacity to combat counterfeit medicines. It is through the distribution chain that counterfeit medicines reach patients. It is therefore essential that distributors, wholesalers, importers, exporters develop and effectively implement business practices that make the distribution chain as impermeable as possible to counterfeits and open to appropriate verification by national authorities. It is known that in many countries unauthorized trade is widespread and that it is difficult to get unauthorized traders to respect rules and regulations. Yet, if unauthorized trade is the result of many factors, local distributors and retail pharmacists may find themselves part of the problem (for having left important areas of the country without effective supply mechanisms)

DECLARATION OF ROME
18 FEB 2006

The participants of the WHO International Conference
'Combating Counterfeit Drugs: Building Effective International Collaboration',
gathered in Rome on 18 February 2006

DECLARE

1. Counterfeiting medicines, including the entire range of activities from manufacturing to providing them to patients, is a vile and serious criminal offence that puts human lives at risk and undermines the credibility of health systems.

2. Because of its direct impact on health, counterfeiting medicines should be combated and punished accordingly.

3. Combating counterfeit medicines requires the coordinated effort of all the different public and private stakeholders that are affected and are competent for addressing the different aspects of the problem.

4. Counterfeiting medicines is widespread and has escalated to such an extent that effective coordination and cooperation at the international level are necessary for regional and national strategies to be more effective.

5. National, regional and international strategies aimed at combating counterfeit medicines should be based on:

a) political will, adequate legal framework, and implementation commensurate to the impact of this type of counterfeiting on public health and providing the necessary tools for a coordinated and effective law enforcement,
b) inter-sectoral coordination based on written procedures, clearly defined roles, adequate resources, and effective administrative and operational tools,
c) creating an awareness about the severity of the problem among all stakeholders and providing information to all levels of the health system and the public,
d) development of technical competence and skills in all required areas,
e) appropriate mechanisms for ensuring vigilance and input from healthcare professionals and the public.

6. The WHO should lead the establishment of an International Medical Products Anti-Counterfeiting Taskforce (IMPACT) of governmental, non-governmental and international institutions aimed at:

a) raising awareness among international organizations and other stakeholders at the international level in order to improve cooperation in combating counterfeit medicines, taking into account its global dimensions
b) raising awareness among national authorities and decision-makers and calling for effective legislative measures in order to combat counterfeit medicines
c) establishing effective exchange of information and providing assistance on specific issues that concern combating counterfeit medicines
d) developing technical and administrative tools to support the establishment or strengthening of international, regional and national strategies
e) encouraging coordination among different anti-counterfeiting initiatives.

The IMPACT shall function on the basis of existing structures/institutions and will in the long term explore further mechanisms, including an international convention, for strengthening international action

Box 7. Declaration of Rome.

and part of the solution (by creating mechanisms that through the existing and spontaneous informal trade permit to provide medicines of assured origin to underserved populations).

Other actors of the public sector and the civil society can contribute to combating counterfeit medicines. Purchasing organizations and NGOs should seriously consider the risk that their operations can be affected by counterfeits and develop appropriate procurement procedures and be vigilant on the field in order to be able to signal suspected cases.

Health professions are crucial to combating counterfeit medicines. Nurses and pharmacists are constantly in contact with medicines and can detect differences that, even if small, can arise suspicion and trigger investigation. Physicians must start to include counterfeiting among the possible causes of adverse reactions or therapeutic failure. Yet, for professionals to be able to effectively play their role, it is necessary that national authorities set up effective systems that permit to collect signals, verify and investigate them, and feed back the results to those who have provided signals.

And what can consumers or patients do? Fear all medicines they come across? No, counterfeit medicines are not invariably present in all pharmacies and hospitals. Consumers should learn to go back to their pharmacist or their doctor when they feel that the medicines they regularly takes seem to work differently, when a new medicine does not work as expected, or every time they experience a side effect. In most cases there will be no counterfeit medicine to blame. However, it is important that patients know what to do when they have a doubt about a medicine. Consumers should always purchase medicines from the officially licensed outlets as there is evidence that the incidence of counterfeits medicines is much lower in licensed outlets.

It is on this basis that WHO has lead the establishment of the International Medical Product Anti-Counterfeiting Taskforce, IMPACT (www.who.int/impact). IMPACT aims at gathering and mobilizing all key stakeholders at the international, regional and national level in order to effectively combat counterfeit medicines within the guiding principles enshrined in the Declaration of Rome (Box 7).

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Chapter 8

Drug Information

Ylva Böttiger, Anders Rane

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I. INTRODUCTION

"*We are drowning in information and starving for knowledge*" (Rutherford D. Roger).

This famous statement is as true for drug information as it is for many other scientific areas today. With the globalisation of access to computer based sources of drug information, this applies to developing and western countries alike. As for drug treatment, no matter how much information is available, there is still the need to search, sort, critically evaluate and digest the information into useful knowledge or guidance in any given therapeutic situation. This is one of the main goals of clinical pharmacology. In developing countries, just a few years ago, the lack of information concerning drugs, in parallel to the lack of the drugs themselves, was a major challenge. Today, with a growing access to both generic drugs, and information about drugs, the right use of available information is the key to success. The more scarce the economical resources, the more there is to gain from the critical use of drug information, both on a community level and for the benefit of the individual patient.

The task of gathering and critically evaluating drug information can be performed on several levels: by individual physicians or prescribers, by local Drugs and Therapeutics Committees, by national authorities or by large international organisations, like the Cochrane Collaboration. This chapter will more specifically deal with the concept and function of the Drug Information Centre.

II. THE WORK AND FUNCTION OF A DRUG INFORMATION CENTRE

Regional Drug Information Centres are health care based services, that concentrate the knowledge on how to search, find and evaluate drug information, and that also have knowledge of regional health care facilities. They keep, as far as possible, updated information sources and maintain expertise within the fields of pharmacology, clinical pharmacology and critical drug evaluation. They can thus support the work of both individual health care workers and local Drugs and Therapeutics Committees, as well as give advice to hospitals and health care centres within the region.

A Drug Information Centre may also serve as a Poison Control Centre, which will include services towards the public. The Poison Control Centre answers questions concerning possibly toxic effects of any kind of ingested substance, animal bites or stings, or other forms of chemical exposure. This kind of service will require a 24-hour attendance, whereas the work of answering drug related questions usually can be limited to office hours.

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Edited by C.J. van Boxtel, B. Santoso and I.R. Edwards. IOS Press and Uppsala Monitoring Centre, 2008.

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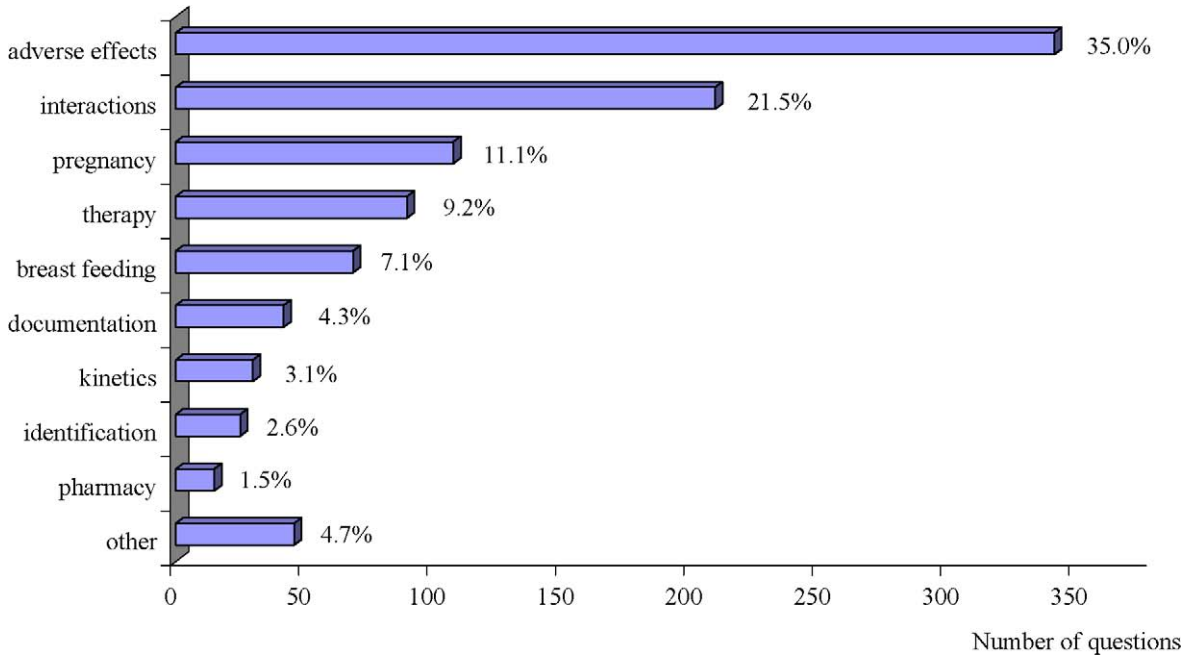


Fig. 1. Types of questions investigated by the Karolinska Drug Information Centre in 2005. The centre was founded in 1974.

Different professionals can work within a Drug Information Centre. The main responsibility for the organisation and the quality of the services performed, both from a medical, scientific, and health economical point of view should preferably be held by a physician with pharmacological expertise, such as a clinical pharmacologist. Otherwise, physicians, pharmacists, nurses, pharmacologists, toxicologists, documentalists or information technicians may all be of good use and contribute to services in different ways, as long as they are well trained and adhere to standardised operating procedures.

The Drug Information Centre should always be available by telephone, but can also answer inquiries by mail, e-mail, Internet based formularies or by functions integrated into local technical systems, such as computerised medical records.

The centre should also be prepared to deal with a wide range of topics. Questions concerning side effects of drugs, drug interactions, and drug use during pregnancy and lactation will be common in relation to individual patients. More general questions concerning drug choice, documentation of effect and dosing may be of relevance to local health facilities or Drug and Therapeutic Committees. For many drugs, there is a lack of information in the labelling to support paediatric drug treatment. Here, the Drug Information Centre can be of good use in aggregating the latest reports. Pharmaceutical questions concerning e.g. drug formulations or identification of active substances from different trade names may also be an important task, especially in the absence of this kind of support from local pharmacies. The type and frequency of questions received by our centre is shown in Fig. 1.

In all cases and types of inquiries, the Drug Information Centre should strive to give evidence based advice, i.e. search available information sources in a standardised manner, and relate the answer to the level and strength of the documentation found.

III. SOURCES OF DRUG INFORMATION

The primary source of information about the benefits and risks of drugs is found in the scientific literature; in articles that have been submitted to independent referees and peer review, and been published in any of the currently available 20,000 biomedical journals. The largest and most commonly used medical bibliographic database, Medline, contains over 15 million citations today, and a search using the word ‘drug’ gives 3.3 million citations.

When using scientific articles to answer a drug problem, one must know how to apply appropriate search strategies to the relevant databases, one has to be able to retrieve the actual articles, and one must carefully read and evaluate the content, including the research methodology, of each publication. Finally, one has to congregate the information found into a sensible conclusion. Having done this, and documented the process, one is by definition as close to the current scientific 'truth' as one will get, and can present an evidence based solution to the problem. Many of the questions put to a Drug Information Centre are quite specific – *does drug A interact with drug B?* – and thus well suited to form the basis of a well defined search strategy in e.g. Medline.

However, in many cases this will be a much to elaborate, expensive and time-consuming process to answer either very simple questions (*what is the half-life of drug Y?*) or questions of a more general character (*what are the current guidelines for the treatment of hypertension?*). If so, there are many secondary sources of drug information, all of which contain information from the primary sources in a processed format, and all which have their different advantages and draw-backs (Table 1).

Medical and pharmacological textbooks, such as, for example, Martindale's *The Extra Pharmacopoeia*, Dollery's *Therapeutic Drugs*, or *The Oxford Textbook of Medicine*, are in many cases both useful and sufficient in answering questions concerning e.g. therapeutic guidelines, pharmacodynamics and pharmacokinetics of drugs, approved indications, common side-effects and established drug interactions. These textbooks provide overviews of large and important therapeutic areas, as well as organised detailed information on e.g. pharmacokinetics properties. However, textbooks are often several years out of date already by the time they are published, and they are not updated very often. One can estimate a mean 10-year-latency for the textbook information. Also, textbooks are not always well referenced and may to a varying degree reflect author bias.

Summary of Product Characteristics (SPC) and package inserts from the manufacturers. This information is based on scientific research performed within the drug company, that may or may not have been published elsewhere, but that has been presented to the drug regulatory authorities in the process of registration. However, the validity and basis of the information given in the SPC cannot be evaluated by other scientists, unless the original study reports have been made publicly available.

Full text databases like *Micromedex* or the online version of *Martindale* or Stockley's *Drug Interactions* have the advantage of being easy to search and are frequently up-dated. References may be directly linked and thus easily retrieved. The information content, as with textbooks, mirrors the selection and bias of the authors.

Review articles are useful tools to grasp larger therapeutic areas, and also to sort out key references within those areas. Again, the selection of material for and conclusions from a review article are those of the authors, and must be subjected to the same scrutiny as in other scientific publications.

The Internet. Several traditional, primary and secondary sources of drug information are now available freely over the Internet, whereas others require some sort of subscription. The main advantage of the Internet-based sources is that they are (or at least could and should be) updated much more frequently than books. Unquestionably, Internet access is of great value to any person or institution dealing with drug information today. As always, the source and quality of the information retrieved must be carefully evaluated. Due to the very fast development and turnover of information on the Internet, no direct links are given in this text. Most of the relevant sources can easily be found by any common search engine, such as Google.

The Internet is already the main source of drug information for many patients. They will relate to, and ask about, this information when they meet health professionals. Not only can the Internet be a source of *information* about drugs. Recently, our centre has dealt with several cases of severe side-effects from unregistered drugs purchased over the Internet.

Reports and guidelines from drug regulatory authorities, health authorities or other independent institutions, like the *Cochrane Collaboration*, are valuable in many aspects. Drug regulatory authorities have, in the process of drug

Table 1. Information sources

Type of query	Sources of information
Therapeutics, rational use of drugs	Goodman & Gilman's *Pharmacological Basis of Therapeutics.* The golden standard of pharmacology texts. Katzung: *Basic and Clinical Pharmacology*.** Martindale: *The Extra Pharmacopoeia*** is probably the most widely used reference source. This encyclopaedia is the basis of many other drug information systems. Dollery: *Therapeutic Drugs.* Detailed drug monographs including e.g. molecular structures and concentration-effect data, that may not be easily found elsewhere. Micromedex.** This is a well-referenced full-text electronic, mainly US based, information system that consists of several different databases: Poisondex system for poisoning information and DrugDex which includes monographs, Martindale, Index Nominum (for identifying foreign drugs), adverse drug reactions, AltMedex for natural products, and more. It is a very comprehensive and practical source of information, but not altogether indispensable, if considered to expensive. Cochrane Collaboration.** Very thorough, evidence based analyses of a large span of different therapeutic areas. FDA home page.* EMEA home page.* In addition to information concerning the work and functioning of European drug regulatory authorities, one can find useful evaluations of drugs, in relation to their registration within the EU. WHO home page.* Under health topics, one can find information on e.g. essential drugs, drug safety, and substandard medicines.
Medicine	Harrison's *Principles of Internal Medicine*. David A et al.: *Oxford Textbook of Medicine*.
Pharmacokinetics	Rowland, Tozer: *Clinical Pharmacokinetics*.
Adverse drug reactions	*Meyler's Side Effects of Drugs.* The most essential encyclopaedia of adverse drug events. Includes registers to both substances and adverse effects, and is very well referenced. *Side Effects of Drugs Annual* (SEDA). A yearly update to Meyler's. *Davie's Textbook of Adverse Drug Reactions*. Chapters on organ systems and their possible adverse reactions, including mechanisms and clinical advice. Lee A, editor: *Adverse Drug Reactions*. Similar information to that of Davie's.
Drug interactions	*Stockley's Drug Interactions*.** The most complete listing of drug interactions. Includes mechanisms, as well as advice on clinical importance and actions. Chapter one gives an excellent introduction to the field. Hansten and Horn: *Drug Interactions Analysis and Management.* Is updated regularly with insert sheets. Levy RH et al.: *Metabolic Drug Interactions*. With information on drug metabolising enzymes, inhibitors and inducers.
Drugs in pregnancy	Briggs GB et al.: *Drugs in Pregnancy and Lactation.* Information sorted by substance, with the main focus on teratogenicity. Schaeffer: *Drugs During Pregnancy and Lactation.* Sorted by treatment indication, which is useful for questions of drug choice.
Drugs and lactation	Bennett PN, editor: *Drugs and Human Lactation*. The only main work on lactation specifically.
Renal failure	Bennett WM et al.: *Drugs and Renal Disease*. Ashley, Currie: *The Renal Drug Handbook*. Davison et al.: *Oxford Textbook of Clinical Nephrology*.
Paediatrics	Yaffe et al.: *Neonatal and Pediatric Pharmacology*.
Natural (herbal) products	Barnes J et al.: *Herbal Medicines.* LaGov B, editor: *PDR for Herbal Medicines*. AltMedex, within the Micromedex information system.
Tropical diseases	Aden Abdi et al.: *Handbook of Drugs for Tropical Parasitic Infections.*
Drugs in sport	World Anti-Doping Agency home page.* Lists of prohibited drugs and therapeutic use exemptions.

*freely available on-line;

**electronic or on-line version available by subscription.

registration, access to unpublished material from the manufacturers, and can thereby evaluate the drug in a better way, less influenced by publication bias. The authors within governmental or independent institutions should openly declare that they have no competing interests, and that they are in no way sponsored by drug manufacturers. Institutes like the Cochrane Collaboration can perform very large and comprehensive analyses of the primary information sources.

Without penetrating the whole area of critical drug evaluation, which would merit a chapter of its own in this book, there are a few basic questions you will have to ask in relation to any source of drug information:

- Is this information manufacturer dependent or independent? This question applies to primary and secondary sources alike.
- For all kinds of evaluated or processed information – by whom, how and why has the primary information been processed?
- Age and half-life of the information? Is there reason to believe that a new study, based on current technology and knowledge would show different results?
- What information is lacking? The phenomenon of publication bias means that the accumulated scientific literature selectively contains reports from studies with positive results, where the primary hypothesis has been confirmed and the so called *null hypothesis* has been discarded.

IV. SUMMARY OF INFORMATION IN RELATION TO CLINICAL CIRCUMSTANCES

Finally, the information retrieved has to be summarised in relation to the present clinical situation. How is the information relevant to my patient? What were the inclusion and exclusion criteria's of the studies performed? What patients were actually studied and of what ethnicity? What doses were studied? Has any studies been performed on children? What resources does the health care system have to deal with the clinical situation, e.g. in terms of monitoring, or in terms of available treatment modalities? In our department, which does also house a large pharmacological laboratory, we do often recommend monitoring of drug concentrations for the guidance of dosing and in the diagnosis of adverse events or drug interactions. This may not be feasible in other health care settings. Guidance on how to process common types of queries is given in Table 2.

V. DOCUMENTATION

The work of the Drug Information Centre should be continuously documented in writing. This for several reasons: to ensure the quality of the work and the evidence-based working method, to answer any medico-legal issues that may arise in connection to the advice given by the centre, to assure the financing of the facility by providing proof of both the quality and quantity of the work performed, to allow research on the type of drug related problems present in the region, to disseminate the information to other parties, and last but not least – to make the work at the centre more efficient. The documentation should include what questions were received from what questioner, what information sources were consulted and by what search strategies, answers given, by whom, and references. Preferably one should also keep track of the working procedure, i.e. time to answering the questions or failure to do so. To keep an in-house database of frequently asked questions and answers, or even better, to share such a database with other centres, saves a lot of daily work. In Scandinavia, there is an ongoing cooperation between eight Drug Information Centres in Sweden, Finland and Denmark, that together create a full text, referenced database of questions and answers handled at the centres.

VI. EDUCATION AND INTERNATIONAL COOPERATION: GLOBALISATION OF DRUG INFORMATION

The Drug Information Centre provides a unique learning environment for the education of clinical pharmacologists, other medical doctors, information pharmacists or information technicians, and for any other health care personnel that need training in clinical pharmacology, drug evaluation and the rational use of drugs.

The Drug Information Centres may also serve as knots in an international web of collaborating centres, sharing their working methods and information sources, including their own Q&A databases, educating and exchanging personnel, and learning from each other's experiences.

Table 2. Guidance on how to answer common type of queries

Information to be retrieved from the questioner

Sex, age and medical history of the patient including the present medical problem, current and recent drug treatment, including dose and indication, time relations for suspected side-effects, stage of pregnancy at the time of drug exposure and maturity of neonates.

The structure and content of the answer will naturally depend on the type of inquiry

Side-effects of drugs

Is there a known pharmacological basis for this possible adverse event?
What has been reported in the literature concerning side-effect *X* as caused by drug *Y*?
Adverse events listed in clinical trials, case reports, and for rare events epidemiological studies, such as case control studies. Data from national side-effects registers or from the WHO register can be of value, but should be interpreted with caution.
An evaluation of the causal relation between drug exposure and symptoms according to an established algorithm, as described elsewhere in this book.
Advice, when appropriate, on the clinical handling of the case; should the dose be adjusted or the treatment be stopped? If so, what other substances could be used? Should one avoid all drugs of the same class or mechanism of action, or of chemical similarity? Is there a drug interaction contributing to the effect?
A recommendation to report the case to the national side-effect register.

Drug interactions

What has been reported in the literature concerning a possible interaction?
Is there a pharmacodynamic basis for interaction – what is the mechanism of action of the drugs involved?
Is there a pharmacokinetic basis for interaction – how are the drugs absorbed, distributed, and eliminated?
If there is a risk for an interaction – what clinical consequences are to be expected and how can these be handled? Can therapeutic drug monitoring be of use? Can dose adjustments be sufficient or should the combination be avoided?

Drugs in pregnancy

Are there literature data supporting that the drug does not cross the placenta? If so, the drug is not likely to cause direct harm to the foetus (but may still act indirectly, as with e.g. hypoglycaemic agents).
Is teratogenicity (risk of malformations) a concern? That depends on the drug as well as the time of exposure, with the most vulnerable period being between week 4–14 of pregnancy (counted from the first day of the last menstrual period).
Are there any other possible effects on the health, well-being or development of the foetus? This has to be computed from knowledge of the pharmacological action of the drug and literature data.
The disease of the mother may pose a risk to the foetus that may on one hand serve as a confounder in studies of foetal outcome, and that may on the other hand also strengthen the treatment indication.
If there is little or no data from humans, animal studies can be taken into account. When looking at results from animal studies, the possibility of toxic effects on the mother animal should be taken into account, as these can affect the pregnancy outcome as well.
The pharmacokinetics of many drugs can change during pregnancy, with an increased dosage need particularly during the third trimester.
Neuroactive drugs should preferably be tapered towards the end of pregnancy to avoid withdrawal symptoms in the newborn.

Drugs and lactation

The age, health and maturity of the baby is of importance, as is the relative contribution of breast milk to the nutrional intake by the baby.
Does the drug transfer into breast milk? Are there data concerning milk concentrations in relation to maternal plasma concentrations? What is the oral bioavailability of the drug?
Are there any reports or studies on the clinical outcome in nursing children? What effects could be expected in the infant? How can the infant or child eliminate the drug?

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Chapter 9

Drug Development

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I. INTRODUCTION

In this chapter an overview will be given of the drug development process, which is both exciting and complex. We will focus on the development of new drugs and neglect developments based on existing drugs. Examples of the latter are improvements of the active ingredient (new ester, salt or non-covalent derivative, single enantiomer of a racemic drug, or the active metabolite of a (pro-)drug, new pharmaceutical formulations, new combinations and new indications). Of the drug candidates in development the majority belongs to the category of chemically synthesized small molecules (also referred to as new chemical entities, NCEs). However, in recent years an increasing number of drug candidates have been produced using biotechnological methods, the so-called biotech compounds, biologic(al)s or new biological entities (NBEs). Examples of the latter category are proteins, monoclonal antibodies (which are also proteins) and peptides, but also vaccines. Of the 28 new drugs approved in 2005 by FDA 8 were biologicals (29%). It is expected that over the coming years this percentage will remain between 25–35%.

The aim of drug development is to gather comprehensive information on the optimal use of a new drug in the treatment or prevention of disease, and to document the quality of the drug product. Efficacy, safety and quality are the main criteria for granting marketing authorization. However, it should be realized that clinical studies carried out during the development of a drug are not generating sufficient data to warrant the safety of a new drug. In fact, this aspect can only be appraised when there has been sufficient exposure to the drug in medical practice over longer periods of time.

For reasons of space we will not discuss the development of the production process nor that of the formulation and presentation form. The reader should appreciate, however, that this is a major part of the overall drug development process, subject to the highest quality requirements and a key factor in the regulatory approval and medical and commercial success of the drug.

II. RECENT CHANGES IN DRUG DEVELOPMENT

Over the past decades drug development has undergone dramatic changes. Only a few decades ago it was an empirical poorly orchestrated regional or sometimes even local activity, often pushed by a 'product champion' within or outside a pharmaceutical company, usually a pharmacologist or a clinician. Support disciplines such as pharmaceutical development, toxicology, pharmacokinetics and drug metabolism, clinical pharmacology and regulatory

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affairs contributed in an independent and unsystematic way. Decision making was erratic and development times were long. The number of failed trials was high and there were many projects that flopped only at the end of phase 3. For those that made it to submission, the registration process was in general slow, often subjective and in some cases even corrupt.

Nowadays, under the influence of economic factors, scientific progress and increased regulation, the drug development process has become much more sophisticated and rational (although there is still considerable room for improvement). To a large extent it has become a global activity with the objective being to launch each new drug in the three major markets, i.e. the USA, Europe and Japan, if possible even simultaneously. Only in this way it is possible to have the maximum return on the huge investment that is now required to develop new drugs.[1] Also the quality and speed of the registration of drugs has improved tremendously. Among the factors that contributed to this improvement are the initiative to harmonize the regulatory requirements globally (International Conference on Harmonisation, ICH), the modernization of the US Food and Drug Administration (FDA: Modernization Act) and the centralization of registrations in the European Union by the European Medicines Evaluation Agency (EMEA).

III. PHARMACEUTICAL MEDICINE

One of the developments that has contributed substantially to the improved quality of drug development is the emergence of Pharmaceutical Medicine. Pharmaceutical Medicine is the discipline concerned with the medical aspects of research, development, evaluation, registration, monitoring and marketing of medicines in the interest of patients. In Great Britain a Diploma in Pharmaceutical Medicine was introduced in 1975, and in 1989 the Faculty of Pharmaceutical Medicine was established as part of the Royal College of Physicians. Subsequently, similar developments took place in other countries.

Pharmaceutical Medicine is usually taught by academicians and senior staff from the industry in post-graduate courses to physicians, pharmacists and other academic staff working in the pharmaceutical industry. It typically covers topics such as pharmacology, toxicology, pharmacy, clinical pharmacology, medical therapeutics, clinical trial methodology, biostatistics, adverse reactions, regulatory affairs, medical information, ethical and legal aspects, pharmaco-epidemiology, pharmacoeconomics, project management and marketing and sales.

For a comprehensive overview of the topic the reader is referred to two recently published textbooks of Pharmaceutical Medicine and to the websites of several courses and institutions mentioned at the end of this chapter.

IV. KEY PLAYERS IN DRUG DEVELOPMENT

To give a better understanding of the environment in which drug development takes place, we will start with a brief description of the key players in this multifaceted endeavor, the complexity of which is not always easy to comprehend from outside the industry. In addition to the pharmaceutical industrial complex which discovers and develops almost all new drugs, these comprise the governmental regulatory authorities, governmental and private research institutes, universities and the medical profession. It is obvious that among these key players cultures are totally different. On the one extreme there is the pharmaceutical industry that combines (sometimes cutting edge) science with (often ruthless) business practises. On the other extreme there are the regulatory authorities that traditionally have a more civil service attitude, although clear improvements have occurred over the recent years.

IV.a. The Pharmaceutical Industry

To illustrate that drug development is almost exclusively a business driven activity we will provide some key data about the pharmaceutical industry.

The world market by pharmaceutical sales amounted to approximately 643 billion US$ in 2006 and this market is expected to grow with an average rate of 6–7% per year. The United States has approximately 48% of the world market, Europe approximately 30% and Japan 9%. By 2020 the pharmaceutical market is anticipated to more than double to

[1] DiMasi and his group of the Tufts Center for the Study of Drug Development have provided figures for out of pocket costs per new drug as high as US$400 million. If the costs of compounds abandoned during testing were also taken into account the figure increases to 800 million US$ (see DiMasi et al., 2003). However, this figure does not stand unchallenged, see e.g. Goozner (2004).

$1.3 trillion, with the E7 countries – Brazil, China, India, Indonesia, Mexico, Russia and Turkey – accounting around one fifth of global pharmaceutical sales.

There are currently 6 drugs that sell 5 billion US$ or more per year, the list being headed by Lipitor® with sales of 13.6 billion US$ per year (see Table 1). From Table 2 it is clear that the best selling therapeutic areas are: cardiovascular (lipid lowering, anemia and hypertension), CNS (psychosis, epilepsy and depression), gastro-enterology (ulcers and gastro esophageal reflux), cancer and asthma. Note that two of the drugs listed in Table 1 are biologicals, and also one of the best selling areas is taken in by a group of biological drugs, the erythropoietin products. Note also the absence of drugs for diseases that are prevalent in the developing world e.g. HIV, malaria and tuberculosis.

The costs for developing a new drug have recently been estimated to be approximately 800 million US$ (but see footnote 1). Since the 1960s these costs have increased tremendously as a result of increased regulatory requirements, increased complexity of the drug development process and greater competition in the marketplace. It should be realized that the costs of the development of a successful drug would be much lower than the figures cited above, if there were fewer failures either in the preclinical phase or during clinical development. In other words, the low probability of success (or the high attrition rate) is one of the major factors that determine the costs of new drug development.

Pharmaceutical companies spent on average 15% of their sales on Research & Development (R&D). For biotech companies this figure is (sometimes much) higher. It should be realized that many biotech companies do not have sales yet and are financed by the income from joint ventures with major pharmaceutical companies, or by venture capital.

It is estimated that the number of NCEs and NBEs in active development was approximately 6100 at the end of 2005. Only a fraction of these will obtain marketing authorization. This is illustrated by the fact that during 2001–2005 on average only 30 new drugs were launched worldwide.

IV.b. Regulatory Authorities

Governments are also key players in the development of new drugs. They regulate and provide guidance for the development and approval of new drugs for marketing. In some countries they also play a role in pricing and reimbursement. After the launch of a new product they closely follow its safety, quality and various other aspects such as inappropriate use, promotion, etc.

In the USA the FDA is the governmental office that oversees drugs in development as well as on the market. The FDA has two offices for drug development and approval. Originally the Center for Drug Evaluation and Research (CDER) occupied itself with NCE type drugs, whereas the Center for Biologicals Evaluation and Research (CBER), dealt with biologics. In recent years some categories of biologicals (e.g. monoclonal antibodies and therapeutic proteins) were transferred from CBER to CDER.

Table 1. Leading products by global pharmaceutical sales, 2006

	Leading brands	2006 sales (billion US$)	% Global sales	% Growth year-over-year (constant $)
1.	Lipitor (atorvastatin)	13.6	2.2	4.2
2.	Nexium (esomeprazole)	6.7	1.1	16.9
3.	Seretide/Advair (fluticasone + salmeterol)	6.3	1.0	10.3
4.	Plavix (clopidogrel)	5.8	1.0	−3.4
5.	Norvasc (amlodipine)	5.0	0.8	−0.5
6.	Aranesp (darbepoetin alfa)	5.0	0.8	35.6
7.	Zyprexa (olanzapine)	4.7	0.8	−0.4
8.	Risperdal (risperidone)	4.6	0.8	12.3
9.	Enbrel (etanercept)	4.5	0.7	18.4
10.	Effexor (venlafaxine)	4.0	0.7	2.7
	Total leading brands	60.0	9.9	8.0

Source: IMS MIDAS®, MAT Dec 2006.

Table 2. Leading therapy classes by global pharmaceutical sales, 2006

	Audited world therapy class	2006 sales (billion US$)	% Global sales	% Growth year-over-year (constant $)
1.	Lipid regulators	35.2	5.8	7.5
2.	Oncologics	34.6	5.7	20.5
3.	Respiratory agents	24.6	4.0	10.4
4.	Acid pump inhibitors	24.1	4.0	3.9
5.	Antidiabetics	21.2	3.5	13.1
6.	Antidepressants	20.6	3.4	3.3
7.	Antipsychotics	18.2	3.0	10.9
8.	Angiotensin-II antagonists	16.5	2.7	15.2
9.	Erythropoietin products	13.9	2.3	11.8
10.	Anti-epileptics	13.1	2.1	10.8
	Total leading therapy classes	184.3	32.9	10.7

Source: IMS MIDAS®, MAT Dec 2006.

The former division now deals mainly with vaccines, gene therapy and blood products.

The application for marketing authorization for NCEs is called a New Drug Application (NDA) and for biologics a Biologics License Application (BLA). Guidances for the development of biologics are in part different from those of traditional drugs, especially with respect to the biotechnological production process and the non-clinical safety testing.

Is has long been the policy of the FDA to work as much as possible as a partner of the pharmaceutical industry from the submission of the IND (Investigational New Drug documentation) before the start of clinical studies until the approval of the NDA before marketing of the compound.

In Europe, at least as far as the European Union is concerned, the old system of national regulatory bodies has gradually been replaced by a centralized system in which the requirements are unified and in which the different countries work closely together. The EMEA is the organization for granting marketing authorization for new drugs in the EU. Marketing authorization can be obtained using either the centralized procedure (approval at once for the entire EU) or the mutual recognition procedure (application in one member state and, after approval, requesting authorization in other member states). Technical and scientific support for ICH activities is provided by the Committee for Proprietary Medicinal Products (CPMC) of the EMEA. With few exceptions, the European agencies have been much more restrained and less approachable than the FDA. However, in recent years there is a clear tendency to more openness and partnership with pharmaceutical companies.

The Pharmaceuticals and Cosmetics Division (Koseisho) of the Pharmaceutical Affairs Bureau of the Ministry of Health and Welfare (MHW) is the regulatory body in Japan. Also in Japan there have been clear changes in the drug approval system, mainly inspired by ICH. One of the most important recent changes is that, under certain conditions, it is now possible to use also foreign data for the approval of new drugs in Japan.

Despite the efforts of the ICH, the regulatory requirements in the different regions are still quite different. For instance, only the USA has the possibility for accelerated approval of drugs to treat life threatening or severely debilitating illnesses (so-called Subpart E drugs).

IV.c. Academia and the Medical Profession

Although drug development is primarily an activity of the pharmaceutical industry, it could not be successful without the collaboration with and input from academia and the medical profession. Much of the basic research that is applied during drug discovery originates from academia and the vast majority of research based pharmaceutical companies have alliances with academic departments e.g. on the mechanism of disease or on new targets for drug discovery. In the development stage there are also numerous collaborations, varying from research

projects to participating in or consulting on development activities. As a result, many academic departments, scientists and clinicians receive sometimes considerable financial support from the pharmaceutical industry. It is obvious that this constitutes a potential conflict of interest and in the worst case may lead to misconduct. To prevent excesses the FDA has recently issued guidelines stating that the financial interest of investigators for drug company studies should be disclosed and the same is now requested by editorial boards of leading scientific journals.

V. DRUG DISCOVERY

Over the past two decades there have been several major changes in the drug discovery process in the pharmaceutical industry. As a result of the molecular revolution in biology and medicine, and the introduction of a wide range of new technologies, the drug discovery process has become much more sophisticated. Based on a rapidly expanding understanding of the pathophysiology of diseases and on molecular biology technologies, new targets (receptors, enzymes, ion-channels, genes) are identified and assay systems are developed to test large numbers of molecules from existing libraries rapidly using robotic systems. This so-called high throughput screening (HTS) or ultra-high throughput screening (UHTS) will identify hits, i.e. molecules with affinity for the target. The medicinal chemist will then try to optimize the hit molecule, aiming at maximal potency and/or selectivity, and when successful this will result in one or more lead compounds for testing in *in vivo* systems. NMR, mass spectroscopy and computer assisted structure-activity relation (SAR) techniques are used in the process of lead optimization. Recent developments in drug discovery are the availability of advanced information technologies (pharmacoinformatics) and the increasing role of genetics in the identification of new drug targets (pharmacogenomics). Potentially this will lead to more specific and more effective medicines.

Drug discovery has become much more integrated with the other main functions of a pharmaceutical company, i.e. drug development and marketing. Discovery is no longer done in an ivory tower with unlimited freedom for the scientist to select topics for research. Nowadays, in most big pharmaceutical companies, the areas of research are chosen in close collaboration with marketing and development, usually as part of a comprehensive therapeutic area strategy. Obviously, the risk of this is the possible loss of creativity and serendipity. Finally, to reduce later stage failures, development aspects such as physico-chemical properties, metabolic stability, pharmacokinetics and intrinsic toxicity are considered in a much earlier phase of development than in the past.

Nowadays, drug discovery is no longer the monopoly of the large chemical–pharmaceutical companies. Since the emergence of a large number of smaller biotech companies in the 1980s attracting high-class scientists with entrepreneurial spirit from academia, these companies have contributed tremendously to the drug discovery effort, alone or in collaborative projects with so-called ‘big pharma’, the traditional pharmaceutical companies.

The discovery process of biologics is different from that of classical drugs (small molecules). Biologics are not picked up from large molecule libraries using smart selection procedures, but they are often based on physiologically functional molecules present in humans. Examples are naturally occurring proteins and peptides, monoclonal antibodies (which are a subclass of proteins), or genetic material (e.g. DNA). They can also be alien proteins or peptides interfering with such human proteins, peptides or genetic material.

Biologics are very difficult or even impossible to manufacture using classical chemical techniques, hence they are generally made using biotechnological methods. Immortalized cells are a commonly used production platform for their production. The origin of these cells can be yeast, bacteria, insects, plants and algae, or mammalian. More recently also immortalized human cells (PER.C6®) have been introduced for the production of biologics. These human cells have the advantage of not introducing non-human proteins as a impurity in the final drug product, which can cause undesired immunogenic side effects. In order to make these cells produce the desired molecule they are genetically modified (genetically modified organism, GMO). Cell-based technologies also take over classical methods of vaccine production using animals or chicken eggs (influenza). This offers great advantages in terms of production speed, flexibility, scale, and purity.

VI. DRUG DEVELOPMENT

VI.a. The Label-Driven Development Plan

Drug development starts with a development plan in which the targeted profile of the compound is de-

fined. This target profile basically follows the format of the desired package insert with the indication, patient population, usage, safety, and dosage and administration as the main items. A clear advantage of a 'label driven' plan is that it determines what information needs to be collected, hence it will help to keep development focused. However, it requires thinking from the right (the desired end product) to the left (the activities during the development process), something that is unusual for many scientists. The plan will contain a schedule (GANTT-chart) showing the activities in the various clinical and non-clinical functions over the time of the project and their interdependency. To identify the time-critical activities, which determine the overall duration of the project, it is important to perform a "critical path analysis". Often this will reveal that activities other than clinical studies, e.g. production of the test material or toxicology studies, are on the critical path.

VI.b. Milestones in Drug Development

The duration of the development process, together with the progressive investments required, make it mandatory to have milestones along the way (see Table 3). At these milestones key data are reviewed and a decision taken to continue if the target profile can still be met, or to stop if this is not the case (go/no go decision). In practice the third option i.e. to adapt the plan to the findings is not unpopular. Although this is seen by skeptics as moving the goalposts, it sometimes will save a valuable project. The obvious risk is to drag on and spend a great deal of money on a dubious project. Obviously, the quality of the decision making is one of the key factors determining the success of a company. It is also the area that still has a great need for improvement, as some recent predictable failures (Posicor, troglitazone) illustrate. It goes without saying that economical considerations play an important role in the decision making, in fact they are the overriding argument, especially as development proceeds. It may interest the reader to learn that in many companies milestone decisions are taken by boards chaired by officials without a scientific or medical background.

There are several 'natural' milestones during drug development, and although there are differences between companies, both in the number and in the names of the milestones, these differences are quite small. The first milestone is the selection of a compound in the drug discovery phase for development. In the past this decision was exclusively based on the pharmacology (potency, selectivity) of the compound. Since there is now greater awareness that compounds with attractive pharmacological properties may fail later because of poor solubility or extensive metabolism, the physical chemistry, preliminary PK and metabolism characteristics of the

Table 3. Phases of clinical drug development

Phase of development	Main objectives	Study population
Phase 1	Tolerability Safety Pharmacokinetics Pharmacodynamics	Usually male healthy volunteers For inherently toxic compounds patients (e.g. anti-tumor agents)
Phase 2	Proof of concept Dose and dose regimen for phase 3 Safety Pharmacokinetics	Patients with the targeted disease, usually excluding those with complications or concomitant conditions
Phase 3a	Confirmation of efficacy and safety (benefit/risk) Comparison with standard therapy and/or placebo Long-term safety	Patients with the targeted disease, including (as much as possible) those with complications and/or concomitant conditions
Phase 3b	Further profiling of the compound	Patients; seldomly healthy volunteers
Phase 4	Investigator driven studies Local marketing support studies	Patients; seldomly healthy volunteers

compound are now also taken into account. Development starts with preclinical safety studies and pharmaceutical work to prepare a formulation for the early clinical studies. This early, non-clinical development is called phase 0.

At the end of phase 0 the second milestone is the decision to start clinical studies, the entry into man decision. The major decision criteria are the in vivo pharmacology of the compound and its safety based on the toxicology, mutagenicicity and safety pharmacology studies.

The third milestone is usually during or at the end of phase 2 when a decision has to be made to embark on expensive and resource intensive phase 2b and or pivotal phase 3 trials. Obviously not only a comprehensive medical/scientific analysis including a judgment on the expected profile of the compound, but also a full financial analysis is part of this milestone.

Before the end of phase 3, a decision is taken whether or not to file the compound, what the content and message of the dossier and what the regulatory strategy will be. Also the final decisions will be made on the production for marketing and on the anticipated pre-marketing requirements. This is the pre-filing decision point.

The final decision is whether to launch the product after regulatory approval or not. Although this seems irrational at first sight, not all products that are approved are also launched. In practice this decision is dependent on the agreed labelling and, in some countries, on the outcome of the price and reimbursement negotiations.

VI.c. Pre-Clinical Development

VI.c.1. Toxicity and Safety Studies

After one or more lead compounds have been selected for further development, more preclinical investigations are needed before it is possible to start studies in humans. The main studies during this phase are toxicity studies in animals. It is important to note that the goal of these studies is not so much to find safe compounds and reject unsafe ones, but rather to learn under which conditions a potentially beneficial compound can be harmful, and to find out how it can be used safely in humans, if at all. Details on the type, duration and extent of toxicity studies needed can be found in various regulatory guidelines issued by ICH, FDA and EMEA and are easily accessible via the internet sites of these bodies. Although there are still differences in the requirements between countries or regions, ICH has achieved major progress in their global harmonization.

Toxicity studies are performed in healthy animals. For NCEs two species are to be used, one rodent (most often rats or mice) and one non-rodent (dog, rabbit, monkey or others). Biologics should be tested in a species in which they are pharmacologically active, usually a monkey. The route of administration is the same as that of the intended use in clinical studies.

The first question to be answered by the toxicity studies is what are the adverse effects of the compound in the species tested, and what is (are) the target organ(s). During the studies the animals will be observed for changes in behaviour, appearance, food intake and body weight. Blood and urine tests will be done regularly as well as special examinations if indicated. At the end of the study the animals will be sacrificed and a full necropsy performed, including microscopy of the various tissues and organs. The next important questions to answer is whether the observed toxic findings are reversible, and whether the occurrence of toxicity will be easy to detect in clinical studies. Obviously the answers to these questions may well determine the fate of the compound, depending on the clinical indication and the expected risk/benefit ratio.

As a principle, the maximal doses used in toxicity studies should be (much) higher than the doses subsequently used in humans. The doses for the definitive toxicology studies, which have to be performed according to Good Laboratory Practice (GLP), are selected after a so-called dose range finding study. At the end of the GLP studies the following should be known about doses: (1) the no-adverse effect dose which is the highest dose that does not produce an adverse effect; (2) the threshold dose which is the lowest dose that produces an adverse effect; (3) the maximal permissible dose; and (4) the therapeutic index (if possible) which is the ratio between the median toxic dose (TD50) and the median effective dose (ED50), and which gives an indication of the safety margin.

In the past the results of toxicology studies were interpreted and extrapolated to the human situation on the basis of the dose/kg or dose/m^2. However, it has long been recognized that measuring the plasma concentration of the compound and its metabolites often provides a better indication of exposure, and therefore this has become mandatory. The area under the plasma concentration–time curve (AUC) and

the peak plasma concentration (C_{max}) are the most frequently used parameters, and for a more reliable extrapolation to the clinical situation, the dose levels discussed in the previous paragraph should be related to these parameters.

The study of absorption, distribution, metabolism and excretion in toxicology studies, usually referred to as toxicokinetics, provides extremely useful information on the pharmacokinetics of high doses and of repeated doses of the compound. The dose dependency of the pharmacokinetics and the possible time effects, e.g. a decrease in exposure over time as a result of enzyme induction, is essential information for the interpretation of the toxicity findings as well as for the planned clinical studies.

With few exceptions, drugs will be developed for use in males and females and both genders will have to be included in the clinical studies. Although there is pressure for women to participate in the first clinical trials, especially in the USA, this is not practised widely, mainly because the studies required to show that it is safe have not yet been performed at the start of phase 1, and waiting for them would delay the project. The standard NDA package of reproductive toxicology studies includes a fertility and early embryonic development study in rats in which the male and female animals are dosed prior to mating, a teratogenicity study (so-called segment II study) in female rats and rabbits and a pre- and post-natal development study in female rats.

Another aspect of toxicity are the genotoxicity studies used to investigate the possible harmful effects on genetic material (DNA). Routinely three tests are used: (1) a test for gene mutation in bacteria (Ames-test), (2) an *in vitro* test for chromosomal damage in mammalian cells or an *in vitro* mouse lymphoma TK assay and (3) an *in vivo* test for chromosomal damage using rodent hematopoietic cells. (ICH guideline S2B). In exceptional cases additional investigations may be necessary (e.g. antibacterial compounds, compounds with a 'suspicious' chemical structure), whereas in the case of biotech products there is usually no need to test for genotoxicity.

Finally the effect of the compound on several body functions is investigated in so-called safety pharmacology studies. The most relevant are the possible effects on the respiratory system, the cardiovascular system and on the central nervous system. Usually these studies are done in rodents, dogs or primates. Lately there has been increased interest in the effect of new drugs on ECG parameters, especially on prolongation of the cardiac QT interval, since this has been associated with the risk for sometimes lethal arrhythmias. *In vitro* and *in vivo* investigations of cardiac conduction are now required for each NCE that enters the clinic.

VI.c.2. Other Preclinical Studies

In addition to toxicity and safety data, the preclinical package to start clinical studies also contains information on the pharmacology, the pharmacokinetics and metabolism and the galenical aspects of the compound. As a rule there is evidence of pharmacological activity and, if possible, of therapeutic activity in one or more animal models of disease. Ideally there is also information on the *in vivo* concentration effect relationship.

Pharmacokinetic (PK) studies in different animal species and additional *in vitro* studies provide information on the compound's predicted human PK parameters, including dose- and time-dependencies, its protein binding, the effect of food on its PK, and the cytochrome P450 isoenzymes responsible for its metabolism as well as the structure and activity of the main metabolites. Also a sensitive assay to quantify the compound and its metabolites in human blood and urine should have been developed and validated.

The galenical information describes the formulation (purity, stability, etc.) of the compound and the analytical method. For intravenous formulations the compatibility with infusion solutions and infusion set material should also be known.

VI.c.3. Toxicity Testing and Biologics

As indicated before, the toxicity testing requirements for biologics differ importantly from NCEs (see ICH S6 guideline). Toxicity with biologics is generally due to immunogenicity (immunotoxicity), or to exaggerated pharmacology. The doses used in toxicity studies do not need to be exaggerated as much as for NCEs, as the objective is not to identify a NOAEL. Pharmacokinetics are often of lesser importance as is the concept of exposure.

Basically safety testing should be scientifically sound, using only 'relevant' animals species (i.e. species in which the biologic to be tested is expected to exert similar effects as in humans). However, such is often difficult to establish. This is exemplified by a recent tragedy that shocked the biotech community. The company Tegenero tested a monoclonal

antibody (TGN1412) in healthy male subjects. The subjects who received active treatment experienced near-fatal side effects. Analyzing what went wrong revealed that (amongst others) the animal species in which the drug was tested for toxicity prior to human administration, turned out to be not relevant. The molecular target of TGN1412 did not have enough molecular similarity in the animal species selected to predict the toxicity later seen in humans, which was due to exaggerated pharmacology.

The authorities in Europe tend to apply different requirements for toxicity testing particularly for biologics, than do the FDA, despite ICH (!). In order to design the appropriate toxicity testing strategy enabling a given clinical development plan one should therefore consult the appropriate regulatory bodies to check its adequacy and regulatory acceptability.

VI.d. Clinical Development

Clinical drug studies can be divided into development studies carried out in the phases 1, 2 and 3a, company driven profiling studies in phase 3b, and company or investigator driven marketing support studies in phase 4 (see Table 3). Here only the development studies will be discussed, i.e. the studies that provide the clinical data of the NDA/BLA. Although the terminology suggests that the different phases of drug development are carried out sequentially, this is not true for phase 1 studies since this term is not only used for the first phase of drug development but also for non-therapeutic (clinical pharmacology) studies performed during later phases of drug development.

Sometimes the terms early and late clinical development are used instead of the phases 1, 2 and 3. Early development refers to all studies before the full development decision point, whereas late clinical development refers to all studies thereafter.

Three key disciplines are involved in the clinical development of new drugs, these are clinical pharmacology, clinical development and biometrics. Although each of the three disciplines has its own expertise and responsibilities, it cannot be stressed enough that drug development can only be carried out successfully if there is a close and harmonious collaboration among the groups, based on mutual understanding and acceptance.

Clinical pharmacology carries out all phase 1 studies and in some companies also proof of principle studies. Usually clinical pharmacokinetics (including PK/PD modeling, simulation and population pharmacokinetics) also belongs to the domain of clinical pharmacology. Clinical development is responsible for late development. In practice this requires the totally different skills of medical expertise, clinical science and organization and running of large clinical trials. In some companies this has resulted in the creation of separate groups, i.e. a science group and an operations group. The third player in clinical drug development is biometrics, which comprises biostatistics and data management. It is hard to underestimate the importance of this discipline for drug development, and in many companies this is one of the biggest departments within clinical development. Biostatistics contributes both to the overall development plan as well as to the design and analysis of individual studies, and data management contributes to the efficient collection and storage of the huge amount of data collected during a development program.

VI.d.1. Phase 1

As a rule, the main studies in phase 1 are a single rising dose (SRD) and a multiple rising dose (MRD) study in healthy volunteers. For compounds given by continuous intravenous infusion, one single study in which different rates of the compound are infused to steady state, is usually sufficient. The objective of both the SRD and MRD study is to investigate the tolerability, safety, pharmacokinetics and when possible pharmacodynamics of the compound. The number of subjects used in these studies is based on empiricism rather than on statistical considerations. At the end of phase 1 the optimal dose range and dose regimen for the following first efficacy trials in patients should be clear.

Various designs are used for the SRD study. We will discuss the two study designs that are most frequently used.

(1) Sequential groups of volunteers receive in a double blind way either active compound or placebo, usually in a ratio of 6–2 or 6–3. The advantage of this design is that volunteers will receive only one dose and that adverse event reporting is not affected by experiences during previous sessions. On the other hand more volunteers are needed, which may create a problem of recruitment.

(2) Cross-over studies in which one or more panels of 4–6 volunteers receive several doses of active compound, with double blind placebo randomly interposed. The advantage of this design is that before giving a higher dose, the reaction

to lower doses in the same subject is known, reducing the risk of exaggerated responses. It also enables collection of dose–response information within one subject. Potential downsides are the risk of carry-over between doses and of subjects dropping out before the study is complete.

For the SRD study in humans a starting dose has to be selected, together with the dosing intervals. When there is a maximal permissible dose, the highest dose is also determined before the start of the study. The starting dose is selected on the basis of the toxicological findings, the exposure in terms of dose, AUC and C_{max}, and the predicted human pharmacokinetics. The dose steps are usually a doubling or tripling of the dose, depending on the expected type of toxicity and the likelihood of non-linear pharmacokinetics. As a rule the next dose is not given before the tolerability, safety and pharmacokinetics of the previous dose have been carefully reviewed. The doses in a first in man study should be flexible and it should be possible to add, delete or repeat doses if circumstances so demand. To enhance flexibility in cases of oral compounds, many companies prefer to use a drinking solution for their early phase 1 studies rather than a solid formulation (capsule, tablet).

In the MRD study, the compound is administered for several days, usually until steady state has been reached plus a few days more. The doses are selected on the basis of the results of the SRD study.

The measurement of pharmacodynamics (PD) parameters in phase 1 studies can be very informative. First of all it may help to define the starting dose for subsequent studies in patients. It may also help to build a PK/PD model, which can be used as a framework for further development.

For oral compounds there is often an absolute bioavailability study and a preliminary assessment of the effect of food on the PK of the compound during phase 1. The information obtained so far will allow the choice of a proper dosing regimen for the first patient study in phase 2.

VI.d.2. Phase 2

Phase 2 is a critical phase in drug development. During this phase it should become clear whether the compound is 'worth' developing further or not. The main objectives for phase 2 are therefore to 'prove' efficacy and to determine the dose or dose range for phase 3 studies. In addition the safety of the compound should be carefully evaluated, but the limited numbers of patients studied often preclude definitive conclusions. Depending on the type of compound and the more or less aggressive development strategy of the company, phase 2 can be conducted in one step or two, i.e. phase 2a and phase 2b. Accordingly, the full development decision (see before) is at the end of phase 2, or between phase 2a and phase 2b.

For innovative compounds representing a new treatment, the large degree of uncertainty about efficacy and safety induces many companies to follow a cautious approach by performing a 'proof of concept' or 'proof of principle' study at the beginning of phase 2 (i.e. phase 2a), before embarking on the much larger and more expensive trials of phase 2b and 3. The objective of this study is to show convincingly that the compound has therapeutic efficacy in the selected disease. If it does, the project will proceed, whereas if it does not, the project will either be discontinued, or another target will be selected. The proof of principle study is usually carried out as a double blind 2- or 3-arm parallel study, with active treatment, placebo, and sometimes an active control arm. The active control arm is primarily used as an internal validation of the study and partly also to obtain preliminary comparative information. It should be realized, however, that since standard treatments do not show efficacy consistently, only in the case of a positive result with the active control and a negative result with the investigative compound can firm conclusions be drawn.

The selection of the dose of the active treatment arm may be critical for the success of the proof of principle study. Depending on the available information and the type of compound, one can use (1) the maximal tolerated dose (assuming a log-linear relation between dose or concentration and effect), (2) a dose that produces a certain pharmacodynamic effect (e.g. a predefined % of inhibition of platelet aggregation for a platelet inhibitor), or (3) a dose that produces a certain exposure, based on extrapolation of preclinical safety and/or efficacy data to the human situation. To prevent later disappointments, the proof of principle study should be fully powered, and the outcome should be statistically significant for a clinically meaningful improvement. Companies that try to save money here (recurrently ill advised by academic opinion leaders with an interest) by doing a limited, often single centre trial, may regret this later when promising results are not confirmed in the larger phase 2b or 3 trials.

A more aggressive phase 2 strategy is to do a study in which proof of principle is combined with

dose finding. In this case, several doses of the investigative drug (usually 3 or 4, covering a 10–20 fold dose range), placebo and sometimes a positive control are studied, often using a double blind parallel fixed-dose design. If the results of such a study are positive, the project can proceed to phase 3 immediately and precious time can be gained. In cases of (the me-too-like type of) compounds with known therapeutic benefit, there is no need for a proof of principle study and the project can proceed directly to dose finding in phase 2. It cannot be emphasized enough that, to be able to draw firm conclusions, which may mean embarking on huge investments or discontinuation of the project, phase 2 studies have to be adequately powered.

In the foregoing, we referred several times to dose finding. Since this topic is very important for the safe and effective use of (new) drugs, it deserves a special discussion. It has been realized for quite some time that, despite extensive development programmes, easily encompassing more than 50 clinical studies, drugs were launched on the market with recommended doses that later proved to be totally wrong. Usually but not exclusively doses were much too high, classical examples being the thiazide diuretics and captopril. The explanation for this remarkable observation is that in the past dose finding was not always done, and when it was done, it was frequently done in the wrong way (e.g. using dose titration rather than parallel designs). Moreover, marketing departments pushed hard for "one dose fits all" compounds since this feature helped them in the promotion.

Nowadays, much more attention is paid to proper dose finding and an ICH expert working group has issued a guideline for the industry entitled "Dose–response information to support drug registration" (this and other guidelines can be found and retrieved from the websites mentioned at the end of this chapter). The main messages from this guideline are that

- dose–response data for beneficial and adverse effects are desirable for almost all NCEs entering the market (for drugs to treat life-threatening disease the requirements are less);
- the data should be derived from properly designed trials as well as from a meta-analysis of the entire database;
- the data should be used to identify a starting dose, titration steps and a maximal dose, as well as adjustments of these for demographic variability and clinical circumstances (concomitant disease, concomitant therapy);
- the endpoints may vary at different stages of development (e.g. pharmacodynamic in early development and clinical in late development);
- the randomized parallel dose–response study with several doses of active treatment and placebo is the most robust design for obtaining population average dose–response data;
- regulatory agencies and drug companies should be open to new approaches in search of dose-response data (e.g. Bayesian and population methods, modelling and PK/PD techniques).

VI.d.3. Phase 3

As mentioned earlier, phase 3a is the last part of drug development ending with the submission of the NDA and Phase 3b will not be discussed here. The main purpose of phase 3a is to confirm the findings of phase 2 and to provide convincing evidence for a favourable benefit/risk ratio. If needed, additional studies will be carried out to fulfill the regulatory requirements (e.g. long-term safety), to support specific claims in the label (e.g. studies in sub-populations or studies on drug–drug interactions or combination therapy), or to profile the compound in its class (comparative trials).

In most cases phase 3a is the largest, longest and most expensive part of a development project. Depending on the drug, the indication, and the endpoint for efficacy, phase 3a studies can range in size from a few hundred to several thousand patients, whereas the duration of the studies can vary from single dose to up to 4 years of treatment. Phase 3a studies are carried out as national (especially in the US and Japan), multinational (especially in Europe), or intercontinental studies (US, Europe, Australia). As a rule they are multicenter trials under the supervision of one or more steering committees with representatives from academia and from the sponsor. Often there is a special committee (data monitoring board, DMB) that has continuous access to all safety data and randomization codes, and this committee has the authority to stop the study, or parts of it, if there is evidence of harm to patients.

The logistics of large phase 3a trials are extremely complicated and require considerable manpower in the headquarters and in the field. Full compliance to Good Clinical Practice (GCP) as well as scientific integrity are prerequisites for the acceptability of these trials to the regulatory authorities, and the 'pivotal' trials undergo detailed inspection to safeguard these

aspects. Since many companies do not have the expertise or the resources needed to run these trials in house, they often rely on CROs, of which there are many specialized in late clinical development.

VI.e. Efficacy Endpoints in Clinical Trials

An area that merits special attention is the choice and acceptability of endpoints in phase 2 and 3 clinical trials. As a rule the approval of new drugs is dependent on the evidence that it causes improvement of one or more clinical endpoints, the definition of a clinical endpoint being how a patient feels, functions, or survives. Whereas this is relatively easy to show for some types of drugs (e.g. pain killers, antibiotics for acute infections), it is much more difficult for others, because it would require large studies running over several years. Especially during phase 2, before there is proof of concept, this would not be feasible. To overcome this hurdle there is currently great interest in the use of surrogate endpoints in drug development. Surrogate endpoints are defined as biological markers intended to substitute for a clinical endpoint. A classical example is the treatment of hypertension where the lowering of blood pressure is widely (although not universally) accepted as a surrogate for the clinical endpoint, i.e. the prevention of cardiovascular complications. More recent examples are the use of changes in viral load as surrogate endpoints in the treatment of HIV infections. Especially since the outcome of the trials with the class 1 anti-arrhythmics flecainide and encainide, in which a positive effect on the presumed surrogate endpoint (i.e. ventricular ectopic beats) was shown to be accompanied by increased mortality due to a pro-arrhythmic effect, it is evident that as a rule surrogate markers have to be validated before they can be accepted as endpoints of clinical studies.

VII. THE FUTURE OF DRUG DEVELOPMENT

As must be clear by now, drug development is a very dynamic activity with high interests at stake. For patients this is the availability of more effective or better tolerated treatments, for pharmaceutical companies it is the return on the huge investments that are needed to discover and develop new drugs. It is not difficult to predict that there will be continuous attempts to speed-up development times and to improve the quality and efficiency of the development and approval process. For instance, PK/PD driven development plans, modeling and simulation of clinical trials and application of pharmacogenomics in clinical trials are exiting new tools that are already practised in some enlightened environments. The same is true for innovative biostatistical methodology, electronic submissions and electronic review of NDAs/BLAs. These and other trends ensure that drug development will remain an intriguing and rewarding challenge for many scientists among which clinical pharmacologists take a prominent position.

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APPENDIX: SOME USEFUL WEBSITES

Regulations and Guidances

International Conference on Harmonization (ICH):
http://www.ich.org/

Food and Drug Administration (FDA):
http://www.fda.gov/

FDA Center for Drug Evaluation and Research:
http://www.fda.gov/cder/

FDA Center for Biologics Evaluation and Research:
http://www.fda.gov/cber/

European Medicines Evaluation Agency (EMEA):
http://www.emea.europa.eu/
European Union Pharmaceutical legislation:
http://ec.europa.eu/enterprise/pharmaceuticals/eudralex

Pharmaceutical Medicine

European Center for Pharmaceutical Medicine (ECPM):
http://www.ecpm.ch
Center for Drug Development Science (CDDS):
http://www.georgetown.edu/research/cdds/
Tufts Center for the study of Drug Development:
http://csdd.tufts.edu/

Pharmaceutical Industry Associations

European Pharmaceutical Industry Association (EFPIA):
http://www.efpia.org/
Pharmaceutical Research and Manufacturers of America (PhRMA):
http://www.phrma.org/
European Association for BioIndustries:
http://www.europabio.org/healthcare.htm

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Section I

General Principles

Part B: General Clinical Pharmacology

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Chapter 10

Clinical Pharmacokinetics

Anthony J. Smith, Sri Suryawati

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I. INTRODUCTION

Students often find pharmacokinetics difficult. Two of the reasons are that a very formal writing style together with many equations make the subject appear much more difficult than it is. In this chapter we have deliberately adopted an informal style and aimed to keep key concepts as simple as possible. We hope we have succeeded and that you will find the chapter helpful as you prepare to become good prescribers.

Why is, amoxycillin administered three times daily, cotrimoxazole twice and phenobarbitone only as a single daily doses? Why was a slow-release theophylline preparation developed and why may it be taken only once a day? Why do we often give analgesics as a single dose but antibiotics as a course of doses, which should be taken regularly for a period of days?

If you could design it, what would an 'ideal' drug do, and how would it behave? Perhaps this depends on what it is being used for. If it is to treat a chronic condition such as high systemic blood pressure then it should be easy to take, not require injection, and should reduce the blood pressure to the normal range and maintain it there without causing adverse effects. If it were hardly metabolized in, or lost from, the body in any way it might be possible to give a single dose and maintain the effect for a very long time – weeks or even months – good for the patient but not so good for the manufacturer who wants to sell lots of his drug! What about a drug for headache? It needs to be easy to take, to act quickly, but it does not need to stay around in the body for a long period once the headache is relieved, and indeed, this could be a disadvantage if the drug produces unwanted or adverse effects. So it needs characteristics different from those of a drug to treat hypertension which ideally requires a long duration of effect.

In the past before clinical pharmacokinetics (literally – "movement of drugs" – implying measurement of the rate of movement of drugs into, out of, and around the body compartments) had been established in the 1970s, dosage regimens were decided largely by trial and error, relying on measurement of the therapeutic effect to tell you when a response had occurred and the appearance of toxic effects to tell you when you had given too much. The ability to measure drug concentrations in body fluids meant a more precise way existed for deciding by what route and how frequently drugs needed to be given to get the best outcome for the patient.

In this chapter we will look at the factors that are responsible for differences in the rate of onset, the duration and size, and the rate of offset – or loss – of a drug's effect.

I.a. Maintaining the Constancy of the Internal Environment

Imagine a lizard waking in the morning and stretching out on a warm rock to absorb the heat and raise body temperature to the ideal for action. Later in the day, observe the snake, which like the lizard has warmed itself in the morning, has hunted successfully, and has now produced excess body heat from exercise and the digestion of food. To get rid of the

Drug Benefits and Risks: International Textbook of Clinical Pharmacology, revised 2nd edition
Edited by C.J. van Boxtel, B. Santoso and I.R. Edwards. IOS Press and Uppsala Monitoring Centre, 2008.

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heat it must find a cool spot and preferably one close to, or in, water.

Reptiles like the snake and the lizard cannot regulate their body temperature, and adopt the temperature of their environment (i.e., they are poikilothermic) – so they cannot survive extremes which put their body cells, and particularly their enzyme systems, at risk. By contrast, we can shiver or sweat to increase or reduce our core temperature, and so human beings can function effectively in a much wider range of temperature than can reptiles. What has this to do with drugs and other ingested chemicals? In just the same way as we mammals have evolved to be relatively independent of environmental temperature so we also have developed a system of screening and filtering out chemical substances that present themselves to us in our diet and from other sources.

We are exposed to plant products (many of the earlier drugs and most of the herbal pharmacopoeia in use today are crude plant extracts), some of which are potentially toxic, as, less commonly, are foods of animal origin. Medicinal drugs are just one of a set of chemicals which are exposed to the range of defence mechanisms put up by the body to protect it from the onslaught of 'foreign' chemicals.

I.b. Perils for Pills

I.b.1. In the Stomach

Think about a drug formulated as a tablet and swallowed. The first process which will affect it will be the dissolution (breaking down) of the tablet under the influence of gastric acidity (or in other cases the higher intestinal pH). This liberates the drug molecules and also exposes them to attack by gastric acid and enzymes. Some drugs are inactivated/chemically modified by gastric acid, and so are relatively ineffective when taken by mouth – a triumph for our defence mechanisms but a therapeutic setback.

> One of the best known examples of this is benzylpenicillin (penicillin G). This was one of the original members of the penicillin family and remains a very valuable antibiotic. If given by mouth it is rapidly destroyed by gastric juice at an acid pH of around 2. As a consequence, on average, only a third or less of an oral dose of benzylpenicillin is absorbed into the systemic circulation, and to achieve high and effective concentrations in plasma and tissues it must be given by a route which bypasses the stomach, normally by intramuscular or intravenous injection. A small modification of the chemical side chain of the penicillin G molecule converts it to penicillin V (phenoxymethyl-penicillin) which is resistant to the action of gastric acid and allows it to be given effectively by mouth.

After the tablet disintegrates in the stomach the drug molecules are dispersed in gastric juice with or without partially digested food, and normally only a small proportion will penetrate the gastric mucosa and enter the blood circulation – partly because the stomach presents only a small surface area for absorption. Drugs are absorbed across mucosal surfaces but there are factors which determine how much is absorbed and at what rate in any particular site. The first set of factors is to do with the drug molecule itself.

- *Size*. Most commonly-used drugs have molecular weights of less than 1000 daltons and their molecular dimensions are small compared with those of the complex lipids and, especially, the proteins of the cell wall. So their size provides little hindrance to crossing cell walls. Molecules as big as moderately-sized proteins (30,000 daltons and above) have much more difficulty in getting across and normally have to be administered directly into the blood stream (e.g., gene transfer, immunoglobulins).
- *Lipid solubility*. Because cell walls comprise mainly lipid, drugs which readily dissolve in lipid will have an advantage in crossing into the cell. Conversely, water-soluble compounds may have great difficulty in crossing the lipid barrier. Aqueous pores do exist within lipid cell membranes and a proportion of the water-soluble molecules may traverse this route.
- *Electrical charge (ionisation)*. Many drugs are weak acids (e.g., non-steroidal anti-inflammatory drugs) or bases (e.g., beta-receptor blocking drugs) and therefore exist in both uncharged and charged forms. The proportion of drug in the uncharged or charged form depends on the pH of the environment in which it finds itself. In most people's stomachs the pH is low (around 2 – i.e., the hydrogen ion concentration is high) and this favors ionization of weak bases but not of weak acids. The converse occurs in the duodenum and upper small intestine where pH is high after gastric acid has been neutralized by pancreatic bicarbonate.

The importance of this is that the uncharged drug molecules are usually the more lipid soluble species and can cross into cells whereas the ionized molecules are inhibited by their charge which acts like a covering of "barbed wire", getting "tangled up" with the charges on the mega-molecules, especially the proteins, of the cell membrane thereby limiting their passage.

Weakly acidic drugs will be less ionized in the stomach and therefore penetrate membranes more readily in this organ while weakly basic drugs will be less ionized and therefore more readily absorbed in the small intestine.

The second set of factors is to do with the environment in which the drug finds itself. It needs time to cross a membrane barrier. Less drug may be absorbed from the gut if the patient has diarrhea with intestinal hurry (often in this situation, oral drugs may not even disintegrate fully and release their contents for absorption – visible tablets may be seen in the faeces).

I.b.2. In the Small Intestine

Gastric emptying through the pylorus and into the duodenum is the next important event. This may occur rapidly or take up to one or two hours, depending largely on what is already in the stomach. So the effect of an oral drug may be delayed or hastened, by taking it with, or before, food.

Once in the duodenum, with its alkaline environment, the drug faces new perils. If it is a small protein or peptide it may be exposed to the action of digestive enzymes such as peptidases which can break it down into smaller fragments with consequent loss of its action.

An example of this is insulin, a naturally occurring hormone produced by the beta-cells of the pancreas. It is composed of two peptide chains linked by disulphide bonds. It is a big molecule with a molecular weight around 5,800 daltons. If taken by mouth, which would be a good alternative to injection for diabetics who are dependent on it, it may survive the assault of gastric acid, but in the small intestine it is seen as just another peptide and becomes a target for digestive enzymes. All sorts of attempts have been made to 'protect' insulin from enzyme attack, including wrapping it in fat molecules (to make 'liposomes') or giving it intra-nasally. So far there has been only modest success with these strategies and so the intestinal defence mechanisms have remained triumphant.

If the drug reaches the small intestine with its vast absorbing surface it stands a good chance of being absorbed, provided it can get across the mucosal surface of the intestinal transporting cells. As we saw above if the drug molecule is of small molecular weight and readily soluble in fat it should be able to cross the intestinal barrier with ease as do, for example, the steroid hormones and their synthetic analogues such as prednisolone. However, if it is water-soluble, and most particularly, if it exists in the lumen of the intestine as a charged molecule it may have great difficulty in getting across.

A good example here is the family of antibiotics called the aminoglycosides. It includes gentamicin, tobramycin, and neomycin. The first two of these are widely used to treat infections caused by gram-negative bacteria. All of these drug molecules share a fairly complex chemical structure, and are known as 'polycations', i.e., there are multiple sites in the molecule where dissociation can occur leaving a large, electrically charged residue. In addition, they are all water-soluble and so we would expect that they would have difficulty in crossing into the intestinal mucosal cell and achieving adequate concentrations in the plasma. So gentamicin and tobramycin must be given parenterally (literally 'alongside/apart from' the gut) to be effective – conventionally by the intravenous route.

Once again the defence mechanisms that keep foreign chemicals at bay have succeeded. However, this can be turned around and used to therapeutic advantage. For example, if an aminoglycoside antibiotic is very poorly absorbed from the gut, a large proportion of any oral dose will remain there and may be useful for treating gut infections.

A good example is neomycin, which is one of the least well absorbed of the aminoglycosides and has a place as an oral drug in the management of hepatic failure – probably because it acts locally and reduces the bacterial load of the large bowel.

Pyrantel pamoate, a commonly-used anti-helmintic, provides another clinical example of exploiting the poor absorption of a drug

in order to eradicate gut pathology. In this instance the drug eradicates intestinal parasites such as roundworm, hookworm, and pinworm.

One of the physiological mechanisms which can help poorly lipid-soluble molecules to cross the small intestinal mucosa is the process of active transport-molecules actively shuttled across the membrane, commonly 'riding' on transporter molecules and moving through the expenditure of cellular energy.

Levodopa in one sense is hardly a drug because it is an amino acid normally found in the body as a precursor of the biologically active catecholamines dopamine, noradrenaline, and adrenaline. However, when given in large oral doses enough of it gets into the brain to be converted into, and increase the concentration of, dopamine which, in turn, often has spectacular and beneficial effects in patients with the movement disorder, Parkinson's disease. Levodopa is an amino acid and it 'rides' the active transport system for amino acids found in the small bowel. In this way even though not very lipid-soluble, it achieves effective concentrations in the blood plasma. However, this ability to 'ride' an active transport mechanism also means that it may have to compete for a place with other amino acids in digested food. Giving levodopa with meals can reduce its absorption by as much as 30%.

The inner surface of the small intestine is not smooth and flat but wrinkled into a large number of finger-like projections called villi, which project into the lumen. If we look at each villus under the microscope (Fig. 1) we find it, in turn, has small finger-like processes projecting out into the lumen – the microvilli. The result of this is that the surface of the small intestine (which is only 300 cm in length – in the relaxed state after death it may measure 6–7 metres), is estimated to have an area of 250 m^2. It is obviously designed to absorb, particularly, nutrients and this is also where most of any drug taken by mouth is absorbed.

There is also a big safety margin in this absorptive process. Patients who have lost substantial amounts of their small intestine in surgical operations often still absorb adequate amounts of food substances and oral drugs. In fact it has been estimated that up to 50% of the small intestine has to be lost before there is a significant impact on food (or drug) uptake.

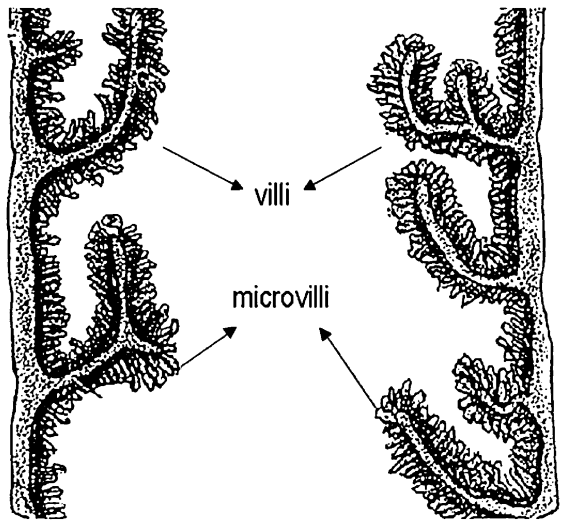


Fig. 1. Longitudinal section of the intestine, showing the villi and microvilli which increase the surface area of the small intestine.

Think now for a moment about what happens when a potentially toxic substance is taken accidentally or deliberately in overdose. The first possible event is that it causes the patient to vomit and so get rid of most of the substance. If that does not occur spontaneously, emptying the stomach using a stomach tube is a good first approach to treatment in many cases. The fact that gastric emptying usually does not occur in a matter of minutes gives a little time for the treatment team to recover some of the drug from the stomach. (By the same argument there is usually little point in passing a stomach tube if the overdose occurred, say, ten hours before, as the stomach contents usually will have emptied into the intestine and be beyond the reach of the tube.) If it is likely that some or much of the drug taken has already got beyond the pylorus and into the small intestine we might be tempted to think that large amounts have been absorbed and intervention is pointless. The counter-measure is totally logical. Activated charcoal in single or multiple oral doses of 50 g provides millions of particles of charcoal also with an immense surface area, which adsorb many drugs and so 'compete' with the small intestine limiting the amount of drug absorbed into the systemic circulation.

There is one more hazard in the small intestine, which may affect a drug. Although drug metabolizing enzymes are found in large amounts in, particularly, the liver, they are present in most other cells

in the body, including those of the small intestine. Some drugs e.g., oral nitrates used in the treatment of angina, are substantially metabolized in the gut wall which reduces the amount of active drug available at target sites in blood vessels.

To return to our medicinal drug and its progress past the body defences. Let us assume it has successfully crossed the small bowel wall and can then take one of two pathways. If it gets into the lymphatic system through the lacteals of the villi it can avoid going to the liver and find itself in the thoracic duct, and ultimately, in the venous circulation. It is extremely difficult to measure the extent of this process in man, but in animals it has been shown to account for only a small portion of drugs absorbed through the intestine. Most absorbed drug passes into the veins draining the intestine, the mesenteric system, which come together to form the hepatic portal system, and eventually the hepatic portal vein.

I.b.3. The Liver

And now the final hazard, and the only remaining obstacle for our drug before it reaches the systemic circulation and is distributed to its target site. The liver stands like a sentinel, and presents a formidable challenge to any chemical molecule seeking to gain access to the circulation. The liver has a very efficient mechanism for extracting nutrients and drugs from the portal venous blood. It removes, for example, amino-acids derived from the digestion of plant and animal proteins in the diet, and rebuilds them into our own human proteins. It also takes up many of the drugs we use in treatment and may do this in a variable way depending on the individual.

> For example, the earliest surviving beta-blocking, drug which is still in use, propranolol, may be extracted variably by the liver during this 'first-pass' through that organ. Some peoples' livers remove only 10% of the drug presented to them in the portal venous blood, others remove as high a proportion as 90%, and so may need much higher oral doses to achieve the same plasma concentration.
> We have heard patients sitting in the outpatient clinic comparing their doses, and concluding that the one taking the higher oral dose must have much more severe disease! It is difficult to explain that in all probability one has a high, and the other a low, hepatic extraction, and that the circulating concentrations of the drug will be very similar in both cases.

There appear to be two important factors that determine how the liver removes different drugs. Many are taken up by a chemical process that can be saturated relatively easily if the drug is presented at a high enough rate. In this case, the capacity of the liver to clear the drug from the portal venous blood is what determines the rate of clearance. If that capacity is exceeded no extra drug can be taken up, and it will pass through the liver and on into the systemic circulation unchanged.

In other cases the capacity of the liver to clear the drug may be so high that what determines the amount taken up is the amount of drug being presented to the liver in the portal blood. If flow is reduced, less drug is removed, and if flow is high much more is taken out. In this case capacity is not the determining factor but blood flow to the liver is. If we consider therapeutic drugs there are some whose hepatic clearance is determined by the intrinsic capacity of that organ, while others are more dependent on flow – or delivery – to the liver. Is this just a theoretical concept or does it have relevance to practical treatment?

> A patient with heart failure developed a serious abnormal heart rhythm, ventricular tachycardia, and it was decided to treat this with lignocaine (also known as lidocaine) by the intravenous route. He was given a loading dose designed to raise the plasma concentration to an effective 2 mg/l, and then given a constant-rate intravenous infusion aimed at maintaining that concentration. In about an hour he was observed to be tremulous and then had a brief generalized convulsion (a fit). The plasma lignocaine concentration was found to be 8 mg/l (desired therapeutic range 1 – no more than 5 mg/l).
> Lignocaine's clearance by the liver is flow dependent. In heart failure cardiac output may be very low and therefore hepatic blood flow through both the hepatic artery and the portal venous system is also low. This meant a lower extraction of the drug from the blood and accumulation of lignocaine until the high plasma concentration produced the central nervous system toxicity.

By now our drug molecule may have suffered many different fates. If the tablet did not dissolve in the stomach or intestine, it may still be bound with all the other molecules and the excipients, and will

ultimately appear in the faeces as an unchanged – if slightly tarnished – pill. If the tablet did dissolve, but for some reason the stomach has not emptied, the molecule may be simply sitting in a pool of gastric juice waiting for the pylorus to relax. If it passed the pylorus it may have been attacked by enzymes in the gut, been metabolized in the gut wall or have been competing unsuccessfully for a place on a transporter molecule. If it was absorbed it may have been taken up into liver cells and transformed into a metabolite (which might be pharmacologically active or inactive, or even on occasions may now have become toxic ...), and be on its way back to the gut in the bile or to the kidney for excretion (Fig. 2). So, for many drugs only a proportion of an oral dose may ultimately reach the circulation and be available to produce its effect.

We refer to this proportion as the oral bioavailability of the drug – normally expressed as a percentage of the oral dose taken. Bioavailability varies according to the physico-chemical properties of the drug molecule and the individual characteristics of the person who takes it. However it is possible to describe and measure the overall bioavailability of a given drug when measured under standard conditions in a group of people, and express the percentage bioavailable as an average figure for the group. That is how we get our "Tables of Oral Bioavailability" that are found in many textbooks of clinical pharmacology. Bioavailability will obviously vary according to the conditions under which it is measured but nevertheless is a useful concept, which has practical consequences as will be discussed in Section II.

As examples of the range of oral bioavailability a very lipid-soluble drug such as the anticonvulsant phenytoin, or the steroidal anti-inflammatory compound prednisolone, would normally have an oral bioavailability greater than 90%, whereas a very lipid-insoluble drug such as the antibiotic, neomycin, has an oral bioavailability of less than 1%.

I.b.4. In the Circulating Blood

Once through the liver on its first pass, the drug is carried in the blood plasma. Variable amounts of it penetrate the cellular components of the blood.

> The anti-malarial drug chloroquine can be present in red cells at up to 200 times the concentration it achieves in plasma, one of the factors making it an effective anti-malarial, as the circulating plasmodium parasites reside largely in the red cells.

For most drugs there is some binding to proteins in the plasma. Drugs which are acidic in type (e.g., the anti-convulsant phenytoin, the anti-coagulant warfarin, many of the non-steroidal anti-inflammatory drugs), bind to plasma albumin, while basic drugs (beta-receptor blocking drugs, local anaesthetics) bind to alpha-1 acid glycoproteins. Lipoproteins may also bind significant amounts of some drugs. The importance of this binding to big molecules is that the free concentration of a highly

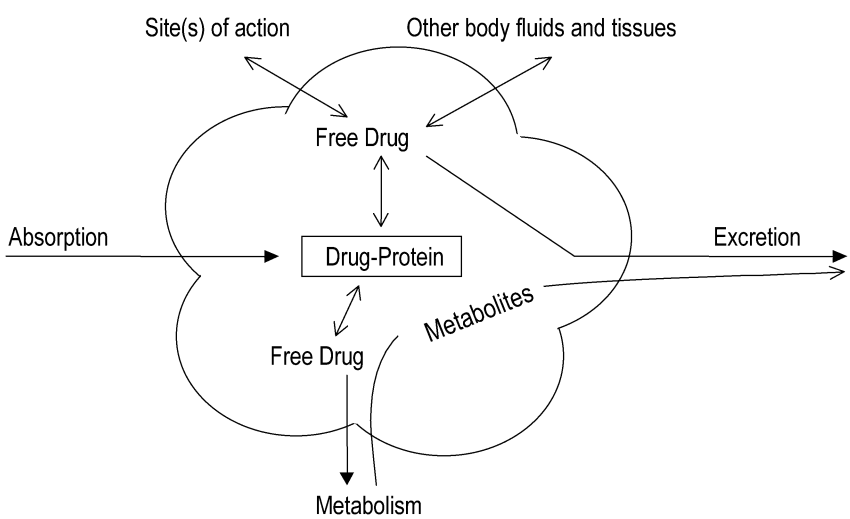


Fig. 2. Illustration of absorption, distribution and elimination processes of drugs in the blood circulation.

bound drug may be very small in comparison with the total amount in the plasma. Warfarin, for example, is normally 99% bound to plasma albumin, with just 1% travelling unbound. Yet it is the unbound, free fraction which is pharmacologically active at the drug–receptor site.

In severe malnutrition where circulating protein concentrations are very low, in uraemia and in pregnancy, the distribution of the drug (e.g., anticonvulsants) between bound and free forms may alter, and when monitoring treatment it may be necessary to get the laboratory to measure free concentrations of the drug. However this can only be done in specialised centres, even in developed countries, and is not usually available elsewhere.

Let us assume our drug molecule has reached its target organ – heart, brain, bronchus, etc. – has bound to its receptor to produce its pharmacological effect, has dissociated from the receptor (perhaps being displaced by the competing endogenous ligand (the name given to any molecule which has the capacity to bind to a receptor) – e.g. beta-blocking drug by noradrenaline/adrenaline), and is once more back in the plasma.

I.b.5. The Final Steps

What are the final steps in the journey? For most drugs there is a 'choice' of two routes. If the drug molecule is very water-soluble it may have had difficulty in getting into the body in the first place, and may have had to have its absorption facilitated in some way. But getting out through the kidney is a much easier process. Once through the glomerulus a water-soluble drug faces no major hazards. Dissolved in watery urine it is unlikely to diffuse back to any great extent through the lipid membranes of the cells lining the lumen of the nephron.

As we saw above, the antibiotic gentamicin has so much difficulty getting into the body by the oral route that it has to be given by injection. Part of this difficulty is due to its high water-solubility. On the other hand it passes through the normal kidney readily, and is effectively unmodified by the cells of the renal tubule – neither secreted nor re-absorbed. In fact, measuring the renal clearance of gentamicin is almost as good as a marker of glomerular function (glomerular filtration rate), as using more conventional markers such as inulin.

Many commonly used drugs, however, perhaps particularly those which act on our (very fatty) brains such as anti-psychotics, sedatives and hypnotics, are very lipid-soluble. Once they move away from their target site they are prone to cross back into cells again, and have no great likelihood of dissolving in water/urine. Indeed, if and when filtered by the glomerulus, they are most likely to diffuse back into cells of the nephron and recirculate! In one sense they are nearer in behavior to that mythical drug, which could be given once and never need to be repeated, mentioned at the beginning of this chapter.

Clearly they do not in fact keep going round and round, and we do have to give repeat doses to maintain the effect. So how are they cleared? Again these molecules 'ride' chemical mechanisms which normally handle lipid-soluble molecules taken into, or produced, in our bodies. These systems were not designed to await the arrival of the pharmaceutical industry and its products in the early 20th century, but are fundamental protective pathways which, like the other mechanisms we have looked at, maintain our chemical homeostasis and protect our internal environment from chemical harm. The greatest concentration of these enzymatic systems is found in the liver, the chemical sentinel, but the metabolic processes they catalyze can also occur in many other organs such as kidney, lung and placenta.

Put very simply two sorts of drug-metabolizing enzymatic processes occur in the microsomes of the smooth endoplasmic reticulum or in the cytosol of liver cells. The first, so-called 'Phase I', reactions may add or subtract a small portion of the drug molecule, commonly by oxidation. This by itself may make a product more water-soluble, but, more commonly, a second step – 'Phase II'– process is required in which the altered drug is coupled (conjugated – literally 'married') to compounds already existing in the liver cells to form salts such as glucuronides and sulphates (Fig. 3).

These conjugated products, being water-soluble, are much more easily lost to the body through the bile and faeces, or through the kidneys. Contrast water-soluble gentamicin and penicillin, which are excreted virtually unchanged by the kidney, with the lipid-soluble chlorpromazine, one of the first effective anti-psychotic drugs used in the management of schizophrenia, which has at least ten major metabolic products – several of them glucuronide conjugates of oxidized forms of the parent molecule.

This story of a pill's 'progress' is summarized in Fig. 4. But medicinal drugs are not always given by

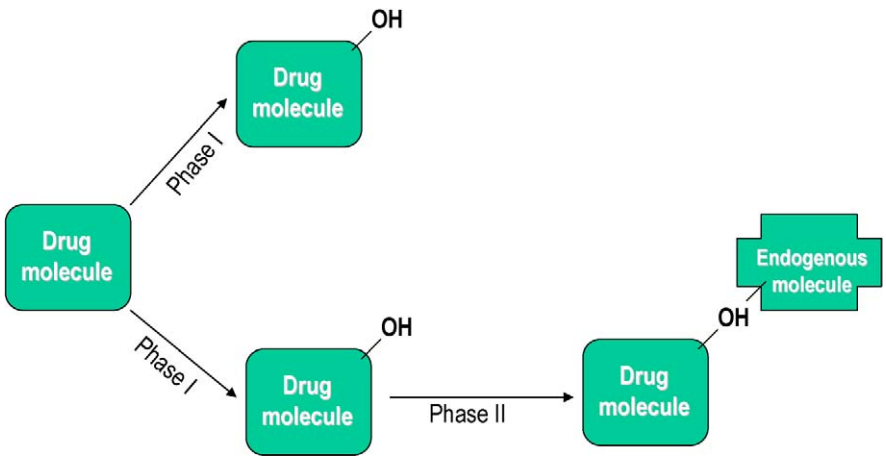


Fig. 3. Phase I adds a small reactive portion to the drug molecule, and Phase II conjugates the Phase I metabolite to an endogenous molecule already existing in the liver cell.

mouth. Think for yourself what differences would need to be made to Fig. 4 if the drug were given:

- Locally, e.g., as an eyedrop
- As a subcutaneous or intramuscular injection
- As a transdermal patch (from which the drug is absorbed through the skin)
- Sublingually (in a preparation designed to be absorbed through the mucous membrane of the mouth)
- As an intravenous injection
- By the rectal or vaginal route in a suppository
- By inhalation e.g., salbutamol in asthma.

How do the chemical defences of the body respond to these different routes of drug administration? Does any of the routes bypass any or all of the chemical defences we have considered above? How would the drug travel? What advantages or disadvantages might each route have? (We will return to some of these ideas later in this chapter.)

This section has given you a brief overview of some of the normal bodily functions that affect how well, or how poorly, an oral drug gets to its site of action, and how it is subsequently cleared. We will look at many of these concepts in more detail later.

Pharmacokinetics is simply the study of the rates of these processes, and provides the basis for deciding how much we need to prescribe, how often, and by what route, to get the best effect out of our drugs. It takes account also of how age, race, disease and other inter-acting factors may modify dosing decisions.

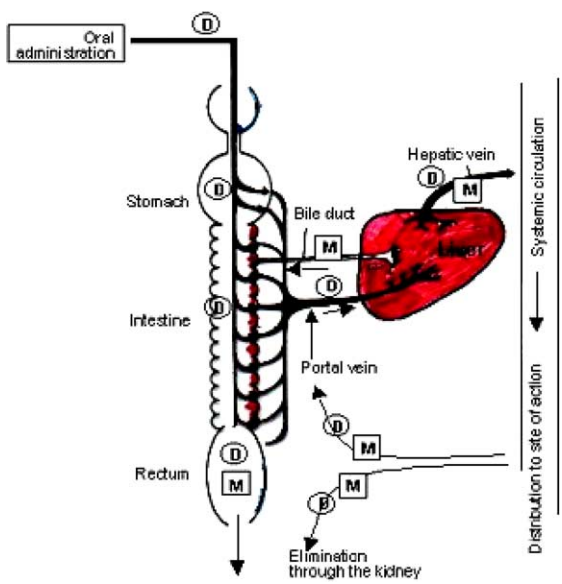


Fig. 4. Absorption of drug administered orally (D = drug, M = metabolite).

II. PHARMACOKINETICS: MEASURING A PILL'S PROGRESS

All the mechanisms we have encountered, which affect the way in which a drug is handled by the body, are important for one major reason – they all work together to determine how much drug is present at any given time at the point in the body where the drug acts – its effector site. Commonly this is at a receptor site in particular cells and organs, and the

concentration there will usually be closely related to the concentration in the blood plasma.

In experiments done many years ago on epileptic patients who were undergoing brain surgery, small brain biopsies were taken at operation. The concentration of anti-convulsant drug was measured in both the brain tissue and in the plasma from simultaneously-withdrawn venous blood. For the drugs phenobarbitone and phenytoin, a linear correlation was observed between plasma and brain concentrations. This suggested that plasma concentrations of anti-convulsants could reflect brain concentrations, and therefore, presumably concentrations at the receptor sites within the brain substance.

Too little drug at the effector site means no therapeutic effect, too much may cause toxic effects to appear. So there is commonly a range of plasma concentrations between which the desired effect is obtained without toxicity – often called the 'therapeutic window' or therapeutic range (Fig. 5).

If all the mechanisms mentioned above are operating at the same time, how can we measure them, and devise a dosing schedule that will give us the plasma concentration we need – and maintain it over a period of time if that is what is required?

The fundamental central concept is that the plasma concentration of any substance, a drug or any endogenous compound such as glucose or cholesterol, is determined by just three factors:

- The rate of *input* into the plasma
- The rate of *loss* from the plasma
- The *volume* in which it is distributed.

It follows that a rise in plasma concentration of any substance will occur if input increases, loss diminishes, or the volume in which it is distributed shrinks. Conversely, a fall in plasma concentration will occur if input diminishes, loss increases, or the volume in which the substance is distributed expands. How can we measure these variables for any individual and any drug?

In Section I we looked at mechanisms which can affect these processes, but we did not group them in this way. If we do we find that rate of input into plasma of an oral drug depends on:

- Rate of dissolution of the formulation (tablet/capsule) in gastric or duodenal juice
- Rate of gastric emptying
- Rate, of uptake through the intestinal wall into the portal venous system
- Rate of passage of drugs through the liver and into the systemic circulation.

Can these be measured? Tablet dissolution can be measured in a laboratory where a tablet is exposed at 37°C to a solution made up to resemble gastric or intestinal juice. This is the method the pharmaceutical

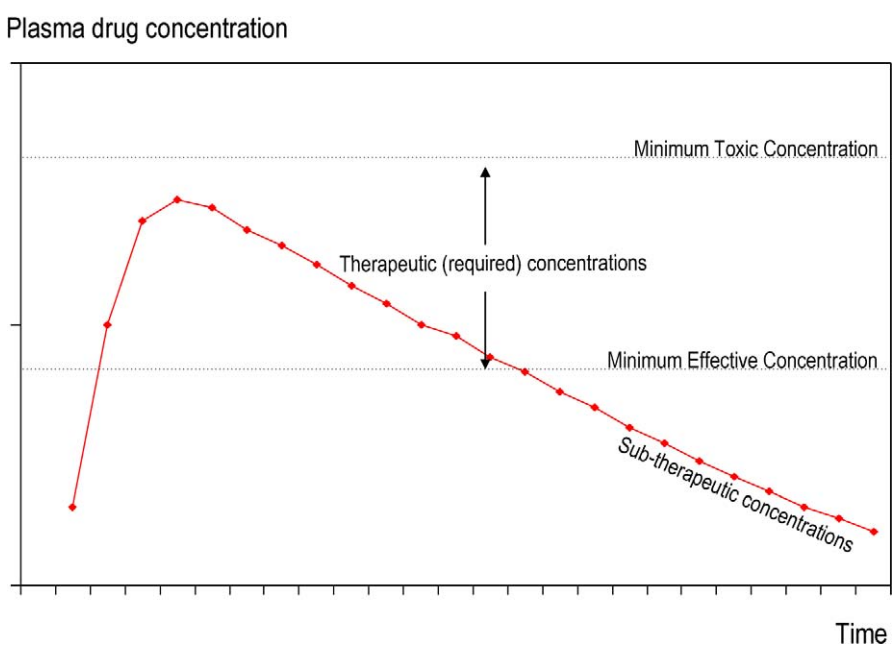


Fig. 5. Simulated plasma drug concentration vs. time curve showing the therapeutic window.

industry uses to ensure that a drug preparation will break down to liberate the active drug in the stomach or intestine, when used clinically.

Gastric emptying can be measured using X-ray imaging, or the passage of a radioactive marker substance from the stomach using external counting of radioactivity – scintigraphy – but these techniques are only useful as research tools.

Even more difficult, though not impossible, is the measurement of drug transfer across the human intestine or across the liver.

Clearly we cannot use techniques like these in routine clinical practice to measure the rate of input of drug into the plasma after oral or parenteral administration. Similar arguments apply to measuring drug loss – it is comparatively easy if it's only through the kidney, but very difficult if loss through the biliary system needs to be measured as well.

Measuring faecal drug loss is a particularly unpleasant process, often involving amalgamating and blending 2–3 days' collection of faeces, extracting the drug contained with solvents or by combustion if the drug is radioactively labeled, and measurement. For most drugs at some point in their development someone has to undertake this task.

How then do we get from the theoretical understanding of how drugs are handled by the body, to a practical set of techniques that will enable us to devise proper and effective dosing schedules, monitor our treatment, and avoid drug toxicity?

II.a. Measuring Drug Kinetics

With just a few relatively simple techniques it is possible to get all the important information needed to devise appropriate dosing schedules. We will only look at the simplest of these, which are of everyday, practical importance in clinical practice. All of these, and several others, are carried out in the process of drug development, and their results must be reported to regulatory authorities before a new drug may be registered for use.

II.a.1. A Single Dose, Given Intravenously

Giving a single dose of drug intravenously means that input into the vascular compartment is known and controlled. Therefore what happens after the injection gives us information about the other two variables, distribution and loss.

Imagine a dose of a drug given intravenously – i.e., 100% of the drug goes into the vascular compartment – followed by measurement of the concentration of drug in the plasma from blood samples withdrawn over a period of several hours. If this concentration–time profile is plotted out on graph paper, it will look something like Fig. 6.

Note that the highest concentrations measured are in the early blood samples withdrawn after the dose is given, and that thereafter the plasma concentration falls, steeply at first and more slowly later. This,

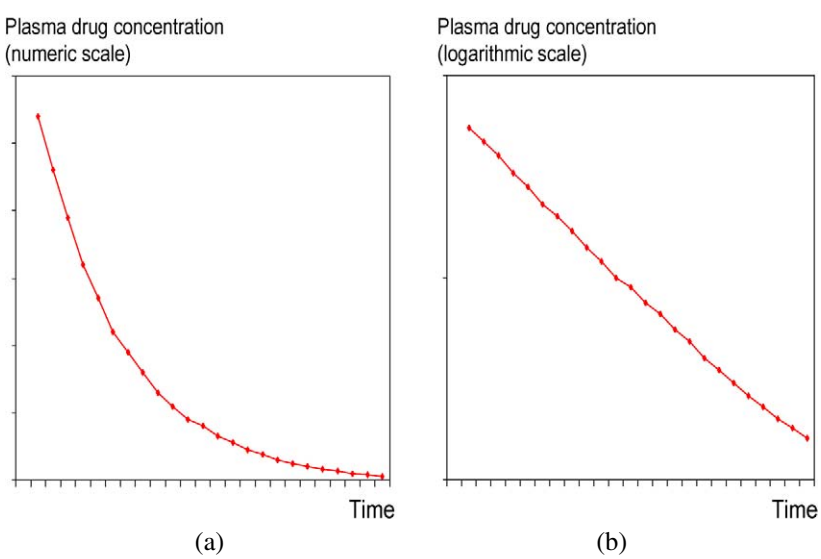


Fig. 6. Simulated plasma drug concentration vs. time curves after intravenous administration: (a) showing the y-axis in numeric scale, and (b) showing the curve when the y-axis is converted to logarithmic scale.

then, is the pattern of *loss* from the vascular compartment – much loss early on, and progressively less as time passes. In almost all cases this pattern of reducing plasma concentrations follows an exponential curve. In simple terms this means that although the *absolute* amounts of drug loss from the plasma diminish each hour, the *proportion* of the total amount in the body lost in each hour remains the same. For example, if 10% is lost in each hour, and 100 mg was the initial dose or body 'load', in the first hour 10 mg is lost, 90 mg remaining; in the second hour 9 mg is lost, 81 mg remaining; in the third hour 10% of 81 mg (= 8.1 mg) is lost, leaving (81 − 8.1 mg) = 72.9 mg ..., and so on.

Note again that each successive hour a smaller *absolute* amount is lost, but this represents a constant proportion of the body load.

If we now plot the same data points, but this time take the logarithm of the plasma concentration, the curved line of Fig. 6a becomes a straight line (Fig. 6b), and we can start to use it to derive some useful information. First of all, let us think of the body as a single, big compartment. What *volume* does this compartment have? If the 100 mg of drug we have injected intravenously were to be distributed instantaneously through not only the vascular compartment but also any other tissue compartments it is able to enter, it would be a bit like putting the drug into a well-shaken container and getting instant mixing. In this case the theoretical concentration of drug in the plasma (C_p) at time zero (0) would reflect the size of the compartment. So, if we extrapolate the C_p–time line back to zero (the dotted line in Fig. 7), we can estimate the plasma concentration of drug at time 0. For the sake of argument let this turn out to be 10 mg/l, which we will call C_p0. Then, if we injected a dose of 100 mg and the C_p0 measured from the graph is 10 mg/l, the volume in which it *appears* to be distributed (usually abbreviated to V_d) is given by

$$V_d = \frac{\text{Dose}}{\text{Concentration } (C_p0)}$$

$$= \frac{100 \text{ mg}}{10 \text{ mg/l}} = \frac{100 \text{ mg/l}}{10 \text{ mg}} = 10 \text{ l}.$$

It has to be emphasized that drug only *appears* to be distributed in this volume; we have not measured any volume directly, but simply divided dose by maximum concentration, i.e. V_d is, mathematically, a proportionality constant.

So, very simply, we have already calculated an apparent volume of distribution for our drug – one of the three variables (input, loss, volume) that determines the plasma concentration of the drug.

The apparent volume of distribution will be reasonably consistent if measured repeatedly in the

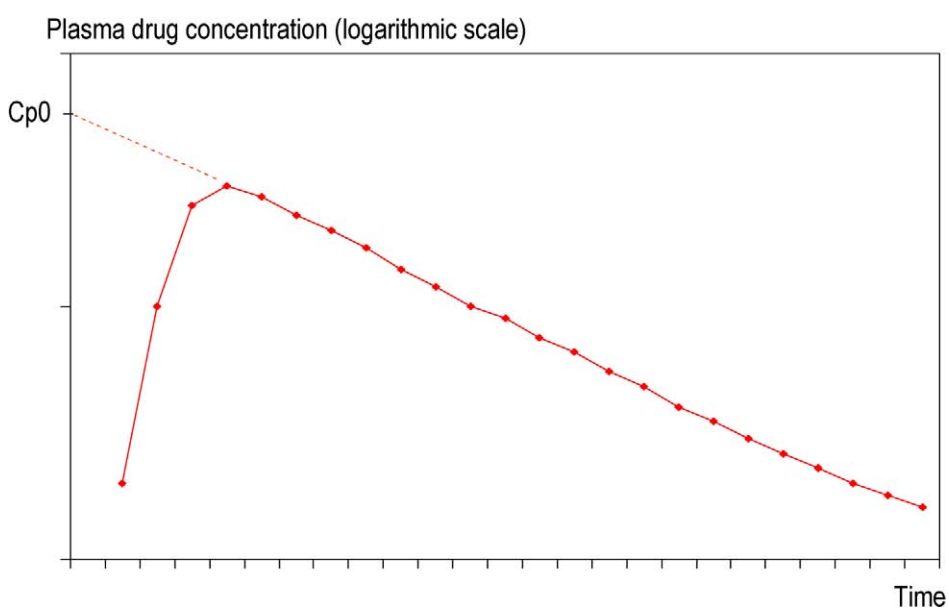


Fig. 7. Simulated plasma drug concentration (in logarithmic scale) vs. time curve.

same individual with the same drug, but would be independent of the intravenous dose given. As you might guess it may change with weight loss and under- or over-hydration. Values given for a range of drugs appear as tables in textbooks, and are usually derived from healthy individuals and less commonly extend to sick patients (it is easier to measure apparent V_d in healthy people!).

If you do look up apparent volumes of distribution for different drugs you will find some which are remarkably high, and you may have difficulty understanding how that can be. Again it is important to remember that apparent V_d is not a real measured volume, but a mathematical expression.

To illustrate this point, let us look at a different drug – say digoxin, commonly used to treat atrial fibrillation with a rapid ventricular rate. This drug is seldom given intravenously because it takes about six hours to redistribute from the circulation into tissues, and there is therefore little or no advantage overall in intravenous administration if the patient can swallow and absorb the digoxin preparation. For the sake of this example, let us assume that 0.5 mg of digoxin has been given orally on two occasions, six hours apart, to a patient with atrial fibrillation and a fast ventricular response.

We ask the laboratory to measure the plasma digoxin concentration at 12 hours after the first dose, and find it to be 1 µg/l. Can we get any idea of the apparent volume of distribution?

The maximum possible amount of digoxin present in the body at 12 hours, if it were completely absorbed and not lost at all, would be $(0.5 + 0.5) = 1$ mg. The plasma half-life (the length of time it takes for the plasma concentration to fall by 50%) of digoxin in normal individuals is around 36 hours, so at 12 hours after the first dose we would anticipate rather less than 1 mg to be retained – probably about 0.6 mg if digoxin in this case is 70% absorbed. So a very *crude* estimate of V_d would be

$$V_d = \frac{\text{Amount}_{\text{in body}}}{C_p} = \frac{0.6\text{ mg}}{1\text{ µg/l}} = \frac{600\text{ µg}}{1\text{µg/l}} = 600\text{ l}.$$

This is a bit of a surprise as the patient only weighs 62 kg and therefore has a total body water content of around 40 l at most. How can an apparent volume of distribution be so much bigger than any physiological volume?

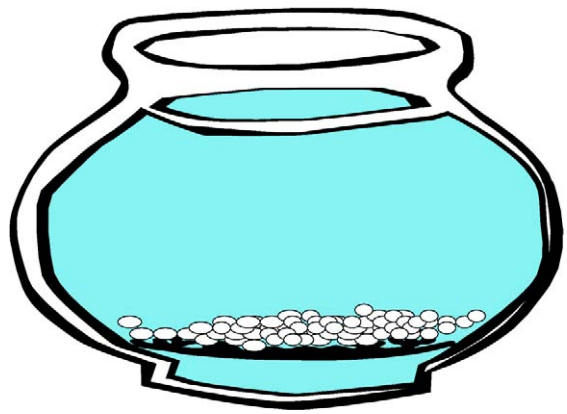


Fig. 8. A fishbowl filled with 1 liter of water containing 500 eggs.

To understand this apparent nonsense, let us look at an analogy. Instead of drugs and blood let us substitute water and ants' eggs.

Figure 8 shows a fishbowl – the sort you have on a table at home for ornamental fish. The capacity of the bowl is 1 liter. For some reason best known to yourself you decide to confirm the volume of the bowl by seeing to what extent ants' eggs are diluted when put in the water. You insert 500 ants' eggs and stir the bowl. When mixing is complete you withdraw a 20 ml sample and count the eggs. If you have done a good job of mixing you should find 10 eggs in the 20 ml sample. Knowing a bit about measuring volumes you calculate as follows:

> I put 500 eggs in the bowl. After mixing I found 10 eggs in 20 ml, i.e., a concentration of 0.5 egg/ml. If 500 eggs went in it appears that they are distributed in a volume of (500/0.5) ml = 1000 ml or 1 liter.

(As you knew the volume of the bowl to start with, this has not got you very far – but is reassuring.)

Now introduce a complication (see Fig. 9). The goldfish has devoured 250 of the 500 eggs, but you did not know it. So now there are only 250 eggs distributed in the water of the bowl. You ensure adequate mixing – producing acute vertigo in the goldfish – and sample 20 ml of the water. You find on this occasion only 5 eggs, or 0.25 egg/ml.

Applying the same formula,

$$\frac{\text{Added eggs (dose)}}{\text{Concentration of 20 eggs}} = \frac{500}{0.25},$$

you find that the *apparent* volume of distribution is $500/0.25 = 2000$ ml, or 2 liters. But you *know* that

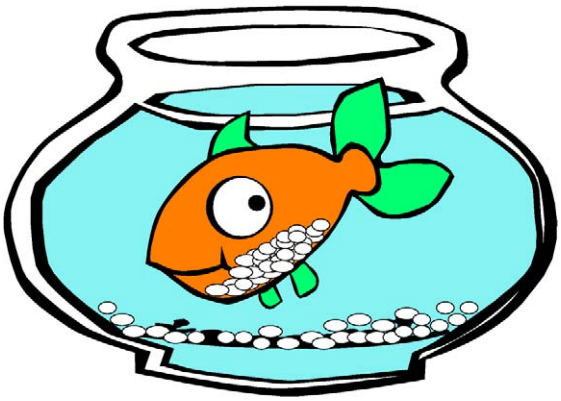


Fig. 9. A fishbowl filled with 1 liter of water and 500 eggs, 250 eggs are in the fish stomach.

the true volume is only 1 liter. So in this instance you appear to have measured a volume double that of actual volume – and it is all because there is a high concentration of eggs inside the fish.

Back to drugs – if we give a drug and it is taken up and concentrated in particular tissues (the 'fish') this is not easy to measure. However it reduces the amount of drug left in the plasma compartment (the 'water' in the goldfish bowl), but it is from this compartment that we take our sample, measure the drug concentration, and do our calculations. So if we measure an apparent volume of distribution greater than any actual, conceivable physiological volume, it tells us one thing. The drug is being taken up and concentrated in tissues outside the plasma compartment.

In the case of digoxin we can visualize what is happening. The site of action and binding site of digoxin is to tissue Na^+K^+ATPase. This enzyme is distributed very widely in tissues, and particularly in excitable tissue, which depends on it to restore sodium/potassium balance to resting levels after excitation. Digoxin preferentially distributes therefore to these tissues, and a disproportionately small component is left in the plasma compartment from which we sample.

It is difficult for us to come to terms with *apparent* volumes of anything. Remember it is an important and useful concept and not a real volume. Later in this chapter (Section IV) we will show how it can be used to calculate doses of drugs – often those which are given in an emergency situation.

However, our experiment with the intravenous drug bolus can give us much more information than the apparent volume of distribution. As we took away all the uncertainty about *input* by putting the drug directly into the vascular compartment, the curve must also be telling us a lot about the *loss* of drug, and the rate at which this is occurring.

Figure 10 compares two curves obtained in the same individual after intravenous bolus injections of 100 mg of two different drugs. Notice that if we extrapolate the curve back to zero both cut the x-axis at the same point, i.e., they have similar apparent volumes of distribution. But the obvious difference is the slope of the two curves. Drug B is being lost from the plasma compartment much more rapidly than Drug A, and the rate of loss, or more exactly the proportion of total body drug being lost in each hour, is much greater for Drug B than Drug A.

This tells us a lot about the rate of drug clearance, but nothing about where it is being lost (kidney, liver, skin, lung). If you visualize it being lost at multiple sites, then the curve represents the sum of the clearance rates through all of these sites, i.e., the total clearance of the drug from the body.

The slope of the line gives the value of the elimination rate constant – often abbreviated to K_{el} – which is measured in units of h^{-1} (think of it as 'per hour') or min^{-1} for a very rapidly eliminated drug. What this means from a practical point of view is that K_{el} is a measure of that *constant proportion* of total body drug load which is eliminated in each unit time period (i.e., a K_{el} of 0.1 h^{-1}, means that 10%, 0.1/1 expressed as a percentage, of the body drug load is being eliminated each hour; a K_{el} of 0.05 h^{-1} implies a constant 5% loss per hour).

Putting together the two ideas of apparent volume of distribution of a drug, and its elimination rate constant, you can see that, if K_{el} is 0.1 h^{-1}, 10% of the volume appears to be cleared of drug in each hour.

So the total *clearance* of any drug is given by V_d (l) $\times$ K_{el} (h^{-1}) = (V_d K_{el}) l/h, and is expressed, as is for example glomerular filtration rate, as units of volume per time period. We will use this concept of measuring clearance later in this section, and in clinical applications in Section IV. Tables of drug clearance are commonly set alongside those for apparent volume of distribution of common drugs in textbooks which list kinetic data.

Before leaving the simple single dose experiment of Fig. 6 there is one more point to make. Drug clearance goes on by losses of constant proportions of drugs in each unit of time. Therefore, theoretically at least, a drug is never entirely cleared! This is not a useful concept for clinical practice, but we do need some way of estimating how long it will take for,

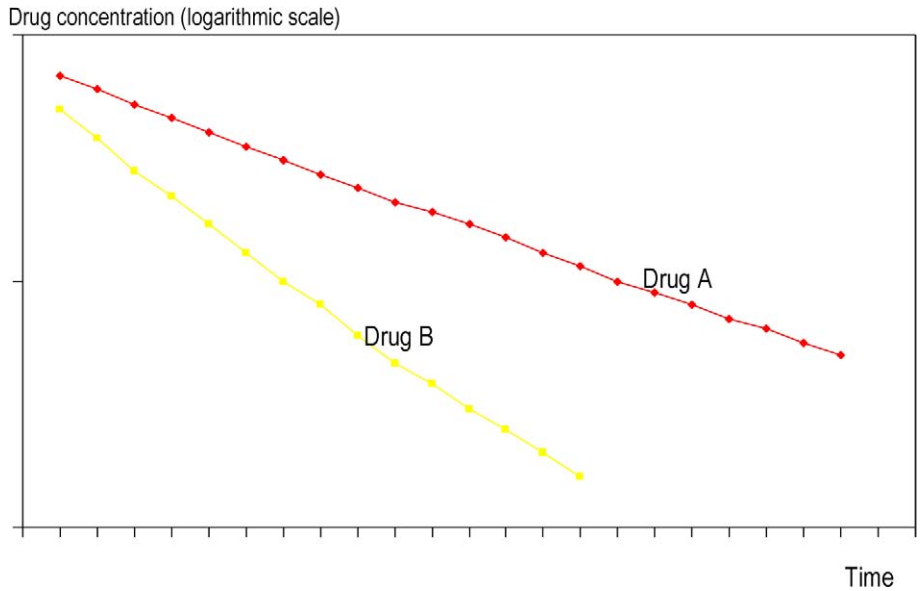


Fig. 10. Simulated drug concentration versus time curve after intravenous administration of two different drugs to the same individual.

say, a very high and perhaps toxic plasma concentration of a drug to fall into the therapeutic range. The convention has arisen of describing this variable for individual drugs as the *half-life*, or $T_{1/2}$ (sometimes written $T/2$), which is defined as the time taken for the C_p to fall by 50%. It obviously is related to the elimination rate constant – the steeper the slope, the shorter the time for plasma concentration to fall by 50% – and conversely the shallower the slope (the lower the K_{el}), the longer the time for plasma concentration to fall by 50%. Thus, K_{el} and $T_{1/2}$ are inversely related, and can be calculated the one from the other:

$$T_{1/2} = \frac{0.693}{K_{el}} \quad \text{or} \quad K_{el} = \frac{0.693}{T_{1/2}}.$$

From one simple experiment with an intravenous drug bolus we have been able to derive estimates of apparent volume of distribution, total drug clearance, elimination rate constant, and plasma half-life. We have however (and quite deliberately by choosing the intravenous route), learned nothing about the *input* side – drug dissolution, absorption and passage through the liver – and that can only be done by giving the test drug orally.

II.a.2. A Single Dose Given Orally

For this experiment we will use the same willing (!) subject, and instead of giving 100 mg by intravenous bolus we will administer the same dose of the same drug orally – preferably on an empty stomach as this will take away the impact of food on gastric mixing and emptying (if we needed to know about interactions with food and gastric emptying we could repeat the experiment on another day after food had been taken).

Again we will take blood samples at intervals after dosing, measure plasma drug concentrations, and plot the results on a linear graph (Fig. 11). The first and obvious thing to note is that the plasma concentrations rise to a maximum at around 1 h, whereas, of course, the early plasma concentrations taken soon after the intravenous bolus were the highest. The time to reach the peak plasma concentration after an oral dose is often abbreviated to T_{max}, and the concentration itself to C_{max} – the maximum concentration achieved after that dose.

Notice that the C_{max} is substantially less than that achieved with the intravenous dose, although we would anticipate the same volume of distribution in this same individual, and similar drug clearance rates. This probably implies that the full amount of ingested drug has not been absorbed from the gastrointestinal tract, or that some has been taken out and lost in the liver.

If we wanted to calculate the proportion of drug absorbed out of the initial 100 mg oral dose we now

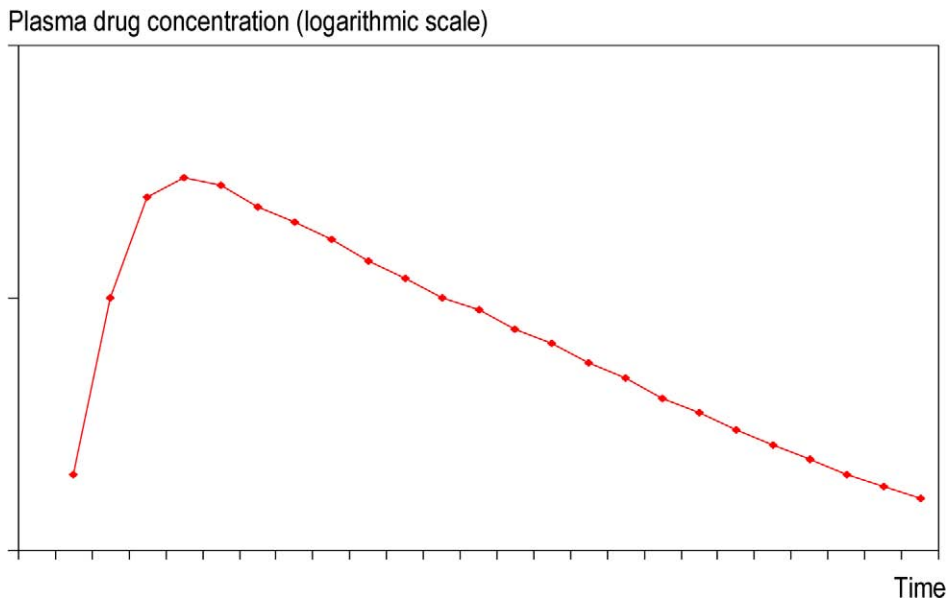


Fig. 11. Plasma drug concentration vs. time curve after administration of oral dose.

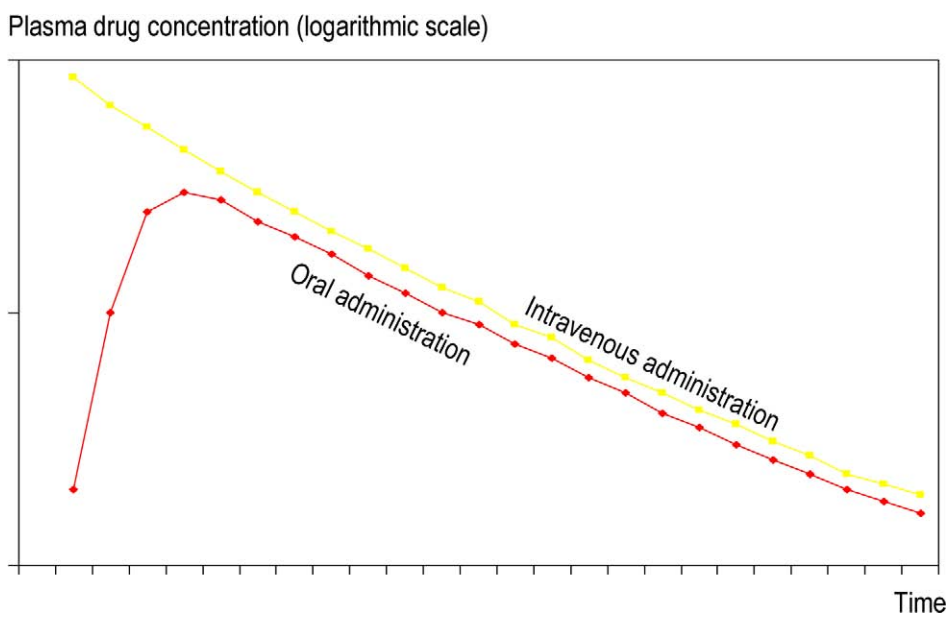


Fig. 12. Plasma drug concentration (in logarithmic scale) vs. time curves after administrations of oral and intravenous doses.

have the data to do so. In Fig. 12 the concentration–time curves for both oral and intravenous dosing of the test drug have been plotted. This immediately points out the difference in C_{max} between the i.v. and oral dosing. Notice also the close similarity of the later points of both curves. At this stage the early absorptive processes are playing little role in determining plasma concentration, which is governed almost entirely by drug clearance. If measures of K_{el} were to be made from both curves (plotted logarithmically) they would be found to be the same.

So the major difference between the two curves is attributable to drug absorption in the oral dosing experiment. The extent of that difference can be measured by comparing the area under each of the curves (there are several mathematical ways of doing this, which can be found in textbooks of pharmacokinetics if you are interested in pursuing this).

The intravenous curve is, by definition, a representation of 100% bioavailability as the drug was put in its entirety into the vein. The oral curve has an area under it approximately 75% the size of the intravenous curve, and this suggests that 25% of the oral dose failed to get into the circulation. The oral bioavailability of the drug is the proportion getting into the vascular compartment, and can be measured if there is an intravenous dose curve available for the same subject at the same dose. In this example, F (the fraction bioavailable) is 0.75. It might be as high as 1.0 (100%) for some steroids, or as low as 0.1 (10%) or even less for poorly absorbed aminoglycosides.

Returning to drug *input*, we can now characterize it by measuring C_{max} and T_{max} – and its extent by estimating oral bioavailability.

II.a.3. Repeated Oral Dosing with Measurements of Blood Plasma Concentration over Time

In clinical practice drugs are given orally whenever possible to avoid injections, but how do we decide how often to give them – once, twice, or thrice a day? (This was the question at the very beginning of this chapter.) Imagine we are repeating the experiment of Fig. 11 but on this occasion we are repeating the oral dose at 8 hourly intervals. The concentration – time profile might look something like Fig. 13. How might the pattern of plasma concentration affect the action of the drug? If the effect of the drug needs to be continuous and uninterrupted, as for an anti-arrhythmic or anti-convulsant drug, then giving the drug 8 hourly will only keep the plasma concentration in the therapeutic range for a total of around 8 of the first 16 hours. Equally, the doses given do not raise the plasma concentration into the toxic range at any point. On the other hand this might be a totally appropriate regimen for an antibiotic, where bacterial 'kill' is achieved by a high transient peak plasma concentration, with rapid fall in concentration thereafter ahead of the next peak.

To improve matters let us increase the size of each dose, keeping the frequency 8 hourly. The profile in Fig. 14 might be obtained.

Now the plasma concentration is in the therapeutic range for 12 of the first 16 hours, but it is also in the toxic range for 4 of these hours. So increasing the dose prolongs the effect, but increases the risk of toxicity. If we go back to the original dose, but give it

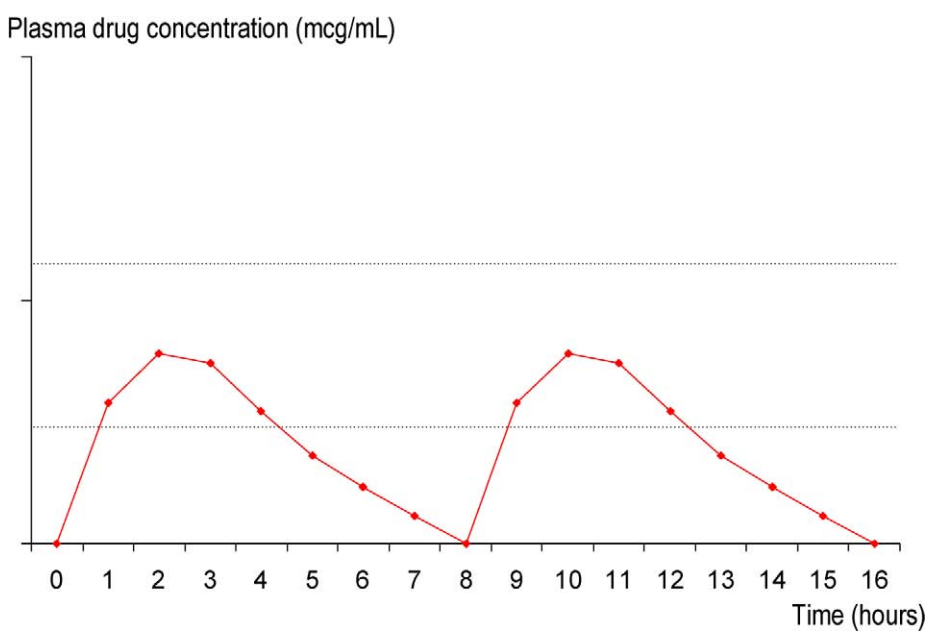


Fig. 13. Plasma drug concentration vs. time curve after administrations of multiple oral doses at 8-hour intervals.

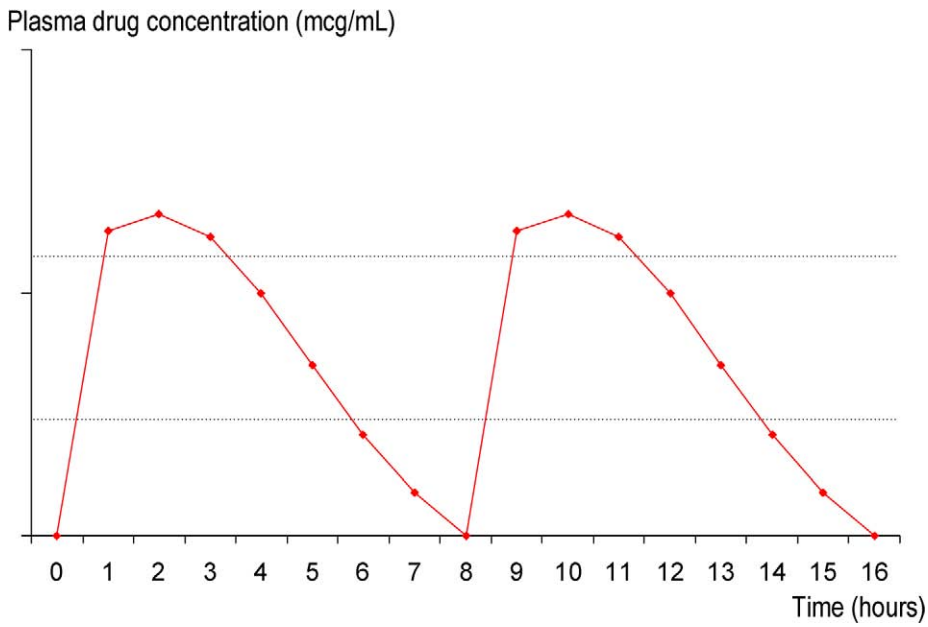


Fig. 14. Plasma drug concentration vs. time curve after administrations of larger multiple oral doses at 8-hour intervals.

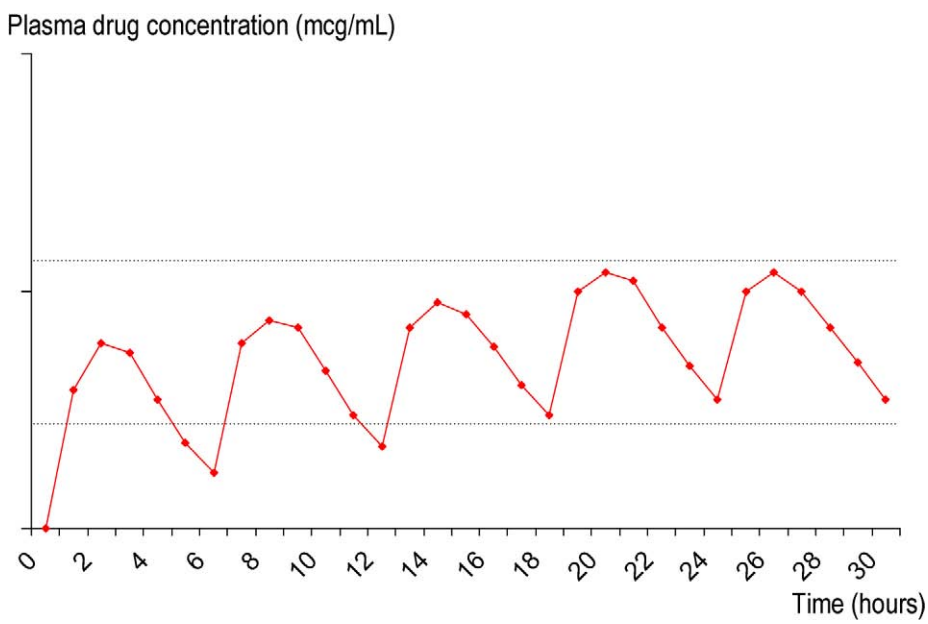


Fig. 15. Plasma drug concentration vs. time curve after administrations of multiple oral doses at 6-hour intervals.

more frequently (6 hourly), we might get the profile of Fig. 15. In this case the peak plasma concentrations rise with each successive dose (because there is residual drug in the plasma at the time each new dose is given), but after 5 doses the plasma concentrations have reached a consistent pattern – oscillating over each dose interval but remaining within the therapeutic range. The major determinant of the time it takes to reach this 'steady state' is the half-life of the drug in the plasma. For oral dosing this usually works out at 5 half-lives when the drug is given at an interval close to its half-life.

At steady state, by definition the total drug clearance, or loss, is equal to drug input and plasma concentration oscillates around an average figure. However two situations occur which can provide problems in dosing.

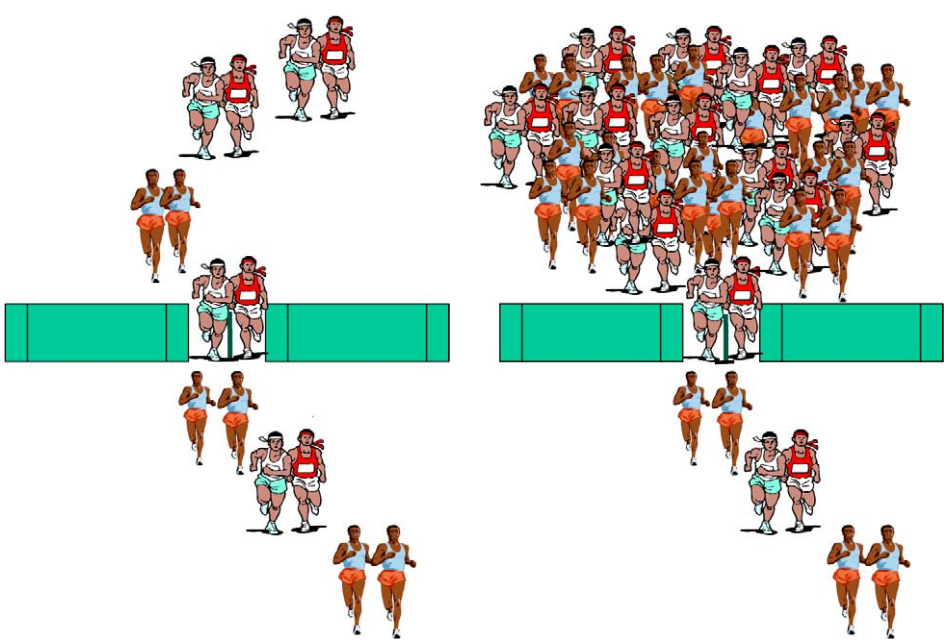
First, think of a drug with a short half-life – say $1\frac{1}{2}$ hours – which you would like to give by mouth but whose effect is critically dependent on its plasma concentration. It is just not practical to ask patients to take a compound every $1\frac{1}{2}$ hours without fail!

The solution to this problem has been the development of oral 'slow-release' preparations – formulations of the drug in a matrix from which it slowly leaches out allowing for intestinal absorption over a period of many hours. T_{max} for these preparations may be as high as 10–12 hours after ingestion.

All new developments have a flip side. The availability of slow-release theophylline has produced new problems for toxicologists. In overdose theophylline is potentially lethal. When a poisoned patient arrives at hospital, a plasma concentration is measured and, for most drugs, it can reasonably be assumed that the absorptive phase would be nearing completion (or can be shortened by gastric aspiration or giving charcoal by mouth). No such comfort exists with slow-release preparations which, beyond the reach of the gastric tube and only partially adsorbed to charcoal in the intestine, may go on presenting fresh drug for absorption for many hours. The technique of whole bowel lavage – literally flushing the gut – has been introduced to combat this problem.

The second problem is that of drugs, which can *saturate* their elimination mechanisms at plasma concentrations, which are within the therapeutic range. Perhaps the most important example is that of the anti-convulsant, phenytoin.

To grasp the concept of saturation think of a narrow gate at the entrance to an athletics stadium (Fig. 16a). As the athletes begin to arrive at the end of the marathon race there is very little hindrance to their entering the ground. As their numbers increase, the narrow gate still allows them to enter at a rate proportional to their numbers. However, as the majority of the athletes arrive, their number exceeds the capacity of the narrow gate to let them in. The capacity of the gate has been exceeded and only a constant number can get into the stadium in any one unit of time (Fig. 16b). If we plotted the rate of entry into the stadium against the numbers of athletes trying to get through the narrow gate it would look like



(a) (b)

Fig. 16. Graphic illustration of the concept of saturation.

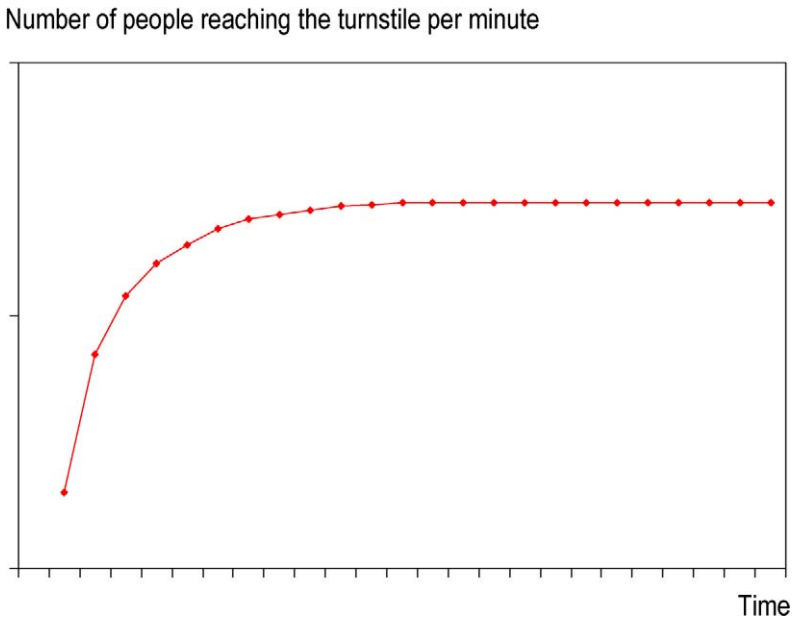


Fig. 17. Saturation of the rate of entry due to a limited capacity.

Fig. 17. In summary, the rate of entry to the stadium is proportional to the number coming to the gate until its capacity is *saturated* when the rate of entry becomes constant no matter how many are trying to get through.

If we apply this concept of saturation to drug elimination we get a similar picture. The anticonvulsant phenytoin depends critically for its elimination on one enzyme reaction (to produce the p-hydroxy-phenyl metabolite) and this, like the turnstile, can exceed its capacity to metabolize the drug. Phenytoin is then eliminated at a constant amount (not a constant proportion) per unit time. If input then exceeds this elimination capacity (and volume of distribution does not change), plasma concentration will rise rapidly into the toxic range.

In clinical practice we increase the dose of phenytoin cautiously when we think we are approaching the saturation point and the manufacturers have recognized this problem by providing not only a standard 100 mg capsule but also a 30 mg capsule so that we can approach the saturation point gently.

This phenomenon of saturation is seen with alcohol (ethanol) which rapidly saturates its first metabolic enzyme, alcohol dehydrogenase, and thereafter is eliminated at a constant rate, which approximates 10 ml per hour. And this is the figure you will find in many textbooks. However, as the C_p reduces it drops down below the saturating concentration and begins to fall by constant proportion (i.e., exponentially) just like other drugs.

A general principle emerges that saturation kinetics apply when a drug's concentration is rising into the toxic range. (This also seems to imply that our enzymes were not designed to handle drugs like alcohol except in very small quantities.) Because the slope of the curve when saturation has occurred is quite flat i.e., not rising at any rate at all, this form of kinetics is referred to as "zero-order" kinetics in contradistinction to the conventional exponential curve which can be expressed by a single exponent (a rising, but consistent slope) and is called "first order". In general terms, "zero-order" kinetics operate mostly when the plasma concentration is in the toxic range.

II.b. Implications of Different Routes of Administration of Drugs

Earlier, in Section I, we looked at some of the many different routes by which drugs can be given but did not follow up on the implications of these for the rate and extent of absorption of the drug. Figure 18 shows some of these routes.

II.b.1. Sublingual

Gyceryl trinitrate is a vasodilator drug used for the relief of cardiac pain on exertion – angina pectoris.

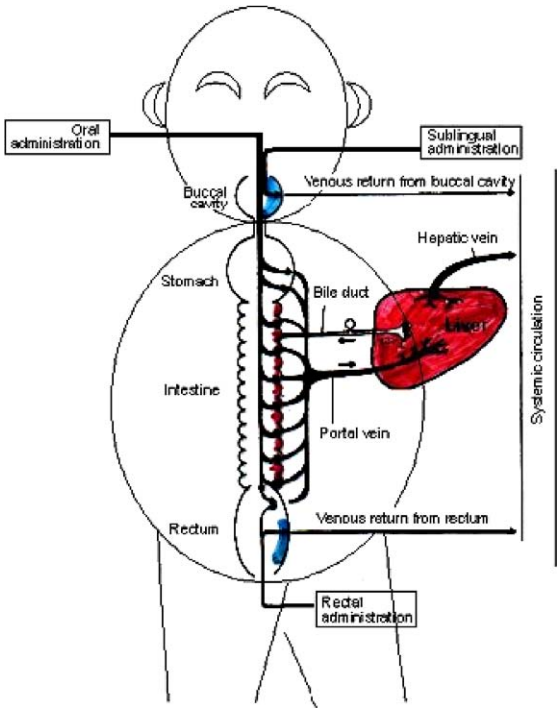


Fig. 18. Absorption processes from different routes of administration.

If swallowed it undergoes extensive metabolism in the gut and liver and only a tiny fraction reaches the systemic circulation and then only after an unacceptable delay. Giving it under the tongue allows the formulation to disintegrate and the active drug is readily absorbed through the buccal mucosa. Drug molecules cross directly into the venous system and rapidly get into the superior vena cava. and therefore into the vasculature. The response to sublingual glyceryl trinitrate is very rapid and this is a very effective way of relieving the pain. Note that the drug is in this way spared the action of drug metabolizing enzymes until after it has acted on its target tissue.

II.b.2. Transdermal

Increasing numbers of drugs are being formulated in a way that permits delivery through the skin. We tend to think of the skin as a poorly permeable layer but in fact it can transport drugs quite rapidly and is a convenient way of giving drugs which we want to leach out of a slow release formulation over a period of a few to many hours.

> One of the toxic hazards of organo-phosphate insecticides comes from their ability to cross the skin and both patients and staff attending them must either have the skin thoroughly decontaminated or protect the skin in some way to prevent further absorption.

Skin presents a big surface area for absorption and drug administration does not involve injection. Amongst the drugs given in this way are glyceryl trinitrate in a slow release preparation, which is often applied to the chest as a patch from which the drug is slowly absorbed over 12–24 hours. There is no good reason why the patch should be applied on the chest of course – except that that's where the patient experiences the pain! The drug might just as well be put on the back as the front of the chest.

How does the drug travel? Recall your anatomy and the venous drainage of the skin and you will realize that drug gets into the systemic circulation without going through the liver – so once again the metabolic impact of going through the portal circulation is prevented.

Other drugs given by this route include oestrogen for the relief of menopausal symptoms, nicotine for the treatment of withdrawal symptoms in patients who have given up smoking and hyoscine for the prevention of motion sickness (for some reason the convention in some countries is to put the patch behind the ear! – presumably this is either because it is out of sight there or because someone decided it should be near to the semicircular canals – the organs concerned with balance – the drug will take its route through the venous system and into the inferior or superior vena cava no matter where it is positioned on the body).

II.b.3. Subcutaneous and Intramuscular

These are common routes used when a drug has to be given by a non-oral route. Insulin is a good example of such a drug for, as we have seen, it is not possible to give it by mouth and all insulin-dependent diabetics learn to give themselves subcutaneous injections – often into the abdominal wall. Think again about the anatomy of the area and you will realize that the drug will be absorbed into the venous system and reach the inferior vena cava without passing through the liver and thus first-pass hepatic metabolism is by-passed.

The intramuscular route is normally used where a muscle bulk is required to receive a large or potentially painful fluid volume – such as repeated doses of antibiotics when the oral route cannot be used,

perhaps because the patient is vomiting. Removal of drug from the muscle can be quite rapid but this depends on the vascularity of the muscle and the nature of the drug formulation. A drug "bound" to a large transporting molecule such as protamine–insulin formulations and given by injection may act as a depot and only allow the drug to be released over a prolonged period of time – e.g., many hours. Depot preparations of antipsychotic drugs may be used in the management of schizophrenia and benzathine penicillin, again in a slow-release preparation, is commonly used to provide prophylaxis against recurrent streptococcal infection in young patients who have had rheumatic fever.

II.b.4. Rectal

Drugs given into the rectum are usually wrapped up in some slow delivery matrix so that they are absorbed slowly. An exception is the antimicrobial metronidazole, which can be given through the rectum to achieve as high plasma concentrations as can be achieved with oral or even parenteral administration.

Again, consider the anatomy of the absorptive pathway. Apart from the anal margin the rectum has venous drainage directly into the portal venous system and so any drug absorbed from the rectum will be subject to extraction and/or metabolism before reaching the systemic circulation. There is therefore no particular advantage to giving a drug with a high first-pass clearance by this route.

Suppositories (the name given to drug preparations, which are inserted into the vagina or rectum) can also be used to allow the slow release of a drug through the night. Examples include the non-steroidal anti-inflammatory drug, indomethacin, used for the relief of the joint pain and morning joint stiffness in rheumatoid arthritis and the bronchodilator drug, theophylline, in patients with asthma who are troubled by nocturnal wheeziness which interrupts their sleep.

II.b.5. Inhaled Route

Several inhaled drugs are used for the relief and management of asthma. The drug, formulated into a solution which can be reduced to fine particles, is inhaled from an inhaler device and most patients over the age of about 6 years can be trained to use the device so as to get an effective dose into the bronchial tree. How far does the drug go? Studies have shown that the inhaled drug (corticosteroid or beta-2 agonist) does not get far beyond the secondary branches of the bronchial tree but is capable of producing a full therapeutic benefit at this level.

It is naïve to believe that the inhaled drug will not be absorbed to some extent. Ask any asthmatic about the effects they experience from two puffs of salbutamol from an inhaler and most will tell you about the fine tremor (sometimes bad enough to prevent them writing for a while) which they get. This must reflect systemic absorption from the bronchial mucosa and re-emphasises the point that many drugs can penetrate most body mucosae.

II.c. More Complex Drug Kinetics

It was emphasized above that the "models" of the body we have discussed in this section are very much an oversimplification. The body does not really behave all the while like a single big compartment and drugs do not always leave the body precisely along a single straight line (when plotted logarithmically) but sometimes the findings are better "explained" mathematically by a combination of loss from two "compartments" each having its own volume of distribution and elimination constant. Full-time pharmacokineticists like to spend their time refining the "models" for particular drugs or medical conditions. But in the world of normal medical practice the conditions are seldom so nicely controlled that we can make these calculations. Very often we are lucky if our patients take their medicines in a way resembling the ideal (it is estimated that only about 50% of hypertensive patients are fully compliant with their medicines), many omit doses and most would not take their drugs precisely at the suggested times. In our experience more complex models are not useful in the clinic and only rarely at the bedside.

However, there is one more relatively recent development in pharmacokinetics, which is important to note. As we went through the measurement of the concentration–time curve for the single intravenous or oral dose, did you consider what the "volunteer" had to do? He or she probably had to be at the laboratory without having had anything to eat, to have a cannula put into one of the forearm veins so that repeated blood samples could be withdrawn at regular intervals – usually up to and beyond 24 hours from dosing. You can see that this would just not be a possible thing to do in a sick child or an elderly patient with a major medical problem. So how do

we get kinetic data about drugs in order to establish their correct dose and dose interval if we cannot get repeated samples from the same individual?

The answer is a technique called population kinetics. In this, blood samples are taken on a few occasions, carefully timed in relation to the previous drug dose, in as big a population as can be observed. The blood samples may be obtained at widely different time points after dosing and all are analyzed for drug concentration. The next step is a statistical treatment of the results which makes the assumption that all the patients belong to one big, if variable, population. A spread of data points is obtained over the dose interval and one gigantic "curve" of concentration–time relationships created. If the population is big enough, the mathematics iron out any awkward individuals whose data do not fit the overall pattern and from this derived "curve" the kinetic parameters we have been discussing can be deduced.

As an example, a study looked at the kinetics of a new drug for the movement disorder, Parkinson's disease. The manufacturing company organized a study in which their drug was given to 275 patients with the disease. It was used in varying doses (this was a dose-finding study in the early stages of developing the drug) and between 5 and 8 blood samples were taken from each patient – generating over 1400 blood samples for analysis in total. From analysis of all these data they were able to calculate the normal kinetic parameters such as clearance, volume of distribution and so on. What is particularly interesting is that the values for these items, calculated in this way, were very close to those obtained from the more controlled type of single and multiple dose studies we have been considering above.

In the next section of this chapter we will look at some of the factors that can influence drug kinetics. There are many of them, yet the general experience is that about 80% of all patients with a particular condition can be treated adequately and well with a "standard" treatment regimen. Most of the variability seems to reside in the remaining 20%.

Population kinetics exploits these resemblances and, by using very large numbers of samples, smooths out some of the differences that do exist. The development of this technique has enabled us to have data to guide our prescribing even where it would be unethical or simply impossible to get the same data from the rigorous investigation of a much more limited number of people.

III. FACTORS WHICH MODIFY DRUG KINETICS

Up to now we have assumed that the people in whom we have examined drug kinetics have been fit and healthy, and physically very similar. In reality people come in all shapes and sizes – young, old, well or sick – and there is no reason to expect that the kinetics of drugs in them will be the same. In fact, the reality is that in clinical practice we will quite often have to adjust drug doses according to a patient's response. The old saying 'the right dose of a drug is that required to produce the desired effect without unacceptable side-effects' is right as far as it goes – and implies that there are major differences between individuals which might well be based on either different drug kinetics or different response to the same plasma concentration. Nevertheless, those who compile national Essential Drug Lists, and Standard Treatment Guidelines, find that the drug list and the dosage guidelines cover the needs of at least 80% of the population – which implies close similarities among most people in any individual population in the way they handle and respond to drugs. It is in the 20% who respond differently that we are likely to find the factors that explain widely differing responses.

As you read through each of the factors that may modify pharmacokinetics, work out for yourself what may happen to drug *input*, *distribution* and *loss*, and therefore to the plasma concentration of drugs affected by these factors.

III.a. Age-Related Factors

For a fuller treatment of age-related factors, see Chapters 12 and 13.

III.a.1. Infancy

More and more babies are being born prematurely (elective Caesarian sections for pregnancy-induced hypertension, diabetes, foetal distress of varying kinds). Neonatal units need highly specialized skills in managing these tiny creatures – occasionally as much as 10–12 weeks premature. Among the very many special problems of the premature baby are those related to drug administration and elimination.

Some oxidative (Phase I) drug-metabolizing enzymes are already present in the human foetal liver as early as 12 weeks after conception. Others progressively appear as foetal age advances, although

so far it has not been possible to find Phase II conjugating enzymes, mediating glucuronidation (the process of adding the glucuronic acid molecule to the drug or its oxidative metabolite(s), which makes the product more water-soluble). This may mean that a drug administered to a neonate may be poorly, if at all, metabolized, or alternatively may be metabolized along an alternative pathway to that of the adult.

> The analgesic paracetamol is largely excreted in the urine of adults as the glucuronide, only around 30% appearing as the sulphate. When human foetal liver cells were incubated with paracetamol, however, they produced the sulphate conjugate but no glucuronide.
> Again, theophylline, which is only excreted in adult urine as oxidative metabolites, is excreted almost entirely as unchanged drug in the urine of premature infants.

Drug-metabolizing enzymes can be very immature in both premature and full-term babies. Therefore, drug plasma concentrations may be much higher after doses (per kilogram) which would be perfectly acceptable and safe in older children.

Renal development is also immature in both the premature and the full-term baby. At birth overall renal function is approximately 20% of the adult value, but increases rapidly up to around one year of age when it is usually the same as that of an adult (when adjusted for body size). Glomerular filtration rate in particular may increase four-fold over the first week of life. As renal blood flow, glomerular filtration rate and tubular secretion of drugs are all low in the neonate, drugs cleared by the kidney need to be given in reduced dose – particularly if the drug has a narrow 'therapeutic window', and the potential to produce toxicity if C_p rises too greatly.

III.a.2. Childhood

Renal function matures to its peak between 5–12 years of age, and glomerular filtration rate may exceed adult values when corrected for body surface area.

Drug-metabolizing enzymes also appear in full range in the liver during early childhood, and some drugs seem to be metabolically cleared more rapidly at this time – e.g., sulphonamides metabolized by acetylation. However, some of the conclusions about drug clearance rates in children have been made only on the basis of altered plasma $T_{1/2}$ for the drug. From Section II you will remember that clearance equals $V_d \times K_{el}$ or $V_d \times 0.693/T_{1/2}$ (because $K_{el} = 0.693/T_{1/2}$). Therefore a change in half-life does not *necessarily* signal a change in clearance unless it can be guaranteed that V_d has not altered as well.

However, for some drugs, such as the anticonvulsant phenytoin, there is good evidence that V_d is not altered and that oxidative clearance is greater than in adult patients.

III.a.3. Pregnancy

Pregnancy is associated with enormous changes in physiological functions which start early in the first trimester with vasodilatation and an increase in cardiac output, possibly secondary to the vasodilatation. Fluid retention follows, and intravascular volume may expand by up to 25–30% by the end of the second trimester. Renal blood flow increases, and glomerular filtration rate may be 50% higher than in the non-pregnant state. Miraculously, almost all of these changes return to normal within a week of delivery.

From the point of view of drug handling, there are several distinct changes, which have been well documented. Firstly, haemodilution results in a lower plasma albumin concentration and therefore an altered partition between free and bound drug for drugs that are tightly bound to plasma proteins. While this does not appear to have a big impact on drug response, some laboratories are able to measure free drug concentration in the plasma and this may be a valuable addition to monitoring if patients are receiving drugs whose effect is critically dependent on free drug concentration – e.g., some anticonvulsants.

Hepatic drug metabolism, on balance, increases although not all families of metabolizing enzymes are affected equally. In one study, pregnant heroin-dependent women in the USA on stable methadone maintenance treatment showed lower plasma concentrations as pregnancy advanced due to stimulation of drug-metabolizing enzymes. Some manifested methadone withdrawal symptoms necessitating an increase in oral methadone dose.

However, the major change with pharmacokinetic implications is an increase in the renal excretion of water-soluble drugs eliminated by the kidney. Penicillins, aminoglycosides (avoided in pregnancy if possible because of the slight risk of ototoxicity to the foetus), and digoxin, all have their renal clearance increased. This may mandate dose revision, although the penicillins are commonly given in doses

in excess of those required to eradicate organisms, so dosage adjustments are not as large as might be expected from the change in renal clearance.

III.a.4. The Elderly

In most countries in the world life expectancy is rising. Therefore the proportion of elderly people in the community is also rising. In Australia it is estimated that at least 80,000 patients are admitted to hospital each year as a direct result of problems with their medication. Many of these are elderly, frail people, often with multiple disease and usually on multiple medications (drug–drug interactions are considered briefly later in this section and, in more detail, in Chapter 16). However some of their problems are caused by a failure to recognize how the physiological changes of ageing may affect drug kinetics.

Many other factors in drug use are also relevant – poor vision and therefore difficulty in reading labels, mental confusion, poor memory leading to failure to remember if tablets have been taken or not, musculoskeletal problems preventing the opening of bottles (particularly the 'child-proof' variety which in our experience are readily opened by children, but only opened with difficulty by the elderly).

However, the physiology of ageing includes poorer gastrointestinal absorption, somewhat reduced hepatic drug metabolism, and, commonly, a loss of lean body mass. While all of these have been documented, none is of as great a significance as the loss of renal excretory function which is *invariably present* in old age.

Glomerular filtration rate increases from infancy and through childhood, and remains at this level until the 30s or early 40s when it begins slowly to fall. Renal size shrinks as nephrons die and are not replaced. By age 65 approximately half of the nephrons have gone, and the process continues through the 60s and 70s. Why is it that many doctors fail to recognize and allow for this when prescribing renally cleared drugs to older people? One possible reason is the fact that serum creatinine, a common marker of renal function, does not tend to increase as patients age.

Apply the same reasoning to this as to the level (concentration) of any other substance in the blood – be it a drug or an endogenous chemical. An unchanging plasma creatinine means, if *volume of distribution* is unchanged, that *input* equals *loss* from the plasma into the urine. Creatinine comes from creatine released continuously from our muscles. In old age muscle mass is less, and the *input* of creatine from muscle to blood reduces. This should lead to a fall in serum creatinine, but commonly it remains unchanged in the 'normal' range. This either means that the V_d for creatinine has reduced – not normally the case in a well-hydrated person – or that creatinine clearance (*loss*) through the kidney has fallen.

> The only way to be sure would be to measure glomerular filtration rate using some external marker substance, which is only excreted through the kidney. Inulin is commonly used for this purpose, but nowadays other markers exist such as ^{51}Chromium-labeled EDTA (ethylene-diamine-tetra-acetic acid) which can be given by intravenous bolus (just like the i.v. drug bolus given in the first experiment in Section II), measuring the C_p of the EDTA at regular intervals, plotting the concentration-time profile, and calculating V_d and K_{el} which multiplied together give the clearance. The great advantage of the EDTA method is that it is radioactively labeled and the measurement simply involves measuring the radioactivity of each plasma sample using a suitable counter.
> In fact elderly people have a reduced creatinine clearance, often balanced by the decline in creatinine input with a resulting normal serum creatinine. This is clinically important because drugs which are cleared through the kidneys need to be given in scaled down amounts to prevent cumulation and possible toxicity – e.g., gentamicin and other parenteral aminoglycosides, digoxin.
> If you have done some clinical work you may have noticed that digoxin tablets come in two dose sizes – 0.25 mg (usually white), and 0.0625 mg (or 62.5 microgram – often blue in colour). One brand name is 'Lanoxin PG'. Did you know that the PG stands for paediatric-geriatric which recognizes the immature kidneys of the infant and the failing kidneys of the elderly and the need to give smaller doses at both ends of life to avoid digoxin toxicity?

Table 1 summarizes the physiological changes related to age or pregnancy.

III.b. Genetic Factors

Over the past 45 or so years one of the most fascinating stories in clinical pharmacology has gradually unravelled. In the 1930s it had been recognized that many of the original anti-infective drugs, the

Table 1. Important age- or pregnancy-related physiological changes which may alter drug kinetics

Age	Physiological change	Possible kinetic problems
Neonate	Immature kidney Immature drug metabolizing enzymes	Risk of C_p rise if dose not adjusted
Children	Enhanced hepatic metabolism	Occasional need for increased dose/kg
Pregnancy	Increased blood volume Increased renal blood flow and GFR Reduced plasma albumin Increased hepatic metabolism	Altered drug distribution between protein bound and free forms Greater excretion of renally-cleared drugs May need increased dose to maintain effective C_p
Old age	Reduced absorption ? Reduced metabolism Loss of body mass →	Few practical consequences
	Reduced renal function →	Risk of toxicity with renally-cleared drugs

GFR, glomerular filtration rate.

sulphonamides, were metabolized by being acetylated and that the reaction (a Phase I reaction) occurred predominantly in the liver. The enzyme involved was called N-acetyltransferase. When the metabolism of isoniazid (a drug still widely used in treating tuberculosis) was investigated in the 1960s it was partly in an attempt to explain the clinical observation that some patients receiving it developed the adverse response of peripheral neuropathy – apparently as a direct consequence of taking the drug – while some others were unfortunate enough to develop jaundice due to hepatitis. There seemed to be no obvious basis for the different adverse effects until the rate of acetylation was compared in patients taking isoniazid (or INH as it is also called). It was shown that acetylation occurred at quite different rates in these patients. Some were rapid and some who were more likely to develop the adverse effects were slow acetylators. The basis for this difference, and the difference in toxicities, was shown to be due to possession of differing forms of N-acetyl transferase (NAT) in metabolizing tissues and especially in the liver. This division of a population into two or more groups dependent on drug metabolizing capacity is known as *genetic polymorphism* (*poly* – many, *morphism* – forms).

It required the growth of molecular genetics to probe the differences more intensely, and to discover in the 1980s and early 1990s that the gene coding for one of the two NAT (NAT I and NAT II) enzymes could exist in various forms, and that each form gave rise to a modified form of the enzyme which conferred properties of rapid or slow acetylation. The story became more complex as people of varying races were investigated, and now there are known to be around 12 variant forms of NAT II which confer rapid, or slow, or intermediate rates of acetylation on their substrates (Fig. 19).

Other drugs that are acetylated were investigated. The anti-hypertensive drug hydrallazine, was known rarely to cause, after a long period, a serious syndrome resembling lupus erythematosus, with skin rash, arthropathy, and occasionally renal impairment. Hydralazine is metabolized by acetylation, and investigation of the, predominantly, younger women who developed this syndrome showed they were also slow acetylators of the drug. Hydralazine is used much less nowadays and rarely for long-term treatment, but in the 1970s it was common practice to measure acetylation status in patients with hypertension to avoid giving hydralazine to slow acetylators who were perceived to be at greater risk of drug-induced lupus.

Another anti-hypertensive drug provided the next step in recognizing and understanding genetic polymorphism. It was observed in the clinic that patients with apparently similar degrees of hypertension required widely differing oral doses of the drug debrisoquine (now superseded and withdrawn from the market) to control their blood pressure. The differences were found to be explained by differing rates of metabolism to the 4-hydroxy-metabolite, some being rapid hydroxylators or 'extensive metabolizers', and some slow, or poor metabolizers.

At this time in the mid to late 1970s, molecular pharmacology was beginning to sort out the

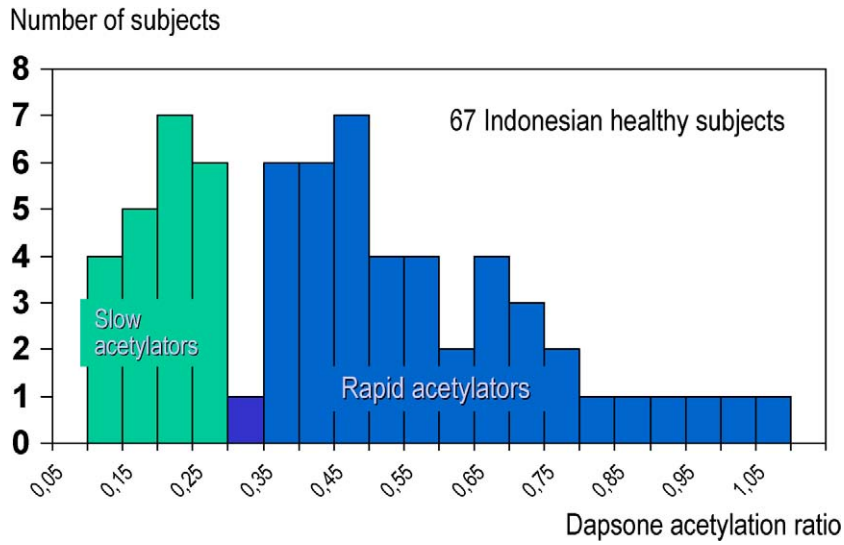


Fig. 19. Distribution of acetylator status among 67 Indonesian healthy subjects (from Santoso, 1983).

many enzyme families which had previously been lumped together as 'mixed function oxidases', found in the microsomes of the smooth endoplasmic reticulum of the liver cytosol. A new naming system for many of these enzymes was introduced at about this time – which always starts with 'CYP' (earlier these enzymes were all classified as 'cytochrome-P450' enzymes from which the 'CYP' comes). The enzyme which hydroxylates debrisoquine was named CYP2D6, and was found to metabolize many other drugs and also to be found in several isoforms – genetically determined differences in enzyme structure conferring differing enzymatic function.

Moreover individuals were found who had multiple copies of the gene (up to 12 copies has been described in one Swedish family), and in these people a substance such as debrisoquine is metabolized so rapidly that virtually no therapeutic effect would be seen, as the hydroxy-metabolite is not pharmacologically active. These variants are inherited, and so it is possible to characterize families by their inherited drug-metabolizing enzymes, and the genes that code for them.

Before this molecular basis for differing response to drugs was understood, ultra-rapid metabolizers would have been thought of as 'non-responders' to the drug – or accused, falsely, of failing to take their medication properly.

When anaesthetics are given it is common practice to give succinylcholine, a depolarizing muscle relaxant with normally a short duration of action. A rare genetic variant is found in some patients who possess a form of butyrylcholinesterase, the metabolizing enzyme, for which succinylcholine has a very low affinity. The consequences are greatly prolonged duration of action of the relaxant. Patients fail to resume spontaneous respiration, and often have to be artificially ventilated, sometimes for days, before the relaxant effect disappears.

More recently the enzyme CYP3A4, which is the most abundant drug-metabolizing enzyme in the liver, has begun to be investigated. It is a major metabolizer of the calcium channel-blocking drug, nifedipine, of the antibiotic erythromycin, of the immuno-suppressant cyclosporin used to treat transplant rejection, and of many other commonly used drugs. CYP3A4 may demonstrate up to a 10-fold difference in enzyme activity between individuals which, again, appears to be genetically determined.

These are just a few of the best known genetic variants that can influence hepatic drug metabolism. By definition, if a drug is pharmacologically active in its own right, these genetic variants will strongly influence the C_p of the drug by influencing its *loss* from the plasma compartment.

There is no other genetic factor, which has a greater effect on drug kinetics than genetically-determined drug metabolism.

III.c. Inter-ethnic Differences

Once genetic polymorphism was recognized it was not long before it was applied to apparent differ-

ences in drug handling between races. However, not all inter-ethnic differences are due to differing metabolism. Not very many years ago a new drug was launched in Australia, and shortly after in South East Asia. The recommended oral starting dose was the same in each locality, but it was not long before patients in South East Asia began to experience adverse effects rarely seen in Australia. First thoughts suggested an ethnic difference in drug metabolism – except that the drug was almost completely excreted unchanged in the urine! The explanation was quite simple. The average Australian weighs around 74 kg and the average South East Asian weighs around 52 kg. The apparent V_d for the drug was directly proportional to the body weight, and so South East Asians were getting the same *input* into a substantially smaller *apparent* V_d with a consequent higher C_p than the Australians.

Inter-ethnic differences in drug metabolism have become a trendy, and often quite exciting, line of enquiry. Results have often been quite surprising. For example:

- Ultra-rapid metabolizers of debrisoquine (see above) are fairly uncommon in many races (1–2% in a Swedish/Caucasian population), but make up 21% of a Saudi Arabian study population, and 29% of a population studied in Ethiopia.
- Alcohol (ethanol) is metabolized initially to acetaldehyde by the enzyme alcohol dehydrogenase. Acetaldehyde is further metabolized by acetaldehyde dehydrogenase. The cumulation of acetaldehyde in the plasma is believed to mediate flushing and gastro-intestinal discomfort, and possibly headaches after alcohol. ('Antabuse', disulfiram, is an inhibitor of acetaldehyde dehydrogenase deliberately given to produce this syndrome as part of the treatment of alcohol abuse.) Caucasian subjects are rarely deficient in acetaldehyde dehydrogenase, but deficiency is common in some oriental populations. This has been suggested to be associated with their low rates of alcohol-dependence.
- A variety of ethnic differences have been described in CYP2D6 function. The metabolic ratio – debrisoquine/4-hydroxydebrisoquine ratio in the urine – for a Chinese population was substantially higher than that in a Swedish comparator group – on average the Chinese are poorer metabolizers of debrisoquine than the Swedes – and there is no clear separation between normal and poor metabolizers, i.e., there do not appear to be two separate populations based on genetic polymorphism.

These are a few illustrations of the emerging pattern of inter-ethnic differences in drug metabolism, which is genetically determined.

Pharmacogenetics is the branch of pharmacology/genetics, which studies these differences and seeks to account for them in molecular genetic terms.

III.d. Environmental Factors

For a fuller treatment of food–drug and drug–drug interactions, see Chapter 15.

While genetic differences between people or races are important, relatively rapid changes in the way drugs are handled by individuals are commonly the result of factors in the environment. A major 'environment' for drug molecules is the food we eat.

III.d.1. Food–Drug Interactions

We have already met several of the important concepts in this topic, so now it is time to round them up and bring out the major principles. In the first place drug molecules clearly might interact with food molecules in the lumen of the gut. Perhaps the best-known example of this is the interaction between the tetracyclines and dietary calcium and iron. The binding, which occurs between them, produces a chelate, which is not particularly lipid-soluble, and therefore the overall absorption of tetracycline may be reduced to the point where plasma levels do not achieve effective antibiotic concentrations. The commonest dietary constituent to produce this binding is milk with its high calcium content. Tetracycline ingestion should be separated from food as far as possible.

Perhaps the most important effect of mixing drugs and food in the stomach is the prolongation of gastric emptying time produced by food. If we think about the time taken for drug molecules to achieve their C_{max} it is obvious that gastric emptying is the major component among several others. Swallowing takes only a few seconds, tablet dissolution some minutes, absorption through the intestine and passage through the liver (except with a slow-release preparation) quite quick at around a few minutes. Gastric emptying is the only component of the *input* processes that can take up to 2–3 hours. It is usually a fairly constant time for any one individual, although the nature of the food in the stomach may shorten or prolong (fatty meals especially) gastric emptying.

Some drugs slow down the rate of gastric emptying to a great extent. Most of them have actions

which are anti-cholinergic (oppose the actions of acetylcholine, one of the endogenous mediators of increased motility), and cause gastric stasis. They include the tricyclic anti-depressants and the phenothiazines such as chlorpromazine. If a patient accidentally or deliberately takes an overdose of one of these drugs, and gets to hospital several hours later, you might be tempted to think that it might be too late to pass a gastric tube and aspirate any tablets. Most often there are still residual tablets – or at least dissolved drug – in the stomach because it has not emptied completely.

Taking drugs with food may not influence the overall uptake and passage into the plasma (the oral bioavailability), but often reduces the C_{max} and increases the time to peak plasma concentration, the T_{max}. If you are looking for a rapid effect, for example from an analgesic, it is usually best to take it either one hour before or up to three hours after a meal.

There are occasional anomalies to the rule that food reduces and delays peak plasma concentration. The anti-fungal drug, griseofulvin, has enhanced absorption if taken with a meal – possibly because it becomes emulsified by bile salts and passes more readily into the lymphatic drainage of the gut which bypasses the liver, entering the venous system directly. The immuno-suppressant cyclosporin, and calcium salts in general, show a similar increase in absorption when taken with a fatty meal.

At the level of the small intestine we have already encountered the case of the amino-acid L-dopa, which has to compete with dietary amino-acids for uptake through an active transporter system in the intestinal wall.

Finally, ingested foods can have an effect on the enzymes that metabolize drugs. Grapefruit juice (probable responsible constituent naringin) has a rapid – after one glass of juice – inhibitory effect on several of the Phase I oxidative enzymes. CYP3A4 in the intestinal wall in particular is inhibited, and drugs which are normally partly metabolized there become more bio-available (*input* increases). In one experiment, the area under the curve of oral felodipine, a calcium channel-blocking drug of the dihydropyridine class, was increased by over 200% after grapefruit juice and, reflecting this, both blood pressure and pulse rate fell to a greater extent than without the grapefruit juice. The same observation has also been made with other dihydropyridines such as nifedipine, or nisoldipine.

Cyclosporine, the immuno-suppressant, had its C_p increased by 300% after grapefruit juice, with the same oral dose (and no evidence of reduction in *loss* or *distribution volume*).

An even more important interaction with grapefruit juice involved the now withdrawn anti-histamine terfenadine. It too is metabolized in the gut wall, predominantly by CYP3A4 enzymes, and into a pharmacologically active metabolite – fexofenadine. However, the parent drug at high C_p is cardiotoxic, producing a prolonged QT interval on the electrocardiogram, and provoking serious cardiac arrhythmias, and on occasion sudden death. Inhibition of terfenadine metabolism by grapefruit juice is believed to have lead to the death of a 29 year old man who had taken just 2 glasses of grapefruit juice on the day he died.

Less potentially serious efforts may be produced by vegetables of the brassica family (cabbage, sprouts, spinach) which increase the activity of some oxidative enzymes, and possibly of conjugating (Phase II) enzymes also, leading to lowered C_p of some analgesics – notably paracetamol.

One other impact of food on enzyme activity is that of charcoal-broiled meats, and also of some constituents of cigarette smoke which enhance the activity of another member of the large cytochrome family of enzymes, the CYP1A sub-family. Enzymes of this group are capable of activating a range of possible carcinogens, and it has been suggested that there is a link between this activation and some human cancers, although the evidence is not yet conclusive.

It is quite wrong therefore to think of food as an inert player in the drug kinetics game. The defensive mechanisms of the gut we considered in Section I have evolved to deal with exogenous chemicals from the environment. Food and drugs are merely two forms of exogenous chemical, and it is not surprising that they may interact at times as the body's defences do not distinguish between them.

III.d.2. Drug–Drug Interactions

By now you will be comfortable with the idea that the body treats drugs as just another set of chemicals to cope with, and also the idea that drugs interact with many molecules in many sites – with gastric acid, with chemicals in food, with enzymes in the gut and others in the gut wall and liver, with plasma proteins in the blood, and (often transiently) with their tissue receptor once they have got that far.

It therefore should not come as a surprise that drugs may interact with other drugs in many different ways. Although drugs may interact positively with other drugs to potentiate their action, it is adverse drug interactions that always steal the headlines – perhaps because some of them have dramatic endpoints.

Many studies on hospital patients have documented the risk and the actual occurrence of adverse drug interactions. Those articles which concentrate on the *potential* of drugs to interact (as judged from the treatment chart) always report a much higher potential for interaction than those that assess *actual* clinical events. Nevertheless it has been known for many years that patients, particularly the elderly who take multiple drugs for multiple conditions, have a much higher rate of adverse drug response than a comparable group taking only one or two different drugs each day. It is probable that a substantial proportion of these are drug–drug interactions. The elderly, of course, are more prone to manifest adverse drug responses because of their declining renal, and to a lesser extent hepatic, function.

> An Australian local study conducted by medical students measured the number of different drugs being taken by patients aged 65 years or more, at the point of admission to a teaching hospital, for an acute medical condition. The average number of different drugs was 6.4 per patient. The students then followed the patients through their hospital stay when the drug regimen was reviewed and amended. At discharge the average number of drugs per patients was ... 6.4, but they were a different set of drugs from those taken on admission! There seems to be two possible morals from this story. In the first place doctors are good at starting drugs, but not so good at stopping them, and secondly, as the populations of both developed and developing countries age, there will be increasing numbers taking multiple drugs for multiple, valid reasons. It is particularly among them that great care should be taken in choosing drugs and especially in monitoring their effect, and ensuring that adverse drug interactions do not occur, or are detected early before catastrophic events occur.

With the expanding availability of medications there is an increasing risk of interactions. Even simple Essential Drugs Lists usually contain 200–300 preparations, and the more generous list of Government-subsidized drugs in Australia numbers over 500 separate chemical entities (admittedly, in the context of over 10,000 that are registered for import and sale).

Studies of doctors' prescribing show that the majority of experienced practitioners prescribe from their own unwritten 'limited list' or 'personal formulary', which usually contains no more than 50 drugs and seldom exceeds 70. Prescribing in a controlled way gives doctors confidence in handling their own 'limited list', and obliges them to be aware of fewer potential interactions than if they prescribe widely using a big range of all the available drugs.

Drug may interact with drug to alter the pharmacological effect by an action on the effector site – a dynamic interaction such as the potentiation of alcohol-induced drowsiness by a sedating antihistamine. However, this chapter is about drug kinetics, and the interactions we need to understand are those altering the rates of *input* to, or *loss* from, the plasma compartment, or the *volume* in which drugs are distributed, i.e., those factors which affect the C_p of the primary drug and therefore its effect.

Logically these interactions can be grouped according to the site at which they occur. Prominence will be given to interactions that commonly cause clinical events.

III.d.3. Interactions Affecting Input into the Plasma Compartment

III.d.3.1. Interactions involving drug absorption. Drugs may bind to other drugs in the gut. We have already met the iron/calcium interaction with tetracyclines, which reduces the absorption of the antibiotic.

Other drug molecules may do similar but less specific things. Cholestyramine, may bind drugs given at, or near, its time of administration – the two best documented interactions are with the anti-coagulant warfarin, and the anti-arrhythmic drug, digoxin. The result is a reduction in *input* and a loss of pharmacological effect.

The very poorly absorbed aminoglycoside, neomycin, may also induce a malabsorption state which can include other drugs such as oral penicillins.

Drugs which alter gastric pH (H_2-blockers such as ranitidine, proton-pump inhibitors such as omeprazole) theoretically should alter the ionization of polar compounds, i.e., those capable of dissociation in the physiological pH range. This in turn should alter the fraction absorbed. However, while

the mechanism undoubtedly exists, the clinical consequences are few.

Changes in gastric emptying induced by drugs, as with food, tend to alter the C_{max} or T_{max} without affecting the overall bioavailability. The anti-emetic metoclopramide accelerates gastric emptying, and is used in this way to speed radiological examination of the gastrointestinal tract. As most drug absorption occurs in the upper small intestine it is not surprising that metoclopramide may increase C_{max} and reduce T_{max}. However, the total drug (paracetamol in one experiment) absorbed is usually not significantly altered.

III.d.3.2. Interactions involving metabolism. This means metabolism which may occur in the gut wall or in the liver. Several drugs inhibit CYP3A4 in the gut wall, including erythromycin, the anti-fungals miconazole and ketoconazole, and the H_2 receptor-blocking drug cimetidine. There is an enormous list of compounds which are metabolized by this enzyme. Some of them are not uniquely metabolized by it, and for them there are 'escape' alternative pathways for metabolism. But significant clinical events have occurred when inhibitors have been given with cyclosporine (ketaconazole, often used in transplant patients, increases cyclosporine *input*), the calcium channel-blocking drugs nifedipine, and felodipine (increased *input*, enhanced reduction of blood pressure).

A different and opposite activity to drug enzyme inhibition is the process of enzyme induction. This simply means that when some drug metabolizing enzymes are exposed to drug substrate their amount increases.

Enzyme induction occurs with a wide range of drugs. Rifampicin, used widely for the treatment of tuberculosis, can induce the metabolizing enyzmes CYP2C9 and CYP3A4, and so (in contrast to ketoconazole which inhibits CYP3A4) produce more rapid metabolism of, for example, cyclosporine, and reduce its effect. Whether this is viewed as reduced *input* (if the relevant CYP3A4 is in the intestinal wall), or increased *loss* as blood recirculates through the liver which also contains CYP3A4, makes little difference to the observable fact that plasma concentrations of cyclosporine fall.

Rifampicin, the anti-convulsants phenytoin, phenobarbitone and carbamazepine, and the steroid dexamethasone, are amongst the best recognized inducers of enzyme function, and their action nearly always leads to a fall in the C_p of the interacting drug. This is usually a cause of reduced activity except in the one case where the parent drug is not the active species. In this event, enzyme induction may increase activity by increasing the rate of metabolism of the parent drug to active metabolite.

III.d.3.3. Interactions affecting the apparent V_d. At one stage in the development of modern kinetic understanding it was believed that displacement of one drug from its binding site on plasma proteins by another with greater affinity was a common interaction which explained many clinical events. Much of this belief came from experiments in the laboratory where it was easy to demonstrate such displacement. Unfortunately, isolated solutions of plasma proteins do not tell the full story, for, in the body, a rising free fraction of a drug is usually matched by enhanced clearance and the re-establishment of a new steady state.

Diuretics which reduce plasma volume may lead to increased C_p of drugs distributed mainly to the plasma compartment such as aminoglycosides.

III.d.4. Interactions Affecting Loss from the Plasma Compartment

III.d.4.1. Interactions in the kidney. Many drugs which are cleared by the kidney appear in the glomerular filtrate, and may also be actively secreted by the cells of the proximal tubule. This particularly applies to weak acids such as the penicillins, and some cephalosporins. This means that the renal clearance of these drugs will normally exceed glomerular filtration rate – indeed up to 70% of penicillin clearance is attributable to this tubular mechanism. For years it has been known that probenecid (a drug used to increase renal uric acid clearance in gout) will compete with penicillin at this site to reduce its *loss*. This can be turned to good use if we want to maintain high penicillin C_p for long periods – particularly if the patient is old and thin, or a child, and the penicillin needed has to be given by injection, e.g., benzyl penicillin for endocarditis or osteomyelitis. Patients can be spared frequent large injections by giving probenecid to maintain high C_p of penicillin.

As you might expect, the converse occurs, and the renal elimination of methotrexate, an anti-folate drug used to treat some malignancies as well as, recently, rheumatoid disease and florid psoriasis, may

be blocked by salicylates and some of the non-steroidal anti-inflammatory drugs. This interaction has provoked methotrexate toxicity. In clinical practice, a big overdose of aspirin may be fatal and needs rapid action – enhancing renal elimination may help. Once undissociated salicylate crosses into the renal tubular lumen on its way through the kidney it can do one of two things. If it remains undissociated it may simply diffuse back through the tubular cells and into the blood, or, if dissociated it may be much more difficult for it to diffuse back and it is more likely that it will pass out of the body in the urine. So the therapeutic "trick" is to create an environment which will favour dissociation and thereby trap the salicylate in the renal tubule. This can be done by giving bicarbonate solution intravenously to raise the urinary pH. It is a valuable strategy which also works for poisoning with other weak acids such phenobarbitone – barbiturates are all derivatives of barbituric acid.

III.d.4.2. Interactions with biliary and gut excretion. Combined oral contraceptives contain both oestrogen and progestogen. The bioavailability of the oestrogen varies widely from subject to subject, and the low-dose preparations sometimes demonstrate how relatively low the C_p is when women experience breakthrough bleeding. Oestrogens are metabolized in the liver, and the Phase I reaction can be accelerated by enzyme induction, for example by phenytoin. Oestrogen is also largely eliminated in the bile as conjugated products. Bacteria in the gut possess enzymes (beta-glucuronidase in particular) which break down these products, releasing free oestrogen which is reabsorbed and contributes to the total plasma concentration. The importance of this recycling is not very great if plasma oestrogen concentrations are well within the range to suppress ovulation. In other cases, however, the recycled oestrogen may be critical to maintain contraception.

In some well-documented cases given oral antibiotics, contraception has failed – presumably because gut bacteria have been killed and the recycled component of oestrogen lost with a consequent fall in plasma oestrogen. It *is* possible to be 'pregnant on the pill' in this case!

III.d.5. Drug Interactions with Herbal and Traditional Medicines

Attitudes to herbal and traditional remedies in developed countries are divided between unjustified scepticism on the part of some health professionals – after all many of our present-day drugs came from plant sources – to those with the mind-set that anything that is natural must be both good and safe – equally untrue as some of the most poisonous chemicals are found within plants. Developing countries have a much more balanced approach, depending as they do on traditional remedies for much primary health care and recognizing that many useful herbal products also have toxic potential.

Research groups are developing in many countries to examine the safety and efficacy of, and produce the evidence surrounding claims for, traditional medicines and most of these maintain an open mind about safety and efficacy until the evidence is sufficient to permit a judgement.

Those who have worked through earlier parts of this chapter will have no difficulty in predicting that the body is likely to treat chemicals from plant sources as just one more set of chemical invaders that should be handled in exactly the same way as foods and Western-style medicinal drugs.

Many patients (67% in one recent survey) in Australia take herbal remedies. Most do not declare these if they are admitted to hospital. The recent story of one herbal preparation reinforces the need to look carefully at possible interactions between preparations from the pharmaceutical and herbal industries.

St John's Wort (Hypericum perforatum, SJW) has been on the herbal pharmacopeia for many years. It is a traditional remedy for depression which has been validated in recent randomized clinical trials. Like many herbal preparations levels of active constituents vary from one preparation to another. As a consequence of its validation as an active preparation it has been widely promoted. Recently it has been shown to interact with a variety of other substances probably through the process of drug interaction.

Two molecular mechanisms for the interactions have been established. First, both hypericin and hyperforin, two of the pharmacologically active constituents of the herb, cause induction of the enzyme CYP3A4 which is responsible for much of the metabolism of many commonly used drugs. Giving SJW to patients also taking the immunosuppressant, cyclosporine, which is metabolized primarily by CYP3A4, has led to near-rejection of transplanted organs as cyclosporine plasma concentrations fell due to increased metabolism. The same mechanism has led to reduced efficacy of indinavir in patients

with HIV/AIDS as indinavir is also metabolized by CYP3A4.

The second mechanism is through induction of the membrane transporter protein, P-glycoprotein (PGP). This is one of the "super-family" of membrane proteins (the ATP-binding cassette (ABC-) transporters) which translocates substrates across many extra- and intra-cellular membranes. PGP was found to be important in cancer chemotherapy as its concentration may be increased by some anti-cancer drugs. This may cause the cancer cells to increase the rate of transport of the drugs out of the cells, reduce their effective concentration and render the cells resistant to treatment. For this reason PGP was originally called Multiple Drug Resistance protein although there is a wide range of drugs which it pumps out of cells and it is found in many places other than malignant cells, including the intestinal wall and the blood–brain barrier. SJW increases the concentration of PGP in intestinal cells which enhances the transport of some drugs back into the intestinal lumen. Reduced absorption and effect of digoxin have resulted from interaction with PGP in patients also taking SJW. A further interaction may occur with warfarin (metabolised by CYP2C9) and possibly with theophylline.

Perhaps the most important biological concept these interactions demonstrate is that many of our defence mechanisms against ingested chemicals are not static but may be enhanced (usually by induction of new enzyme or transporter molecules) or inhibited by either the primary drug being used for a medical condition or by another drug being used at the same time for another co-existing condition.

III.e. Kinetics in Disease

While a lot of basic kinetic research has been done in normal human volunteers (because the conditions of the experiments can be standardized in them and it is also ethical to take, with consent, the multiple blood samples needed), the practical purpose of drug kinetics is to improve our ability to treat patients and we cannot assume that drug kinetics will remain the same when someone is ill. Many research reports and reviews have been written about changing kinetics in disease and what follows is only a brief summary.

Intuitively it would seem likely that drug kinetics would be influenced most by diseases of those organs most concerned with absorption, metabolism and excretion. While this is true, diseases of the distribution system – the heart and blood vessels – can lead to profound changes in a drug's access to its target site or its excretory mechanism.

> A dramatic and sad example of this occurred in one of last century's many wars. United States troops serving in Korea were often badly wounded. They would be treated at a fieldpost – often with intramuscular morphine. They often required more morphine for their pain on the way to the next hospital and, if they had to make a further transfer to the base hospital yet more analgesic might be given – sometimes because of the apparent lack of effect of the earlier doses. At the base hospital, resuscitation was instituted and, to the surprise of many doctors, these young men began to show signs of morphine poisoning. Some died before it was recognized what was happening. In retrospect, the reason for this is not all that obscure. Most of the soldiers were in hypovolaemic shock with low blood pressure, low blood volume, and as part of the shock syndrome, systemic circulation was minimal with intense vasoconstriction – hence the poor therapeutic effect. The repeated doses of morphine were usually given intramuscularly into the buttock or thigh but their clearance into the systemic circulation was minimal until resuscitation occurred and the peripheral circulation was restored. Blood flow to the muscle increased and all the morphine injected became available – all at once. This was the reason for the morphine overdoses and the occasional death. Thereafter it has become standard practice to give morphine in emergency directly into the veins and not into poorly perfused muscles.

III.e.1. Diseases of the Gastrointestinal Tract

Drugs continue to be absorbed after even the most major resections of the stomach – C_{max} may be higher and T_{max} earlier if gastric contents move more rapidly into the upper small intestine. The intestine itself has enormous redundancy – i.e., there is far more than is actually needed – and disease, including moderate forms of malabsorption, such as coeliac disease, make relatively little impact although salts of iron and folic acid are often transported poorly and deficiencies may occur.

Exocrine pancreatic function leads to a lower pH in the intestine and some drug formulations designed to release their contents into the intestine may fail to do so.

Vomiting and diarrhea from any cause will obviously alter the likelihood of any medication being absorbed. In migraine even before the attack is fully developed and before vomiting has occurred, gastric stasis exists. Taking a prophylactic dose of aspirin or paracetamol is unlikely to be effective if it does not pass the pylorus. Suppository forms of e.g., ergotamine, have been developed to permit self medication early in the attack.

Obesity is not exactly a gastrointestinal disease but is a condition characterized by an unusually high percentage of body fat – normally 15–18% in males and 20–26% in young females. Definitions vary but obesity is commonly defined as having more than 30% of total body weight composed of fat.

Minor obesity is not associated with altered drug kinetics but moderate to severe is. Obesity is not associated with altered absorption or bioavailabilty for those drugs which have been studied. As might be expected the major impact of obesity is found in the distribution of highly lipid-soluble drugs. Fat acts as a reservoir for drugs which readily dissolve in it. Benzodiazepines, thiopentone (the induction anaesthetic agent), the calcium-channel blocking drug verapamil and lignocaine all have much higher volumes of distribution in obesity than do less lipid-soluble compounds like the aminoglycoside antibiotics and the non-steroidal anti-inflammatory drug, ibuprofen.

This increase in V_d has an impact on the loading dose of some antibiotics (cefotaxime, vancomycin), of lignocaine (for which a doubling of the total body weight from 69 to 124 kg is associated with nearly a two-fold rise in V_d from 186 to 325 l) but has little or no effect on loading doses of theophylline. All of these compounds may be given in urgent situations by the intravenous route and so knowledge of their apparent V_d is important in determining the safe and effective loading dose.

Drug half-life depends on both the total drug clearance and the volume in which the drug appears to be distributed – $T_{1/2} = V_d \times 0.693/CL$ – for most drugs that have been studied in obesity drug clearance tends to be the same or slightly increased. V_d, by contrast, is often substantially greater and therefore measured drug half-life is greater. In simple terms, there is a much bigger volume from which to eliminate the drug and it takes longer.

Rates of hepatic enzyme processes are either unchanged or slightly increased in obesity. Phase I oxidative processes and conjugation to glucuronides – Phase II – are commonly enhanced and account for some of the observed increases in overall systemic drug clearance.

The other important factor in drug clearance is that obese subjects in general have a higher glomerular filtration rate than non-obese subjects and clearance rates of some drugs handled by glomerular filtration such as the aminoglycosides and vancomycin are consistently higher in obese individuals.

From a practical point of view very obese people require careful assessment before giving them a loading dose of a drug with a narrow therapeutic ratio (the ratio between the effective and the toxic dose) such as gentamicin, lignocaine or theophylline, and careful monitoring of the effects of such drugs either clinically or, if available, by therapeutic drug monitoring.

III.e.2. Heart Failure

This condition commonly shows a low cardiac output and organ congestion – of the lungs, liver and gastrointestinal tract in particular. Reduced perfusion of gut, liver and kidney can alter drug handling in heart failure but unfortunately there is no simple rule that fits all drugs.

Gut oedema can reduce drug bioavailability, increasing T_{max} and reducing C_{max}. If the response to oral drug is less than would have been expected or absent altogether, consider this explanation and, if appropriate and necessary, change to a parenteral preparation.

Metabolism of drug during the "first-pass" through the liver may be reduced if its extraction depends on blood flow as hepatic blood flow is characteristically low in heart failure. This mechanism leads to a higher C_p of drugs in this group (e.g., lignocaine, an example discussed earlier in the chapter).

Microsomal enzyme function may also be depressed in heart failure and hepatic drug clearance reduced leading to elevated C_p of drugs cleared in this way.

Renal clearance is usually decreased. Renal blood flow in particular is often poised critically and the use of, for example, a non-steroidal anti-inflammatory drug may cause heart failure and/or renal failure in people with existing cardiac conditions or some pre-existing degree of chronic renal failure. These non-selective inhibitors of the cyclo-oxygenase enzyme

reduce the production of vasodilator prostaglandins in the kidney which are critical to the maintenance of renal perfusion. Theoretically cyclo-oxygenase 2 inhibiting drugs such as celecoxib (and rofecoxib) might have been expected to spare renal prostaglandin production and therefore not be associated with renal impairment. A meta-analysis of 114 randomised trials published in 2006 suggests that celecoxib does not have a deleterious effect on renal function when used in conventional doses whereas rofecoxib (a drug which has appeared and then been withdrawn since the last edition of this book!) was associated with a dose-dependent reduction in renal function (see Zhang et al., 2006).

III.e.3. Hepatic and Renal Disorders

III.e.3.1. Hepatic disease. The liver, like the gut, has enormous redundancy and up to 80% of the organ can be removed without affecting many of its functions including most of the metabolic processes involved in the metabolism of drugs.

In end-stage liver cirrhosis, the major impact on drug kinetics is on the first-pass clearance of drugs that normally have extensive extraction as they pass from the intestine to the circulation. In cirrhosis, there is commonly the development of vascular shunts between the portal and the systemic circulation (this is thought to be one of the reasons for portal-systemic encephalopathy – the non-extraction of toxins which normally would be cleared by the hepatic parenchymal cells) and this allows drugs to by-pass the liver and get into the circulation unmodified. For drugs that are active in their own right this means an increase in plasma concentration and effect. For drugs that need to be metabolized to an active metabolite (pro-drugs) this will mean a reduction in plasma concentration As examples, the oral bioavailability of labetalol, an antihypertensive drug is doubled, in hepatic cirrhosis, as is that of pethidine, the potent analgesic. A similar effect is seen with morphine and the beta-blocking drug propranolol. Thus the enhanced effect of these compounds in patients with cirrhosis is not, as might be expected, due to a reduction in metabolism but rather an increase in oral bioavailability.

If a patient with liver disease also has ascites and oedema, the V_d of some drugs may be increased and biliary obstruction may impair the excretion of drugs cleared through the bile.

III.e.3.2. Renal disease. This produces some predictable effects and some which have surprised clinicians until their mechanisms became clear.

The example of morphine is perhaps the most surprising. Less than 10% of morphine is excreted unchanged in the urine, and so would not be expected to be affected by renal failure. However, the clinical observation is that patients with severe renal disease respond to morphine as though it were cleared through the kidney! The explanation is quite straightforward. Morphine is metabolized extensively to two glucuronides. Morphine-6-glucuronide is pharmacologically active and accumulates when water soluble drug excretion is impaired. Morphine-3-glucuronide, by contrast, does not have an analgesic effect but can produce a strange syndrome of restlessness and anxiety. Both of the metabolites are readily soluble in water and therefore their plasma concentration rises in renal failure. Which one dominates the clinical picture depends on their relative concentrations but, if it is the 6-glucuronide, a condition resembling morphine overdose may be produced.

A similar toxic outcome can occur with pethidine in renal impairment – again not mediated through the parent drug but through a more water-soluble metabolite, nor-pethidine, which has pro-convulsant properties and may produce fits.

It is therefore important not to lose sight of the fact that many lipid-soluble drugs are metabolized to water-soluble products, which may be pharmacologically active in their own right.

More easily predictable effects occur with drugs with a low therapeutic ratio which are excreted to a major extent through the kidney. These include the drugs we encountered as potential hazards for the elderly (as the dominant kinetic difference in the aged is the loss of renal function). Thus, digoxin, lithium and gentamicin are all drugs that need to be monitored carefully in renal disease. The penicillin and cephalosporin antibiotics are also affected by this excretory impairment but their therapeutic ratio is much greater and they are unlikely to produce clinical adverse effects as a result of cumulation.

Changes in drug absorption are variably reported as diminished (particularly if the patient had been receiving aluminium salts by mouth to reduce the elevated plasma phosphate found in renal failure) or increased and the V_d of some compounds is increased. These appear to be relatively unimportant compared to the loss of excretory capacity.

However, in patients with renal failure there is a strange and currently unexplained observation in relation to non-renal clearance. If this is measured for some compounds it also is found to be depressed even though it is the kidney that is diseased and not the liver! The picture becomes a little clearer if the same non-renal (presumed hepatic) clearance is measured again in patients after renal dialysis when the hepatic clearance has been found to have risen to control values. Recent animal experiments have demonstrated that the circulating inhibitor of hepatic cytochrome P450 may be parathyroid hormone. Parathyroidectomy of rats with chronic renal failure prevented the reduction in liver cytochrome activity (see Michaud et al., 2006).

III.e.3.3. Assessing renal function. It is not practical to expect that, renal function – glomerular filtration rate in particular – will commonly measured by sophisticated methods and a simpler way of assessing it must be used. Many different formulae have been used for this purpose but perhaps the most useful is that devised by Cockcroft and Gault which requires knowledge of the patient's age, weight and sex together with the serum creatinine. The estimated creatinine clearance is given by the formula below:

Creatinine clearance (ml/min) = (140 − age) × (weight (kg))/(72 × serum creatinine (mg/dl)); for women the result is multiplied by 0.85.

As many tables of drug doses in renal failure given in reference books are related to the creatinine clearance, this gives a practical and useful measure to be used in the hospital or clinic.

In general in renal failure therefore the doses of commonly given drugs may need only to be reduced by a small amount as the V_d in which they will be distributed is little affected by the disease. However the dose *frequency* of renally-cleared drugs will need to be reduced. A common example is that of gentamicin, which can be given in a similar loading dose but whose C_p will fall much more slowly than in someone with normal renal function. Gentamicin is commonly dosed at 8-hourly intervals in patients with normal renal function (although increasingly the tendency is to give once daily doses that have been shown to be equally efficacious) but perhaps only once a day or less frequently if renal function is severely impaired.

Although this is a good example of the difference disease makes to drug kinetics, there is a very good argument – in any country in which plasma concentrations of gentamicin cannot be measured reliably or frequently – for *not* using this aminoglycoside at all in renal disease but selecting an alternative. The argument often hinges on cost. Gentamicin is cheap and widely available while alternatives are usually very expensive. The counter argument is that the cost of gentamicin must also take into account the cost of laboratory monitoring and when this is done the alternative antibiotic may not look all that expensive after all.

Finally, in countries where is it available, renal dialysis presents other challenges as many drugs are lost from the body in the course of peritoneal or haemodialysis.

For those who like the ability to calculate things for themselves, it is relatively easy to predict how much drug is lost in dialysis – the dialysis is effectively another clearance mechanism which operates alongside whatever remaining clearance the patient has for the drug in question. From the equations we have used it follows that

$$T_{1/2} = \frac{0.693 \times V_d}{CL}.$$

If it is possible to measure the $T_{1/2}$ of the drug in question during the period that the patient is hooked up to the dialysis machine, to estimate the V_d for that substance (and the existing intrinsic clearance has been measured during the non-dialysis period – from a similar exercise of repeated plasma concentration measurement), then it is possible to work out how much drug is being lost through the dialysis process itself. Even in the more sophisticated centres of the developed world this would be a heroic exercise and would seldom be done unless a fervent pharmacokineticist was a member of the ward team.

In summary, then, there are many factors which may have an impact on the way drug kinetics perform in any individual. Age, genetic make-up, racial background, interactions with food, other drugs and even herbal medicines may all play a part. In the even more complex arena of single or multiple diseases it may all become very difficult to unravel. It is really quite surprising that only about 20% of any patient population will require to receive a different regimen from that contained in the Standard Treatment Guidelines. Being aware of all these possibilities should make us much more cautious prescribers who take care to monitor closely the effect of the drugs we give in these varied circumstances.

III.f. The New Biopharmaceuticals and Their Kinetics

After fifty years the promise anticipated when the molecular structure of DNA was described in 1955 is finally resulting in the production of many new medicines from recombinant DNA technology. In 2003, the US Food and Drug Administration, for the first time, licensed more new products produced by biotechnology than by conventional chemical synthesis or modification. Almost all the products now available (currently at a price which makes them prohibitive for less well-resourced countries) are proteins or related molecules and they have led to advances in the provision of coagulation factors (factors VIII and IX), hormones (human growth hormone, human insulin), interferons, vaccines, growth factors (haemopoietin), thrombolytic drugs (alteplase, tenecteplase) and monoclonal antibodies directed against particular cellular targets (rituximab which induces death of malignant B lymphocytes in lymphoma, or infliximab which acts as an antibody to tumour necrosis factor and is increasingly used in rheumatoid arthritis and other arthropathies. Note the ending "mab" to the approved name of a medicine indicates it is a **m**onoclonal-**a**nti**b**ody). These new medicines have several differences from the conventional low-molecular weight substances which we have concentrated on in this chapter.

The first difference is their size. As protein macromolecules they have molecular weights exceeding 1000 daltons (Da) – some as high as 250 kDa. Remember the criteria for medicines to cross biological membranes and you will realise that proteins are likely to have big problems in getting to their effector site unless there is some form of transport mechanism that can take them across cell membranes.

Secondly, as proteins they are vulnerable to digestion in the gut and therefore have to be given by either subcutaneous or intravenous injection – insulin is a prime example (see Section I.b.2).

Third, they can act as antigens and generate an immune response which may result in a lower effective concentration of the protein at its effector site (because some of it is bound to the antibody) or occasionally in a clinical allergic syndrome – most particularly if the protein has been derived in whole or in part from non-human DNA (mouse DNA is incorporated with human in some production systems and this tends to produce more common immunological responses than proteins which come from pure human DNA).

Fourth, they are difficult to measure in body fluids. There are very precise ways of measuring very small quantities, in plasma or urine, of almost all conventional medicines and this has made it possible to make the kinetic measurements we have been considering earlier. Some of the techniques for the big protein medicines are not as reliable. For example, one way of tracing a big molecule's progress through the body is to label it with a radioactive tracer. Biopharmaceuticals can be labelled with, for example, radio-iodine (Iodine-125) which can be counted in samples of plasma or urine. However as proteins are similar or identical to normal proteins they can be metabolised and the label can become part of a metabolite or another breakdown product. Counting the iodine radioactivity in this case will not be measuring the parent molecule alone.

Fifth, there are often additional clearance mechanisms for protein medicines which are more important than the renal and hepatic routes we have been considering. Two examples will illustrate this.

- Filgrastim is a recombinant form of the natural granulocyte colony-stimulating factor (G-CSF). It is used in many oncology units to prevent the reduction in circulating neutrophils, after cancer chemotherapy, and thus protect patients from infection. It is partly excreted by the kidney but the predominant way in which it is cleared is by neutrophils themselves. In being taken up into the site where it acts it is also taken out of the circulation. As the patient improves so the clearance increases. This is a direct result of the increase in mass of the white-cell population resulting from the action of G-CSF.
- Recombinant erythropoietin, a hormone normally secreted by the kidney, which stimulates the production of red blood corpuscles, also shows interesting clearance mechanisms. Arguing from the G-CSF case you might guess that it will be taken up by the cells of the bone marrow which is its site of action. This is the case, and up to half of the clearance of erythropoietin is through the marrow itself.

Finally, the kinetics of recombinant proteins can be modified by complexing them with other big molecules such as polyethylene glycol (PEG), an inert substance which confers different properties on the molecule making it less easy to stick to endothelial cells, more difficult to pass out of the blood

and, probably, less immunogenic. This is so common a modification that the medicines treated this way can be recognised from the PEG prefix to the approved name. Filgrastim has a pegylated version which shows very different kinetics from the non-pegylated form – most especially a much longer elimination phase which allows patients to have a single injection in a day and still maintain the recovery of their neutrophils count.

This is a rapidly evolving area of research and will undoubtedly become both more important as a form of pharmacotherapy and also more precise as measurement techniques are improved.

IV. HOW DO CLINICAL PHARMACOKINETICS HELP US TO TREAT PATIENTS?

IV.a. Calculating 'Loading' Doses

You are called to the Emergency Department where a known epileptic is having recurrent grand mal seizures. A friend, who has come with him, says he knows he has not taken any of his anti-convulsant medication for at least a week, as he has been travelling and he had left the drugs behind.

The Senior Resident comes to your aid. "What does he usually take?" You have found out that phenytoin is his regular drug. "If he has been off his medication for a week, that's more than 5 half-lives ($T_{1/2}$ phenytoin = 24 hours), and he'll have none on board. You'd better give him a loading dose intravenously" ... and off goes the Resident.

How do you decide how much to give? In this instance, firstly, as with all prescribing decisions, you need to be sure what you are aiming to do. Your aim is to raise the plasma concentration of phenytoin from zero to somewhere in the therapeutic plasma concentration range. This range has been well established, and, when you look it up, you find it is between 10–20 mg/l – let's say you set your target midway between these points, at 15 mg/l.

How can you calculate the dose to achieve this concentration? Remember the experiments above in which an apparent volume of distribution of a drug was calculated by giving a known amount intravenously (i.e., 100% bioavailability), and measuring the plasma concentration at various time points afterwards (Fig. 6).

When you did this, and extrapolated the curve back to zero you obtained a measure of the plasma concentration that would have been achieved if instantaneous mixing had occurred (C_p0). If you had given 100 mg of drug, and C_p0 was 4 mg/l it would appear that the drug had been diluted in 100/4 l, i.e., the apparent volume of distribution of the drug was 25 liters. The simple equation is,

$$\text{Apparent volume of distribution} = \frac{\text{Dose}}{\text{Plasma concentration at time 0 } (C_p0)}.$$

Now, let us use this relationship to work out the dose for our patient. We will rearrange the equation to read (by bringing the Dose across to the left-hand side and the V_d to the right-hand side):

$$\text{Dose} = \text{Apparent volume of distribution} \times C_p0.$$

We know that the C_p we want is 15 mg/l. How do we find the volume of distribution? Many pharmacology texts give important volumes of distribution for key drugs (see for example Appendix II, in Brunton et al., editors, 2005). These are average data but are quite adequate for our purpose.

Phenytoin has an apparent V_d of 0.64 l/kg. So now we need to know the patient's weight. His friend says he weighed 75 kg just a week ago. Now you can simply calculate the dose you need to give.

The V_d is $(75 \times 0.64) = 48$ liters.

The C_p we want is 15 mg/l

and so the intravenous dose is (48×15) mg = 720 mg, which can probably be safely rounded up to 750 mg given by slow intravenous injection over five to ten minutes.

You will need to check the plasma concentration you achieve because the patient's phenytoin kinetics may differ from the average, but you will not be out by much and will have the confidence of having derived the dose in a logical and defensible way.

Now try this one for yourself – another patient with a rhythm disturbance, but this time a cardiac, not a cerebral, arrhythmia.

Mrs. Chen is 68 and has suffered a myocardial infarction. An ECG showed ventricular tachycardia, she was successfully defibrillated and now, to maintain sinus rhythm, your consultant asks you to 'load' her with lignocaine. She weighs 85 kg and the C_p he wants you to achieve is 1.5 mg/l. You look up the V_d

for lignocaine (also known as lidocaine), and find it to be 1.1 l/kg. How much lignocaine will you give?

$$(84 \times 1.1 \times 1.5)\ \text{mg} = 138.9\ \text{mg}.$$

In this case an intravenous infusion of just under 150 mg lignocaine given over a few minutes should bring the C_p into the therapeutic range.

When giving intravenous loading doses it is important to give them over a period of several 'circulation times' – i.e., the length of time it takes blood to circulate throughout the whole circulation. Cardiac output is approximately 5 l/min and the total blood volume is 5 litres, and so it follows that the circulation time is usually about one minute. The injected drug must have time to be diluted in the venous blood to prevent too high a concentration reaching sensitive tissues – e.g., the electrical conducting system of the heart, which would be the first tissue to be reached by a drug injected into an arm vein.

To emphasize the principle, let us look at one more example. You are about to treat Mr. Shrestha, a 42-year old man who has suspected gram-negative sepsis. Intravenous gentamicin will be your main antibiotic, and he is sick enough to make you want to raise the peak plasma concentration to the therapeutic range (8–10 mg/l) just as soon as possible. He weighs around 55 kg and the volume of distribution of gentamicin is approximately 0.3 l/kg. What loading dose will you give?[1]

The principle that emerges from these three examples is a simple one. The only factors important in calculating an intravenous loading dose of a drug are the desired plasma concentration and the apparent volume of distribution. Other kinetic parameters do not come into this very straightforward calculation.

IV.b. "Topping-up" a Low Plasma Concentration

Let us complicate the clinical picture a little. A colleague who does not understand drug kinetics at all has given an intravenous dose of phenytoin to our first patient. He knew several hundred milligrams would be needed but became too frightened to give much more than about 200–300 mg. The problem is that it is now an hour after the dose and he cannot remember precisely how much he gave – in fact it was all a bit of a guess! Can you help him out?

[1] The loading dose for Mr. Shrestha should be 165 mg.

Well, you can, but you will need one more piece of evidence before you do the calculation. Fortunately the laboratory is not closed and they do have the ability to measure plasma phenytoin. It takes about 30 minutes to get the answer from the lab – 6 mg/l. Remember the therapeutic concentration that was needed to give the patient a therapeutic level was 15 mg/l.

So, each litre of blood is short of $(15 - 6 = 9)$ mg of phenytoin. The V_d for the drug in this patient is 48 litres so he needs to be 'topped up' by an additional $9 \times 48\ \text{mg} = 432\ \text{mg}$.

Note that exactly the same reasoning applies to both an initial loading dose and a dose to raise a sub-therapeutic plasma concentration into the therapeutic range.

IV.c. Working out the Rate of a Continuous Intravenous Infusion

Working out the rate of a continuous intravenous infusion is another job you may have to do – although in most hospitals there are protocols or other guides that already take account of the kinetics of the drugs used. This is how they were devised in the first place.

Let us look again at the second patient of the three above. You gave her enough lignocaine to bring her C_p up to 1.5 mg/l, and now you want to keep it there. Lignocaine is fairly rapidly cleared from plasma through the liver as we have already seen. Therefore, to maintain steady state your continuing infusion needs to match exactly the loss of drug from the plasma compartment if the plasma concentration is to be held constant. The principle is very simple. If the plasma concentration of the drug is to remain constant, then

WHAT GOES IN MUST EQUAL

WHAT GOES OUT

Total body clearance ('what goes out') is given by the apparent volume of distribution (l) × elimination rate constant (K_{el}) (as we have seen above, V_d is measured in litres, and K_{el} as a fraction of 1, per unit time. A K_{el} of 0.1 implies that 1/10th of a body's load of drug is cleared each hour). Clearance therefore has units of volume per unit time – put in another way it means the fraction of the total V_d cleared of drug per unit time.

V_d for lignocaine in this lady is $(84 \times 1.1)\ \text{l} = 92.6\ \text{l}$. K_{el} can be derived from the accepted plasma

half-life ($T_{1/2}$) for lignocaine, which is approximately 1.8 hours, and K_{el} will then be 0.693/half-life = 0.693/1.8 = 0.38.

Using this figure for K_{el} we can now calculate the clearance as $V_d \times K_{el}$ – or (92.6 × 0.38) = approximately 35.2 l/h. So, if this volume is cleared of drug in each hour and the concentration of drug in this volume is 1.5 mg/l, about 35.2 × 1.5 mg is lost from the body in each hour – and this works out at around 53 mg of lignocaine.

This, then is the amount of lignocaine you would need to infuse intravenously each hour to maintain the plasma concentration at, or very close to, 1.5 mg/l. As you can see it is quite close to 1 mg/min and many of the protocols you will find on the wards or in the coronary care or intensive care units will suggest a rate of infusion for maintenance of 1 mg per minute.

To make it simpler, and to avoid all that calculation from first principles published clearance values can be used – for lignocaine this is given as 9.2 ± 2.4 ml/min/kg (this is listed by its US name – lidocaine – in: Appendix II, in Brunton et al., editors, 2005). This figure converts to an average of 46 l/h, which is a little higher than the one we calculated above. Using this figure we find we need an infusion rate of (46 × 1.5) mg/h = 69 mg/h, a marginally higher figure than from the first calculation but still in the same vicinity of around 1 mg/min.

Looking at the same problem in a slightly different way, let us rearrange the equation to:

$$C_p \text{ (at steady state)} = \frac{\text{Rate of infusion (what goes in)}}{\text{CL (what goes out)}}.$$

Think about the units for this equation. C_p is the target plasma concentration that you want to achieve in the patient and is measured in weight/volume – for example, mg/l. Rate of infusion is measured in weight/time – for example, mg/h. Drug clearance (CL) is measured in volume/time – for example, l/h. (Satisfy yourself that the units on the left-hand side of the equation are the same – once time ("hour") has been cancelled out – as those on the right-hand side.)

It may not be very helpful in the wards to say that the patient is to receive, say, 60 mg lignocaine per hour as the nurse will want to know what volume of solution it is in and how much is to be run in per minute. For example, if 60 mg of lignocaine is dissolved in 120 ml of solvent (perhaps normal saline solution) then 2 ml of the solution will need to be infused each minute if 60 mg are to be delivered at a constant rate over an hour.

Depending on the giving set that you are using, 2 ml per minute can be converted into a number of drops per minute – and that can be counted at the bedside. In practice we rarely have to work out such infusion rates. If infusing a drug produces a measurable outcome, e.g., slowing of a pulse or reduction in blood pressure, we can use these measurements to guide the rate of infusion (as with sodium nitroprusside infusion in hypertensive emergencies).

When using an anti-arrhythmic such as lignocaine, however, we are trying to stay within the "therapeutic window", steering a course between too much drug (toxicity – such as convulsions) and too little (loss of control of arrhythmia), and we have no clear guide from physical measurements until disaster strikes. Indeed when we have the correct infusion rate nothing should be happening! In these circumstances, being able to calculate (and verify by a laboratory measurement) an appropriate infusion rate gives a great deal of confidence and reassurance.

IV.d. Calculate the Next Dose and Dose Interval for an Intravenous Drug

We have met the aminoglycoside antibiotic gentamicin before. It is cleared from the body almost entirely by renal excretion. While it is a very effective and important antibiotic, it is also very toxic if plasma concentrations are too high for too long. While there is good evidence that a peak plasma concentration of around 10 mg/l is needed, if only briefly, after an iv injection to provide optimal bactericidal action, there is also evidence that keeping the lowest ('trough') concentration, between doses, above 1 mg/l for long periods is associated with ototoxicity – damage to the VIII cranial nerve – both auditory and vestibular divisions, and nephrotoxicity (uptake of the drug in high concentration into renal tubular cells which can lead to acute, but usually reversible, renal failure). So for gentamicin there is a very critical 'therapeutic window', and our dosing must take that into account. Most hospital laboratories have the ability to measure plasma gentamicin concentrations, which helps us with monitoring and adjusting doses.

Most recently in simple, uncomplicated patients the tendency has been to use single daily doses of gentamicin, and evidence from clinical trials supports this.

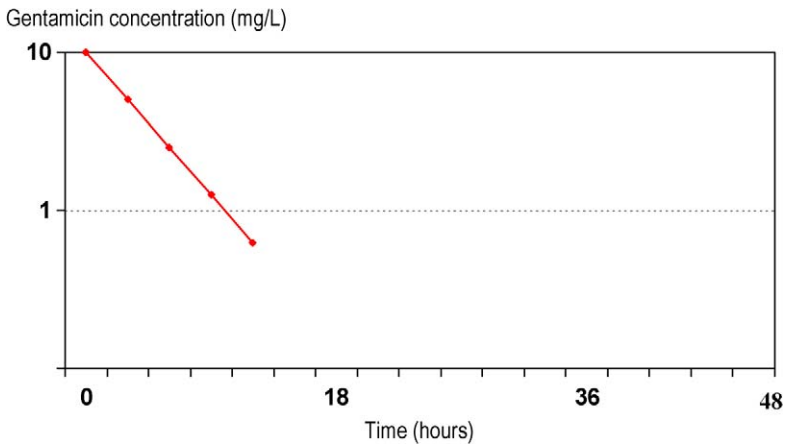


Fig. 20. Gentamicin concentration drops from 10 to 0.625 mg/l after 12 hours (4 half-lives) in a patient with normal kidney function.

If we go back to our patient Mr. Shrestha, with gram-negative sepsis, what would we expect to happen to his plasma gentamicin concentrations after we have given him his loading dose? You remember that you calculated that a single intravenous dose of 165 mg would be expected to give him a peak plasma concentration of 10 mg/l. How long will it be before his C_p has fallen to 1 mg/l or below? Figure 20 will help you understand this, but you can also work it out for yourself. The quoted plasma $T_{1/2}$ for gentamicin derived from many studies is 2–3 hours. Let us take a cautious approach and assume in our patient, the $T_{1/2}$ is 3 hours. Then the C_p at 3 hours post-dose will be 5 mg/l (remember plasma half-life is the length of time it takes for the C_p to fall by 50%):

- at 6 hours (2 half-lives) it will be 2.5 mg/l
- at 9 hours (3 half-lives) it will be 1.25 mg/l
- at 12 hours (4 half-lives) it will be 0.625 mg/l

and so on up to the next dose at 24 hours – if you were dosing once in 24 hours – the C_p will be below your 'toxic trough' level of 1 mg/l.

Now consider a patient who already has some degree of renal failure, yet who needs gentamicin. As we have already seen the loading dose to get the drug concentration into the desired range depends only on the apparent volume of distribution (dose: $V_d \times$ desired C_p) so that part of the calculation is unchanged, and the loading dose will be very similar. However, renal impairment means reduced renal clearance of gentamicin, and the half-life of the drug may be very much increased. Let us assume it is as high as 12 hours and do the same calculations (see Fig. 21).

C_p at time zero = 10 mg/l

- at 12 hours (one half-life) it will be 5 mg/l
- at 24 hours (2 half-lives) it will be 2.5 mg/l
- at 36 hours (3 half-lives) it will be 1.25 mg/l
- at 48 hours (4 half-lives) it will be 0.625 mg/l

So, to ensure that the C_p does not remain above 1 mg/l for long periods, we will probably recommend that the next dose of 165 mg i.v. will be given at 48 hours from the first.

In renal failure changes in apparent volume of distribution do occur, and changes in a patient's hydration in particular can influence this, and therefore the renal clearance. However, the main message is that reduced renal function reduces the renal clearance of gentamicin, and this must lead to an increase in dosing interval.

How do you know or calculate the gentamicin half-life in an individual patient? Tables and nomograms have been drawn up relating renal function derived from a knowledge of serum creatinine and the patient's age (Cockcroft and Gault equation, see Section III.e.3.3) with gentamicin kinetics. These can be useful, but if you want to derive values for a particular patient there is no substitute for measuring plasma gentamicin concentrations at, at least, two points around 2 hours after the first i.v. dose, and again not less than 4 hours after. From these you can measure a half-life for yourself (Fig. 20) and know that you are dealing with your own patient's data and not estimating dose from a theoretical table.

If you are working in an area which does not have the facility to measure plasma gentamicin, tables can be used, but it might be more appropriate, as discussed earlier, to consider alternative effective antibiotics. While they might be more expensive, the

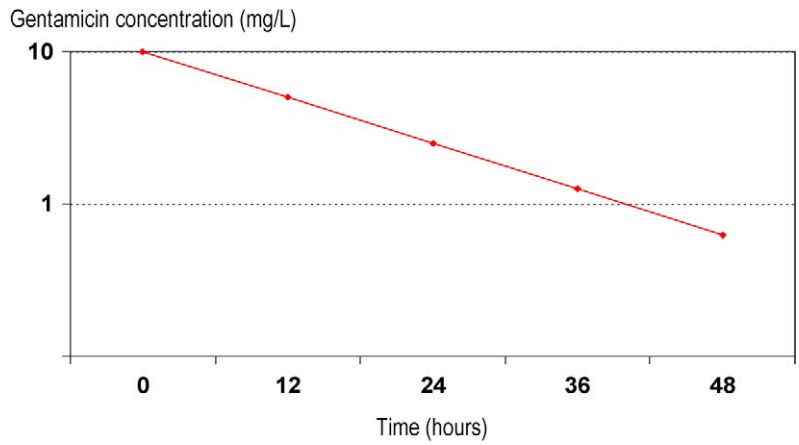


Fig. 21. Gentamicin concentration drops from 10 to 0.625 mg/l after 48 hours (4 half-lives) in a patient with renal impairment.

cost does not include the laboratory expense of measuring plasma concentrations, which must be factored into the cost of using, and monitoring, gentamicin.

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Chapter 11

Clinical Pharmacodynamics

Gunnar Alvan, Gilles Paintaud, Monique Wakelkamp

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I. INTRODUCTION

Drugs are molecules that interact with macromolecular structures in the body to produce effects that are intended to be beneficial, most often through modification of pathophysiological processes. Some drugs may also be designed to kill intruders, such as bacteria and parasites, or endogenous cells that have lost their growth control and behave as cancer cells. Because a pharmacological effect requires the association of a drug molecule with a receptor structure, one may assume that the more active drug is available at the effect site (biophase), the more effect will be produced. This is basically correct, but reality is more complex as will be shown below when discussing various relationships between drug concentrations and drug effects. The term pharmacokinetic–pharmacodynamic (PK–PD) analysis has been coined to include both the evaluation of pharmacokinetics, which denotes the systematic description of drug transfer through the body, and pharmacodynamics, which means the study and control of drug effects.

Biopharmaceuticals deserve some attention here. At the moment a considerable part of the drugs newly approved by regulatory agencies belong to the so called biologicals. These medicines have a number of characteristics that set them aside from low molecular weight drugs. Their activity can strongly be influenced by their complicated shape based on secondary, tertiary and (sometimes) quaternary structures. These structures cannot be fully defined with our present set of analytical techniques and approaches. They often are the same as (or closely resemble) endogenous proteins. Those are challenging issues but those challenges need to be met and PK/PD studies with biologicals have been published.

II. THE RECEPTOR AS A MEDIATOR OF PHARMACOLOGICAL EFFECT

The receptor concept is fundamental for pharmacodynamics. About 100 years ago, in the early days of physiological and pharmacological research, the assumption arose that chemical entities such as nicotine, curare, chemotherapeutic agents and antibodies would exert their effects through interaction with receptors or "receptive substances". This idea was clearly different from previous images of "toxic" or "poisonous" actions on the body. The concept presented by P. Ehrlich (1845–1915) that agents have to be bound in order to have an effect is still largely valid. *Ligands* are either endogenous or externally provided molecules that bind to specific sites. At present, a major aim of pharmacological research is to characterise the structure and function of receptors. After sequencing the DNA coding for a receptor, the influence of its aminoacid sequence and three-dimensional structure on receptor functioning can be studied. There is a pronounced amount of homology among receptors, and similar receptors

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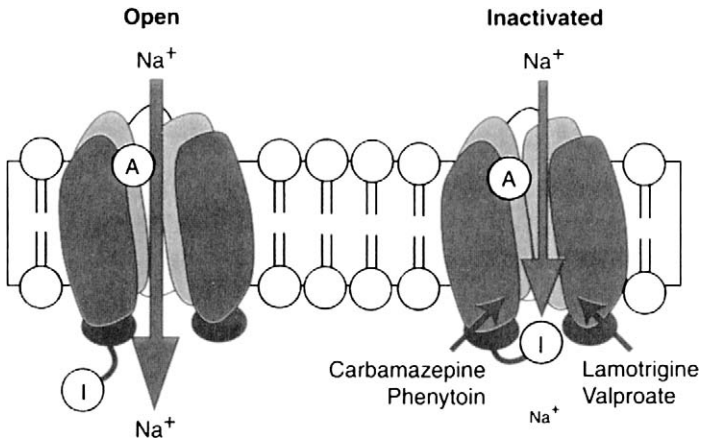


Fig. 1. Example of a receptor structure. Some anti-epileptic drugs interact with a receptor site on a Na^+ channel and enhance the activity of the inactivation gate (I) decreasing the ability of neurons to fire at high frequencies. (A) indicates the activation gate of this ion channel. (Reprinted by permission from McNamara JO. Emerging insights into the genesis of epilepsy. Nature 1999;399(Suppl):A15-22, © 1999 Macmillan Magazines Ltd.)

may be classified into groups indicating both functional kinship and evolutionary history. For some receptors, the conformational changes related to their physiological function are known (Fig. 1). Research on receptors is extremely important for the understanding of disease mechanisms and to find new drug targets. Receptors and their tissue distribution are also responsible for the selectivity of drug action. The present chapter emphasises the analysis of the time course of drug effects in man, which is a key issue in clinical pharmacology. The reader is referred to pharmacological textbooks for a more comprehensive overview on receptor pharmacology. However, some introductory concepts will be presented here.

II.a. Receptor Characteristics

Receptors are an integral part of the tissue where they are located and are functional as soon as the tissue has been developed in the embryo. A cell is capable of synthesising receptors, as well as degrading them. Following sustained stimulation, the rate of receptor degradation may increase, leading to a decreased number of receptors and thus a decreased pharmacological response to a stimulus. This is called *receptor downregulation*. Following a decrease in stimulation, the cell may respond with an increase in receptor density. This is called *receptor upregulation*, which results in an increased response to a stimulus.

Receptors are coupled to *effectors*, producing an effect after a number of events have taken place. If the receptors largely outnumber the effectors, it is said that there are *spare receptors*. These receptors are fully functional and do not differ from 'normal' receptors. An abundance of spare receptors will make an association between a drug molecule and a receptor very likely. In this situation, a drug will exert its pharmacological effect already at relatively low concentrations because a sufficient number of receptors will be occupied and each activated receptor will trigger an effect by coupling to an effector. The existence of spare receptors increases the sensitivity of the system. Spare receptors may be demonstrated by irreversibly inhibiting a fraction of the receptor population. It will then be seen that the maximum pharmacological effect still can be obtained, but at higher drug concentrations. This reflects that more of the drug has to be present to give the same number of drug–receptor associations.

Receptors can mediate the action of endogenous signalling compounds and may therefore be viewed as *regulatory proteins*. Such receptors are the physiological targets for neurotransmitters and hormones. Other types of receptors include *enzyme proteins*, *transport proteins* and *structural proteins*. For example, statins inhibit an enzyme catalysing the synthesis of cholesterol and loop diuretics inhibit an enzyme that facilitates the re-uptake of salt in primary urine.

II.b. Signalling Mechanisms and Receptor–Effector Coupling

Between the extracellular or intracellular presence of a drug molecule close to the receptor site and the

observable pharmacological effect lies a cascade of events that may need to occur. At present, at least four different mechanisms of receptor activation and elicitation of intracellular events are relatively well known:

(a) lipid soluble drugs may cross the cell membrane passively, reaching and activating intracellular receptor proteins that will then associate with the cell nucleus and modify gene expression (e.g. corticoids and thyroid hormone);
(b) the drug may act on an extracellular part of a transmembranally located receptor, leading to conformational changes at the intracellular part of the receptor (e.g. the nicotinic acetylcholine receptor);
(c) the drug may interact with a transmembrane ligand-gated ion channel and change its permeability for the specific ion(s);
(d) the drug may stimulate a transmembrane receptor that will activate a GTP-binding signal transducer protein (G protein). The G protein will then influence the activity of second messengers such as cAMP or calcium ions to trigger further effects. The action through G proteins allows the transduced signal to be amplified since the activity of the G protein–GTP complex will exist for a much longer time than the initial interaction between the ligand and the receptor and the generation of second messengers will be sustained.

II.c. Agonists and Antagonists

By definition, a drug that exerts a pharmacological action through the stimulation of a receptor is called an *agonist*. A drug that can elicit the maximum response (E_{max}) in a tissue or the intact body is called a *full agonist*. A full agonist is considered to trigger an efficient receptor–effector coupling. A drug with less efficient coupling will not be able to produce the full response at *any* drug concentration and is therefore called a *partial agonist*. The intensity of a drug response is described by the term *efficacy*. Hence, a partial agonist drug has less efficacy than does a full agonist. A drug that produces a considerable effect at a low concentration has high *potency* (Fig. 2). High potency corresponds to a low value of the parameter $C_{50\%}$, the drug concentration associated with 50% of maximum effect. Obtaining sufficient efficacy is often a more pronounced problem in drug development than achieving enough potency. Within reasonable limits, a somewhat low potency of a drug can be compensated for by adjusting the dose size and dosage schedule. However, an ideal drug would have sufficient efficacy to reach therapeutic goals, it would be highly *selective* in order not to activate non-therapeutic pathways and it would be sufficiently potent to limit the body load of administered chemicals. Such a drug would have an excellent (high) *therapeutic index*, which is a term reflecting the ratio between a drug dose (or concentration) associated with adverse effects and a therapeutic dose (or concentration).

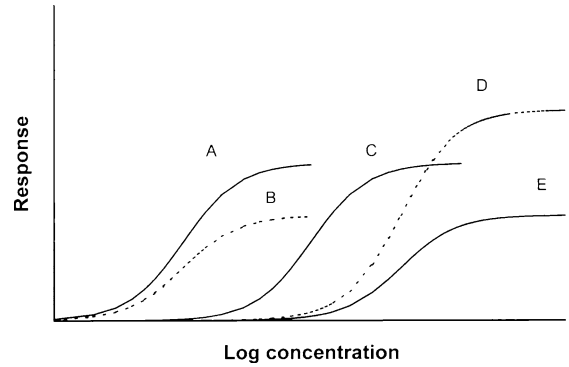


Fig. 2. The meaning of *efficacy* and *potency*. Drug B has lower efficacy than drug A, but the same potency. Drug C has the same efficacy as drug A, but lower potency. Drug D has higher efficacy but lower potency than drug A. Drug E has lower potency and lower efficacy than drug A.

Antagonists are drugs that occupy a receptor without activating the effector. Their presence on the receptor will decrease the possibility of an endogenous agonist to bind and produce an effect. This interaction is called *competitive antagonism* and can be described mathematically. The effect of a competitive antagonist can in principle be overcome by simply increasing the concentration of the agonist. Commonly used drugs such as atropin (a muscarinic receptor antagonist) and beta-adrenergic blocking drugs are competitive antagonists. A drug may also act as an *irreversible antagonist*, which means that it binds irreversibly to its receptor which is then inactivated. Once this has occurred, the decreased response cannot be overcome by *any* dose increase of the agonist. Full effect will be restored only when the perturbed receptor has been replaced by a new receptor.

Often in biology, diminishing returns are observed, which means that a less than proportional increase in effect is obtained when the intensity of the stimulus is increased. The simplest explanation is

that the number of receptors and effectors on the target tissue is limited. The availability of any other activity necessary for the development of response, e.g. a transport function, cofactor or responding mechanism, may also be limited. With increasing drug concentrations, 'saturation' of the effect will gradually occur. The fraction of occupied receptor sites increases when more drug molecules enter the biophase, until no more binding sites are available.

III. BASIC PHARMACODYNAMIC MODELS

Experimental concentration–effect data can be analysed using an appropriate PK–PD model. Such models can:

- describe the relationship between pharmacological effect and drug concentration quantitatively in a concise and condensed manner;
- increase understanding of some of the mechanistic aspects of drug action;
- have predictive value, e.g. with respect to different doses or routes of administration of the drug.

Primary model selection should be based on the experimental data observations but other information may also be useful, such as knowledge of the drug's mechanism of action, results from earlier studies, or concentration–effect relationships of related compounds. The performance of different models can be systematically tested by using a nonlinear regression program, which has readymade routines for common models and also allows the user to formulate his own models. Model selection and validation is an important issue, which is however beyond the scope of this chapter.

III.a. The E_{max} Model

The simplest model that can be used to describe an entire range of concentration–effect data is the E_{max} model. This model has been obtained by applying the law of mass action, analogously to the derivation of the Michaelis–Menten equation for enzyme kinetics or equations for drug–protein binding. It can be obtained realising that concentrations of drug $[D]$ and receptor $[R]$ determine the concentration of the drug–receptor complex $[DR]$, that undergoes spontaneous dissociation (Eq. (1)). The probability that the complex is formed is proportional to the concentrations of both drug and receptor available and an association constant (k_{ass}). The dissociation is proportional to the concentration of the complex and its characteristic dissociation constant (k_{diss}):

$$[D] + [R] \underset{k_{ass}}{\overset{k_{diss}}{\rightleftarrows}} [DR] \tag{1}$$

Forming and breaking up of the complex occur at equal rates when equilibrium is established:

$$[D][R]k_{ass} = [DR]k_{diss} \tag{2}$$

Equation (2) can be rearranged into:

$$[D][R]/[DR] = k_{diss}/k_{ass} = K_d \tag{3}$$

The dissociation and association constants have been combined into a new constant, K_d. The total concentration of receptor $[R_T]$ equals unbound receptor concentration $[R]$ plus drug–receptor complex concentration, $[DR]$:

$$[R_T] = [R] + [DR] \tag{4}$$

If the drug effect (E) is proportional to the concentration of drug–receptor complex:

$$E = k[DR] \tag{5}$$

then maximum drug effect (E_{max}) would be obtained when all available receptors are occupied by the drug:

$$E_{max} = k[R_T] \tag{6}$$

It is now possible to form the ratio E/E_{max}:

$$\begin{aligned} E/E_{max} &= [DR]/[R_T] = [DR]/[DR] + [R] \\ &= 1/1 + ([R]/[DR]) \end{aligned} \tag{7}$$

Equation (3) can be used to exchange $[R]/[DR]$ for $K_d/[D]$ and Eq. (7) can therefore be transformed into:

$$\begin{aligned} E &= E_{max}/1 + (K_d/[D]) \\ &= E_{max}[D]/(K_d + [D]) \end{aligned} \tag{8}$$

It follows that the effect is at half maximum when $[D] = K_d$. In pharmacology, Eq. (8) or the so-called E_{max} model is conventionally written as Eq. (9):

$$E = (E_{max} \times C)/(C_{50\%} + C) \tag{9}$$

where E is drug effect, and C is drug concentration.

III.b. The Sigmoid E_{max} Model

In a pioneering paper by Hill (1910), Eq. (9) was empirically modified to yield the sigmoid or S-shaped E_{max} model:

$$E = (E_{max} \times C^s)/(C^s_{50\%} + C^s) \qquad (10)$$

This equation uses the same symbols as Eq. (9), but a dimensionless parameter s has been added. This parameter is called exponent or sigmoidicity factor and determines the slope and shape of a (sigmoidal) concentration–effect relationship (Fig. 3). Although the exponent theoretically may reflect cooperativity (conceived as the number of molecules that interact with the receptor), the value of s generally does not have any physiological meaning but rather reflects the steepness of the concentration–effect curve. When analysing concentration–effect observations using an E_{max} model, the inclusion of a slope factor is frequently found to improve the fit of the model to the data. Thus, s can simply be regarded as a fitting parameter and its value does not need to be integer. Other synonymously used symbols are n and γ. A value of $s < 1$ will produce a curve that is steep at low drug concentrations and shallow at high concentrations. If $s > 1$ there will be little increase in effect at low concentrations while the effect is increasing rapidly in the concentration range close to $C_{50\%}$. At high values for s, e.g. $s > 5$, an 'all or nothing' type of concentration–effect curve will be observed, as shown in Fig. 3.

Interestingly, a logarithmic transformation of the concentration axis will produce an S-shaped effect curve that is perfectly symmetrical around the point $(\ln C_{50\%}, E_{max}/2)$.

Sometimes a pharmacological effect is the sum of more than one drug effect. This may call for the combination of two or more models, as shown in Fig. 4 where both tachycardia and bradycardia are implied as drug effects. In this case, the model used consisted of two equations equal to Eq. (10), but with an opposite direction of effect on heart rate and different model parameter values.

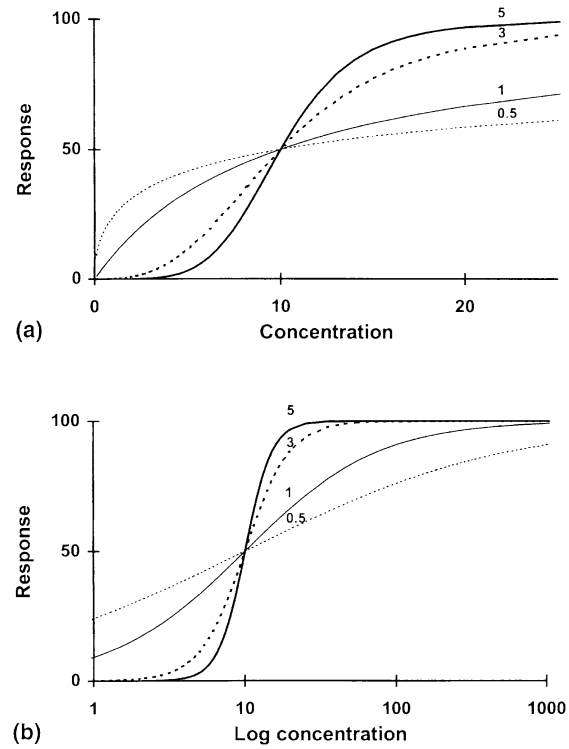


Fig. 3. Concentration–effect relationship for the sigmoid E_{max} model with $s = 0.5$, 1, 3 and 5, respectively. (a) Linear concentration scale, (b) logarithmic concentration scale.

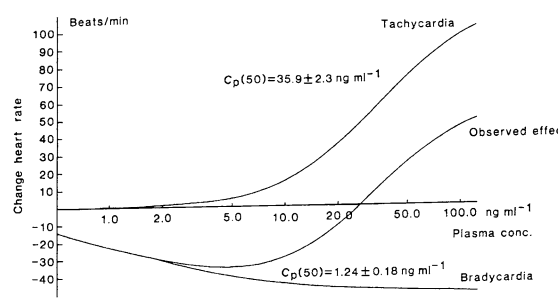


Fig. 4. Change in heart rate produced by apomorphine in the rat. Slowing of heart rate predominates at low drug concentrations, while tachycardia is most prominent at high steady-state concentration. Two sigmoid E_{max} models have been combined for the PK–PD analysis. $C_p(50)$ corresponds to $C_{50\%}$. (From Paalzow LK, Paalzow GHM, Tfelt-Hansen P. Variability in bioavailability: concentration versus effect. In: Rowland M, Sheiner LB, Steimer J-L, editors. Variability in drug therapy: description, estimation, and control. New York: Raven Press; 1985.)

IV. PHARMACOKINETIC ASPECTS OF DRUG ACTION

In pre-clinical *in vitro* work, the pharmacological effects of drugs can be studied by using small pieces of tissue immersed in organ baths to which different amounts of pharmacological agents are added. Compared to this relatively straightforward situa-

tion, studying drug effects in patients introduces a number of complicating factors that are discussed in the sections below.

IV.a. The Active Drug Fraction

The pharmacological effect is exerted by unbound drug molecules. Thus, if only total drug concentrations (e.g. in plasma) are analysed, one should consider whether these measurements are reflective of the concentrations at the site of action. If the unbound drug fraction is more relevant than the total concentration, e.g. because of saturable protein binding, it should be used as the independent variable in the PK–PD model. Figure 5 shows the consistency of the PK–PD relationship between total, as well as unbound quinine concentration and hearing impairment in man.

It may also be the case that the pharmacodynamic effect of a drug is exerted by both the parent compound and its metabolite(s), which implies that both should be included in the PK–PD model. Also, a drug may exist in two chiral forms with different kinetic and dynamic characteristics.

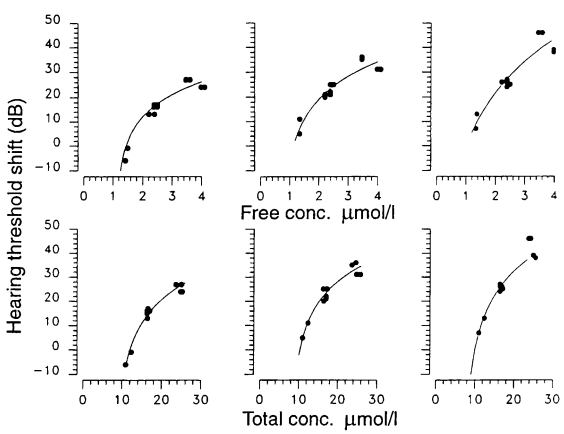


Fig. 5. Observed hearing threshold shift (dB) at 1, 2 and 4 kHz versus measured unbound (upper panel) and total plasma quinine concentration in a subject who received a computer-controlled quinine infusion. The reduced sigmoid E_{max} model has been applied and is shown as the solid line. Note that the y axis is by definition a log scale. (From Karlsson KK, Berninger E, Gustafsson LL, Alvan G. Pronounced quinine-induced cochlear hearing loss. A mechanistic study in one volunteer at multiple stable plasma concentrations. J Audiol Med 1995;4:12-24, with permission.)

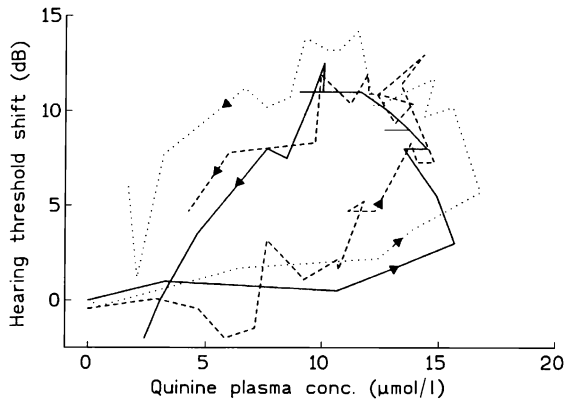


Fig. 6. Counterclockwise hysteresis appearing between hearing threshold shift and quinine plasma concentration in a subject who received two identical oral doses (dotted and solid lines) and an infusion (dashed line) of quinine. (From Paintaud G, Alvan G, Berninger E et al. The concentration–effect relationship of quinine-induced hearing impairment. Clin Pharmacol Ther 1994;55:317-23, with permission from MOSBY Inc.)

IV.b. Drug Distribution and Analysis of Time Lag Between Concentration and Effect

When creating a graph of the relationship between the time course of the plasma concentrations of a drug in the body (plotted on the x-axis) and the time course of the observed drug effect (plotted on the y-axis), a loop with a counterclockwise direction may be obtained. This means that there are more than two values of effect that correspond to a single plasma concentration (Fig. 6). The phenomenon is called counterclockwise hysteresis or just hysteresis, provided that the model describes a stimulatory (positive) response. If the drug effect would be inhibitory (negative), the direction of the hysteresis would be clockwise.

There may be several reasons for this pattern to be observed. One obvious reason is distribution, i.e. the drug needs time to reach its site of action, and the time lag between the measured drug concentration in plasma and the drug effect is due to distributional delay. In order to describe such a plasma concentration–effect relationship, a PK–PD model that allows for drug distribution to the site of action, e.g. the effect compartment model may be used.

The effect compartment model assumes that the pharmacological effect is produced in a hypothetical, exceedingly small compartment, added to the

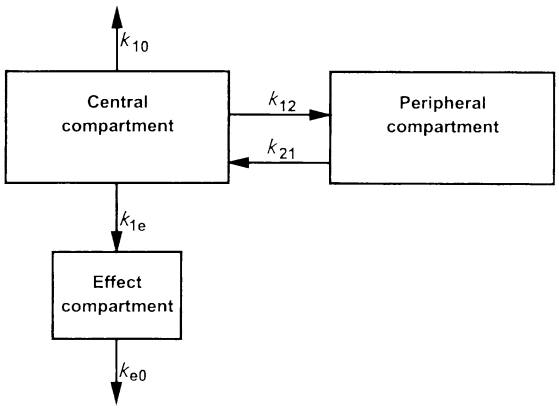


Fig. 7. Scheme of the effect compartment PK–PD model.

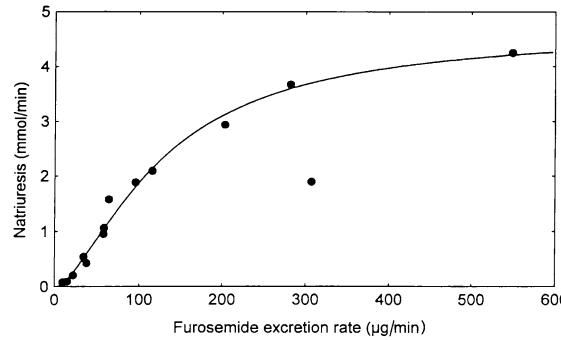


Fig. 8. Relationship between natriuresis and furosemide excretion rate. The first observation representing counter-clockwise hysteresis has not been included in the fitting of the sigmoid E_{max} model. (From Wakelkamp M. Furosemide dosage input – consequences for diuretic effect, tolerance and efficiency. Diss. Karolinska Institutet, Stockholm; 1997.)

PK model (Fig. 7). This compartment does not influence the pharmacokinetics of the drug because its volume is assumed to be negligibly small. The parameter k_{e0} serves to characterise the time needed to equilibrate the effect compartment with the central compartment where drug concentrations are measured.

The treatment of the data proceeds as a two step procedure. First, a suitable PK model is fitted to the concentration–time data. Then a PD model is fitted to the data as described by the PK model, simultaneously solving for pharmacodynamic parameters (e.g. E_{max}, $C_{50\%}$, s) and the effect compartment parameter k_{e0}.

IV.c. Sampling from Sites Other than Plasma

Instead of using an effect-compartment model to link the plasma concentration profile with the time course of drug effect, one may consider sampling closer to the actual site of action of the drug. For example, loop diuretics are known to act on a $Na^+2Cl^-K^+$ co-transporter in the kidney, localised in the apical cell membrane facing the lumen of the thick ascending limb of the loop of Henle. The physiological task of this co-transporter is to facilitate the tubular re-uptake of sodium, chloride and potassium ions. Loop diuretics are transported by the acid secretory system into the primary urine, reaching their endoluminal site of action. The availability of drug at this site is thus more relevant for the effect than are drug concentrations in plasma. Although primary urine is extensively processed when passing through the tubular system, with an approximate 99% re-uptake of electrolytes and fluid, the urinary excretion rate of loop diuretics may serve better for PK–PD evaluation than their concentration in plasma (Fig. 8).

Other examples of sites of action where changes in drug concentration may not be well represented by changes in the "plasma compartment" are the local deposition of drugs in the lungs through inhalation, the specific binding of proton pump inhibitors to gastric parietal cells, drugs applied to intact skin, drugs targeted to interact with organ-specific sites of action (e.g. 5-alpha-reductase inhibitors of the prostate gland and hormone receptors in the mammary gland and the gonads) and drugs that act in the CNS inside the blood brain barrier. In some of these examples, drug concentrations may be obtained through microdialysis of the actual tissues. In other cases, PK–PD evaluation will have to rely on information more distant from the site of action, e.g. the administered dose or the AUC.

If drug effects are produced inside transformed endogenous cells such as cancer cells or cells invaded by microorganisms, it would be preferable to know the drug concentration within these cells. However, for beta-lactam antibiotics, it has been possible to model drug effects as bacterial killing rates based on plasma concentrations. This implies the assumption that there is a proportional relationship between the drug concentrations outside and inside the target cell.

V. PHARMACODYNAMIC ASPECTS OF DRUG ACTION

V.a. Clinical Effects, Endpoints and Biomarkers

In clinical trials, the evaluation of drug response is often based on indirect (or surrogate) endpoints. Such indirect endpoints are supposedly closely correlated to the actual clinical effects of interest (the clinical endpoints), which may be difficult to measure or follow-up. A *clinical endpoint* is a characteristic variable that describes how a patient feels, functions or survives. For example, a measured decrease in blood pressure induced by anti-hypertensive drugs is only an *indirect endpoint*, since the clinical endpoint is the risk reduction in morbidity and mortality related to arterial hypertension. Another example of an indirect endpoint is the decrease in blood lipid levels commonly used to monitor the efficacy of lipid-lowering drugs. Indeed, a causal relationship between lowered lipid levels and a decrease in morbidity and mortality has been shown for statins. A *biomarker* has been defined as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention". Biomarkers may relate to both therapeutic and safety aspects of drug effects. They can be particularly useful as response measurements in PK–PD modeling.

V.b. Methodological Aspects

A PK–PD model generally should not be used to extrapolate far beyond the range of concentration-effect observations that formed the basis for selecting the model. For example, using Monte Carlo simulations, it has been shown for (sigmoid) $E_{\max}$ models that when data observations reach less than 95% of the actual maximum effect, the $E_{\max}$ and $C_{50\%}$ parameters will be estimated with considerable imprecision and bias. A practical difficulty is that for drugs exhibiting a small therapeutic index, it may not be possible in a study to reach $E_{\max}$, because toxicity precludes this. A good example is quinine (discussed below). In few cases e.g. for anticoagulant drugs, it has been possible to study drug effects up to $E_{\max}$, because of the availability of an adequate rescue therapy (vitamin K). If effect levels close to $E_{\max}$ cannot be reached, an $E_{\max}$ model should preferably not be used for PK–PD modelling, since its parameters are rendered unreliable. Instead, a simpler model such as a linear or exponential model should be considered to describe the range of data available. Figure 5 depicts the reversible hearing impairment caused by quinine in a human subject, analysed with the following exponential PK–PD model: $E = k(C - b)^s$ where b is a limit for the concentration associated with no measurable effect. This exponential model may be viewed as a reduced sigmoid $E_{\max}$ model for drug concentrations much below $C_{50\%}$. If the slope factor is close to one, the relationship between concentration and effect approaches linearity on a linear scale.

V.c. Basal Effect or Baseline

Since drugs interfere with (patho)physiological processes in the body, the basal effect may be defined as the level of response when no drug is present, e.g. blood pressure before initiating treatment with an anti-hypertensive drug. Assuming that a drug effect can be observed and measured, it is not possible to quantify this effect without some knowledge of the basal effect, as the drug-induced response reflects the change from baseline. Basal response should not be confused with placebo response, which is a treatment-induced change from baseline, where treatment did not contain any pharmacologically active compound. If the baseline is fixed and not subject to any systematic measurement error, one may simply subtract its value from the observed effects, in order to obtain the drug-induced effects. However, in most cases, basal effects are subject to non random measurement error, as are drug induced effects, and may display considerable variation, not only between individuals but also within the same individual over time. Consider for example basal blood pressure or pain score. In many cases, the drug may influence the level or activity of endogenous substances responsible for maintaining the baseline effect (e.g. the case for hormone and hormone antagonist drugs), and this is another reason it has been argued that the baseline effect should be integrated into the pharmacodynamic model. For the sigmoid $E_{\max}$ model, the parameter E_0 can be added to estimate the basal effect:

$$E = (E_{\max} \times C^s)/(C^s_{50\%} + C^s) + E_0 \qquad (11)$$

A study design should desirably include a baseline period with repetitive baseline measurements to obtain adequate initial estimates. Time-variable changes, such as circadian rhythms may warrant a more complicated basal effect model. If drug effect

is studied in a disease of continuously changing intensity, such as rheumatoid arthritis, inflammatory bowel disease or psoriasis, special care in study design is warranted. For example, basal disease activity could be modelled by introducing treatment-free study periods or one could implement a parallel group design with the number of patients sufficiently large to render intra-individual changes in disease activity insignificant.

V.d. Irreversible Effects

Although most drug–receptor interactions are reversible, some drugs act irreversibly through covalent binding. For example, anti-cancer drugs, in particular alkylating agents, act by binding covalently to DNA. For these types of drugs, the relationship between cytotoxic effect and clinical effect is typically complex. A useful variable to evaluate may be the area under the concentration–time curve (AUC) as an estimated measure of total cumulative drug exposure.

Irreversible drug–receptor interactions are not unique to anti-cancer agents. Commonly used drugs such as aspirin and proton pump inhibitors act by covalent binding to their target structures as well. Aspirin acts by irreversible acetylation of certain amino acids, which are essential for the action of both cyclo-oxygenase 1 and 2. Since platelets do not synthesise proteins, the effect of aspirin on platelet aggregation lasts for the remaining life of the platelet (7–10 days). Proton pump inhibitors such as omeprazole, lansoprazole and pantoprazole are pro-drugs that are first transformed to their active forms (sulphenamides) in the acidic compartment of the parietal cell, followed by covalent binding to the H^+,K^+-ATP-ase enzyme. The degree of suppression of gastric acid secretion is correlated to the AUC and is not related to the plasma concentration of the drug at a given time.

V.e. Bell Shaped Concentration–Effect Relationships

Bell shaped concentration–effect relationships (an E_{max} curve, followed by a decrease in effect when concentrations are further increased) have been observed for a number of drugs. Concerning serotonin 5-HT_3 receptor antagonists, a decrease in effect was reported with increasing doses of tropisetron and dolasetron. This implies a bell shaped concentration–effect relationship, which may be due to the fact that these drugs also possess 5-HT_4 receptor agonist properties and therefore gastric prokinetic activity.

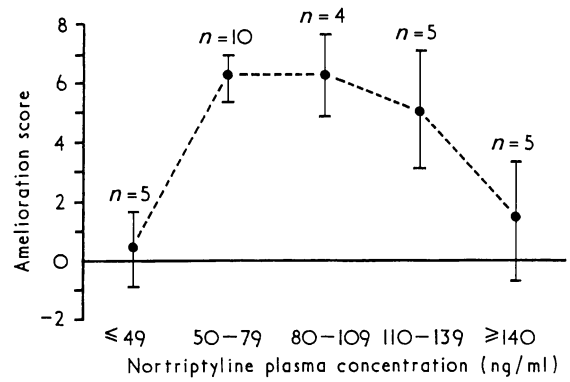


Fig. 9. Relationship between amelioration scores in depressed patients and steady-state plasma concentrations of the antidepressant nortriptyline. Both low and high concentrations are associated with minimum therapeutic effect. (From Asberg M, Cronholm B, Sjöqvist F, Tuck D. Relationship between plasma level and therapeutic effect of nortriptyline. Br Med J 1971;3:331-4, with permission from the BMJ Publishing Group.)

Neuroleptic and antidepressant drugs interact with a number of different receptors in the brain, which may partly explain their PK–PD relationships. Figure 9 shows the bell shaped concentration–response relationship for the antidepressant drug nortriptyline.

V.f. Immediate versus Cumulated Effect, the Efficiency Concept

Instead of describing drug effect by using common pharmacodynamic parameters ($E_{max}, C_{50\%}, s$), one could derive a new variable E/C, also called efficiency (*Eff*). The efficiency concept also is used in areas other than pharmacology and is generally defined as the ratio between the output of a useful response and the input of a factor causing that response. For the sigmoid E_{max} model, efficiency can be derived by dividing both sides of Eq. (12) by C as follows:

$$\begin{aligned} Eff &= E/C \\ &= (E_{max} \times C^{s-1})/(C^s_{50\%} + C^s) \end{aligned} \qquad (12)$$

Efficiency decreases with increasing drug concentrations when the effect approaches its maximum value, E_{max}. The shape of an efficiency curve is shown in Fig. 10.

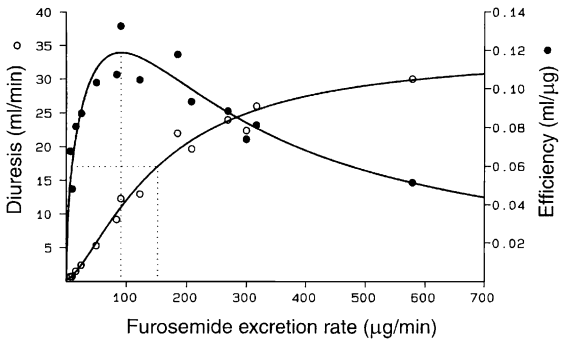


Fig. 10. Diuresis (○) and diuretic efficiency (●) in a subject after the administration of furosemide 0.5 mg/kg. (From Alvan G, Helleday L, Lindholm A, Sanz E, Villén T. Diuretic effect and diuretic efficiency after intravenous dosage of frusemide. Br J Clin Pharmacol 1990;29:215-9, with permission.)

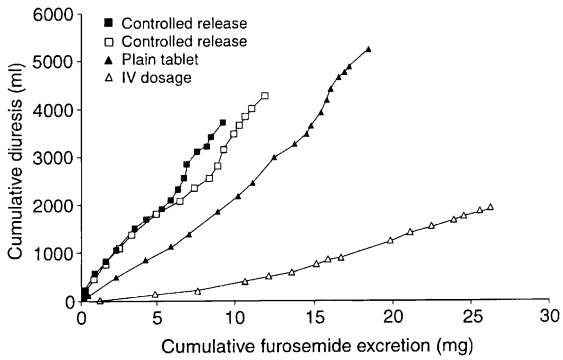


Fig. 11. Cumulative mean diuresis versus cumulative mean furosemide excretion following 60 mg doses given as two controlled release tablets (boxes), as plain tablets (closed triangles) and following an intravenous dosage of 0.5 mg/kg (open triangles). (From Paintaud G. Kinetics of drug absorption and influence of absorption rate on pharmacological effect. Diss. Karolinska Institutet, Stockholm; 1993, reproduced by permission.)

This figure demonstrates that there is a maximally efficient drug concentration at which the highest effect per unit stimulus is obtained ($C_{\text{eff max}}$). The value of $C_{\text{eff max}}$ is only a function of $C_{50\%}$ and s as $C_{\text{eff max}} = C_{50\%}(1-s)^{1/s}$. This is true for $s > 1$, while efficiency is ever increasing with decreasing concentrations for $s < 1$.

Applying the efficiency concept may help to explain why certain drugs with slow absorption and incomplete bioavailability characteristics (the case for many controlled release formulations) may still produce a satisfactory total pharmacological effect over time. This has been convincingly shown for loop diuretics. With the administration of a controlled release formulation of furosemide, drug excretion rates close to $C_{\text{eff max}}$ will be attained for a longer period of time, compared to a plain tablet. The least efficient dosage form of loop diuretics is the intravenous bolus dose. Although this kind of administration will lead to a maximum pharmacological effect at some point, overall efficiency will be decreased, since most of the drug will be excreted by the kidneys at a high rate, which is associated with a low efficiency (Fig. 11).

V.g. Indirect Response Models

Drug distribution does not constitute the sole explanation for the appearance of a counter-clockwise hysteresis. Another reason may be that once the drug has reached its site of action, the cascade of receptor-related and post-receptor events leading to the measured drug effect takes time to develop and lags behind the increase in plasma concentration. Thus, changes in drug concentration (even at the site of action) do not instantly change drug response. In other words, the drug response may be called 'indirect'. Based on previous work, Dayneka et al. (1994) presented a family of four basic indirect response models. The general assumption of these types of models is that a change in a physiological response variable (R) with time reflects the result of a balance between a zero-order production rate (k_{in}) and a first-order elimination rate (k_{out}) (Eq. (13)):

$$\frac{\mathrm{d}R}{\mathrm{d}t} = k_{\text{in}} - k_{\text{out}} \times R \tag{13}$$

An instructive example is the physiological variable serum creatinine. Creatinine is an endogenous metabolite formed from, and thus reflecting, muscle mass. Total body muscle mass is sufficiently constant to render measurement of serum creatinine useful for assessing actual renal function. The serum value of creatinine (R) is namely dependent on the continuous (zero-order) input of creatinine into the blood (k_{in}) and its renal elimination rate, which is a first-order rate process ($k_{\text{out}} \times R$). In case of an extensive muscle breakdown, k_{in} will temporarily increase. It may also be permanently low, for example in old age when muscle mass is reduced. Likewise, creatinine clearance may decrease for various reasons, described by a decrease in k_{out}. An increase in creatinine clearance may occur as well, for example following recovery from renal disease. According to pharmacodynamic indirect response models,

drugs act upon k_{in} and/or k_{out}, stimulating or inhibiting phenomena described by these rate constants, thereby causing a change in the response variable. Realising that a reversible positive response may be obtained by stimulation of k_{in} or inhibition of k_{out} and a reversible negative response may be due to inhibition of k_{in} or stimulation of k_{out}, the following four equations may be derived:

$$\frac{dR}{dt} = k_{in} \times S - k_{out} \times R \quad (14)$$

$$\frac{dR}{dt} = k_{in} - k_{out} \times I \times R \quad (15)$$

$$\frac{dR}{dt} = k_{in} \times I - k_{out} \times R \quad (16)$$

$$\frac{dR}{dt} = k_{in} - k_{out} \times S \times R \quad (17)$$

S represents a stimulation function related to the drug concentration C e.g. as follows:

$$S = 1 + (E_{max} \times C^s)/(C^s_{50\%} + C^s) \quad (18)$$

Analogously, the inhibition function I may be expressed as:

$$I = 1 - (I_{max} \times C^s)/(C^s_{50\%} + C^s) \quad (19)$$

Other stimulation or inhibition functions may be appropriate as well.

Indirect response models have been successfully applied for a number of drugs that display a relatively slow onset of effect compared to their distribution to the site of action. Examples are corticosteroids, warfarin, furosemide and terbutalin. Such models are also particularly appropriate if the measured response is a change in circulating blood cells or endogenous proteins (e.g. hormones or cytokines).

V.h. Tolerance and Counteraction

Tolerance may be broadly defined as diminished responsiveness upon repeated exposure to the same drug or as a decrease in effect over time for a given concentration of drug. Tolerance development has been most frequently demonstrated for drugs that act upon the central nervous system, such as opiate analgesics, nicotine, benzodiazepines, ethanol, cocaine, amphetamine and other adrenoceptor activating drugs. The term is not well defined, in the sense that many different physiological and pharmacological mechanisms may be involved in the development of tolerance. For example, chronic exposure of receptors to an agonist may stimulate receptor uncoupling and breakdown, leading to a decrease in receptor density. Such receptor downregulation has been implicated in the reduced response to beta-receptor agonists such as isoproterenol.

Changes in the availability of cofactors and activity of control mechanisms at the cellular and subcellular level may lead to a decreased affinity between the receptor and the drug or to a decreased receptor-generated response, often called "receptor desensitization". For example, tolerance to opiates has been attributed to up-regulation of the cAMP pathway and persistent changes in transcription factors. Another mechanism for tolerance development is the presence of homeostatic control systems that counteract the primary effect of the drug, hence called "counteracting mechanisms". Rapid administration of antihypertensive drugs may lead to a compensatory increase in heart rate, as has been shown for nifedipine. The action of powerful diuretic drugs, such as furosemide, has been found to activate the counteracting renin–angiotensin–aldosterone and sympathetic nervous systems. A pharmacokinetic explanation for a decreased response upon repeated exposure to a drug is autoinduction, sometimes referred to as metabolic tolerance. This mechanism may partly explain the development of tolerance to drugs such as antiepileptics and ethanol. Some drug responses show virtually no tolerance e.g. inhibition of salivation caused by certain psychotropics or the miotic response to pilocarpin.

Acute within dose tolerance may be revealed by a clockwise hysteresis (proteresis) loop in the effect vs. concentration data plot for a positive response. The visibility of such a hysteresis is influenced by the drug input rate and sampling frequency, especially if the clockwise hysteresis is neutralized by a distributional counterclockwise hysteresis. Another aspect is that drug input rate as such may have a profound influence on the rate and extent of tolerance development, a phenomenon which has been reported for e.g. benzodiazepines and nitrate drugs. This has important implications for study design and drug formulation development. Tolerance development after multiple dosing may be observed as a progressive decrease in cumulated response after each dose. However, any quantification of these changes requires knowledge of the drug's concentration–response relationship. If an E_{max} model is used, receptor downregulation may be modelled as a time

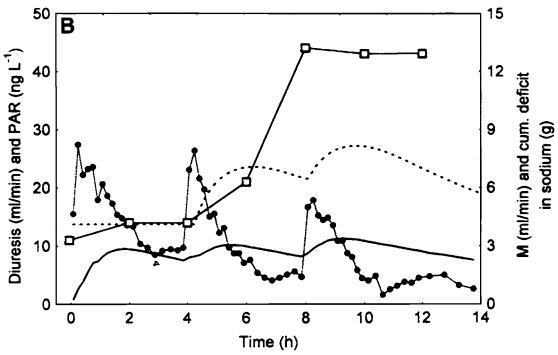


Fig. 12. Diuretic response (●), decreasing when three 30 mg doses of furosemide were administered intravenously at 4-hour intervals, plasma active renin (□), simulated modifier of response (dotted line) and sodium deficit (solid line). (From Wakelkamp M, Alvan G, Gabrielsson J, Paintaud G. Pharmacodynamic modeling of furosemide tolerance after multiple intravenous administration. Clin Pharmacol Ther 1996;60:75-88, with permission from MOSBY Inc.)

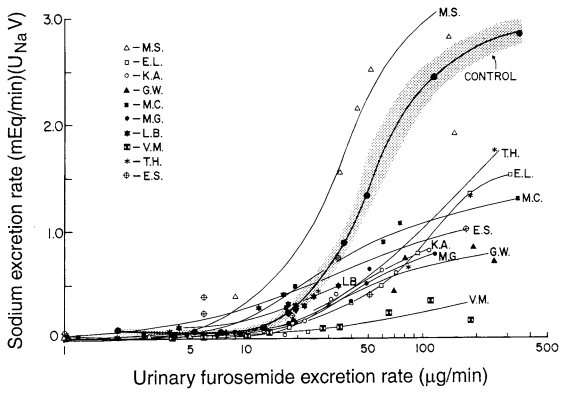


Fig. 13. Relationship between furosemide excretion rate and sodium excretion rate in control subjects and patients with heart failure. The heavy line with large circles and shaded area represent mean and SEM in the controls. The drug is much less potent and efficacious in all but one of the patients compared to the controls. (From Brater C, Chennavasin P, Seiwell R. Furosemide in patients with heart failure: Shift in dose–response curves. Clin Pharmacol Ther 1980;28:182-6, with permission from MOSBY Inc.)

dependent decrease in E_{max}, and receptor desensitization as an increase in $C_{50\%}$. A more flexible approach, using the "hypothetical antagonist model", has been applied to analyze tolerance development to nicotine and morphine. Tolerance development was described using the generation of a hypothetical substance (e.g. a metabolite) in a separate compartment, acting as a noncompetitive antagonist of the effects of nicotine and morphine. Modelling of tolerance development has also been expanded to indirect response models, by adding tolerance parameters which stimulate or inhibit the rate constants of production or loss of response (k_{in} and k_{out}, respectively) (Fig. 12). Examples of these tolerance models applied to furosemide and prolactin can be found in the literature.

A decreased responsiveness induced by disease is shown in Fig. 13. Cardiac insufficiency is associated with a decrease in E_{max} and an increase in $C_{50\%}$ for furosemide.

V.i. Signal Transduction and Mechanistic Models

Drugs interfere with a vast range of physiological functions in order to produce their pharmacological effects. Examples are the inhibition of coagulation factor synthesis (warfarin), the promotion or repression of gene expression (steroids, antisense nucleotides), inhibition of an electrolyte co-transporter (furosemide), inhibition of ATP-ase (digitalis) or binding to specific receptors (e.g. benzodiazepines, neuroleptics). Some of these interventions will inevitably need some time to occur. Pharmacodynamic indirect response models offer a method to evaluate the time lapse as part of the model. However, the effect compartment approach offers a method to allow for the time needed to complete drug distribution. Both types of models should be viewed as oversimplifications of reality, since distribution, as well as receptor and postreceptor events are part of the cascade of events during the pharmacological action of a drug (Fig. 14). Thus, when pre-receptor distributional events are rate limiting, the drug response may be adequately described by an effect compartment model and when postreceptor events are rate limiting, an indirect response model may be more appropriate to describe the concentration–effect relationship. If several of these factors play a role, a combined PK-PD model can be used (Fig. 14).

Mechanistic models can describe pharmacological and physiological events in a more refined fashion and with greater utility than empirical models. Such models make more advanced and more realistic assumptions about drug distribution and effects. Mechanistic models may be used to find optimal sampling times during clinical trial design and to model clinical trial outcomes. The application

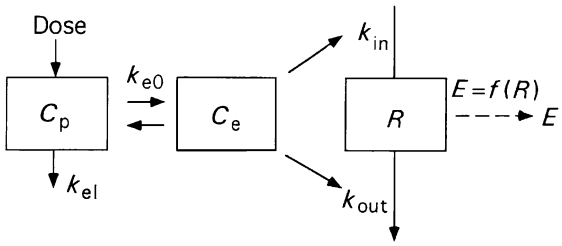


Fig. 14. Schematic description of pharmacokinetic and pharmacodynamic determinants of drug action. Distribution from the measurement site (C_p) to the biophase (C_e), determined by a distribution rate constant k_{e0}, is followed by drug-induced inhibition or stimulation of the production (k_{in}) or removal (k_{out}) of a mediator (R), transduction of the response R and further transformation of R to the measured effect E, if the measured effect variable is not R. (Modified from Jusko WJ, Ko HC, Ebling WF. Convergence of direct and indirect pharmacodynamic response models. J Pharmacokinet Biopharm 1995;23:5-6.)

of mechanistic models should ideally provide better ways to improve drug response in relation to dosage, including optimisation of drug input profile based on schedule dependency and other factors, such as changing receptor functions or counteractive mechanisms.

V.j. Considerations on Biologicals

Biopharmaceuticals are protein macromolecules, usually prepared by recombinant DNA technology, which are used as therapeutics. This group includes replacement hormones such as insulin, cytokines such as interferons, and monoclonal antibodies.

Many biopharmaceutical preparations are heterogeneous and may be difficult to fully characterise. Certain fractions of a preparation may have different biological activity or kinetics than the intended product. It is important that such fractions are appropriately qualified. The proportions of these fractions may be altered when production changes are made or they may be different between similar products produced by different manufacturers. Because of their proteinaceous nature and their novel mechanisms of action, all preclinical and clinical development steps must be re-evaluated. For pharmacokinetic studies, blood concentrations should be measured by specific analytical techniques (most often ELISA), which quantify the active protein and not one of its fragments or inactive forms, such as antigen–antibody complexes. For PK–PD studies of monoclonal antibodies, relevant biomarkers are most often circulating cells (e.g. CD20 lymphocytes during rituximab therapy) or cytokines (e.g. vascular endothelial growth factor during bevacizumab therapy). Indirect response models are therefore particularly appropriate. The concentration–effect relationship of monoclonal antibodies is usually more complex than for conventional "small chemical" drugs because their pharmacokinetics can be influenced by the number of accessible antigens ("antigen mass"); a parameter that will change with time during treatment. In this case, there is interaction between the biopharmaceutical concentration and the concentration of its target, potentially leading to differences in dynamics and kinetics.

V.k. Quantal Response and Survival Rate

As an alternative to evaluating a continuous effect parameter, one may instead define a quantal response or response entity. The Y-axis is then expressed as the probability of reaching this pre-set response, which could be a certain level of blood pressure reduction or the presence of a neurological reflex, etc. During the experiment, the absence or presence of the quantal response is assessed. Logistic regression is performed to estimate the probability of response at each drug concentration. Figure 15 shows an analysis of a quantal response in anaesthesiology.

Survival rate may be a useful endpoint to study in severe medical conditions, associated with significantly decreased longevity. Patients who are recruited for treatment may be followed prospectively and the loss of patients in the study groups is described with Kaplan–Meier statistics. Differences in survival rates between groups are tested by the Log-Rank statistical test, while the influence of a continuous variable such as drug concentration can be tested using the Cox's regression model.

VI. PERSPECTIVES

A major problem in pharmacotherapy is the extensive inter-individual variability in pharmacokinetics, as well as pharmacodynamics, which motivates more research efforts in order to better understand and control how drug effects are produced. Another route to be examined is "schedule dependency" which denotes the possibility that the overall drug response is dependent on how the dosage schedule is constructed. It remains a necessity to understand and

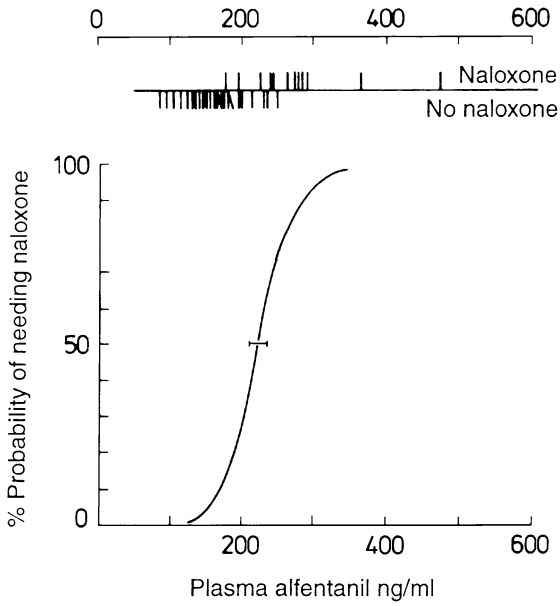


Fig. 15. Relationship between the alfentanil plasma concentrations and the probability of needing naloxone to restore adequate spontaneous ventilation. The diagram at the upper part shows the alfentanil plasma concentrations of the patients who required naloxone (upward deflection) or did not require naloxone (downward deflection). The plasma concentration–effect curve for this clinical endpoint (lower part) was defined from the quantal data shown in the upper diagram using logistic regression. Bars indicate SE of $C_{50\%}$. (From Ausems ME, Hug CC, Stanski DR, Burm AGL. Plasma concentrations of alfentanil required to supplement nitrous oxide anaesthesia for general surgery. Anaesthesiology 1986;65:362-73, reproduced by permission.)

control the production of drug effects through thorough knowledge of a drug's concentration–effect relationship.

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Chapter 12

Drug Therapy in Pediatric Patients

Gregory L. Kearns, John T. Wilson, Kathleen A. Neville, Margaret A. Springer

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I. INTRODUCTION

In stark contrast to adults, the use of drugs in infants, children and adolescents embodies a unique element which must be considered to ensure drug safety and efficacy; namely, the impact of development on both drug disposition and action.

Development, *per se*, represents a continuum of biologic events that enables adaptation, somatic growth, neuro-behavioral maturation and eventually, reproduction. The impact of development on the disposition of a given drug is determined, to a great degree, by age-associated changes in body composition (e.g. body water spaces, circulating plasma protein concentrations) and the acquisition of function of organs and organ systems which are important in determining drug metabolism (e.g. the liver) and excretion (e.g. the kidney). While it is often convenient to classify pediatric patients on the basis of postnatal age for the provision of drug therapy (e.g. neonate $\leqslant$ 1 month of age; infant = 1–24 months of age: children = 2–12 years of age; and adolescents = 12–18 years of age), it is important to recognize that the changes in physiology which characterize development may not correspond to these age defined 'breakpoints'. In fact, the most dramatic changes in drug disposition occur during the first 18 months of life where the acquisition of organ function is most dynamic. Additionally, it is important to note that the pharmacokinetics of a given drug may be altered in pediatric patients consequent to intrinsic (e.g. gender, genotype, ethnicity, inherited diseases) and/or extrinsic (e.g. acquired disease states, xenobiotic exposure, diet) factors which may occur during the first two decades of life.

In addition to the physiological and psychological development that is quite evident during the first two decades of life, it is apparent that ontogeny can also have a profound impact on drug action. While current information rarely permits one to profile a predictable relationship between age and pharmacodynamics, age-associated differences in the dose versus concentration versus effect relationship are evident for many therapeutic drugs. It is not known, however, whether these differences represent discrete and definable 'events' associated with drug receptor interaction (e.g. receptor number/density, affinity, kinetics of association/dissociation) or alternatively, age related differences in the complex milieu of post receptor biochemical events (e.g. the availability and residence of second messengers, the number and types of G-proteins, alterations in transmembrane ion flux capable of altering activity of channel-linked receptors, etc.).

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For a practitioner to develop a rational and sound pharmacotherapeutic approach to the pediatric patient, it is essential that he or she considers the developmental 'factors' (physiological, psychological and pharmacological) that make infants, children and adolescents different from adults. It is the goal of this chapter to provide the reader not with a drug-specific overview of pediatric clinical pharmacology but rather, a premise upon which to consider the potential impact (both therapeutic and toxicologic) of ontogeny on drug disposition and action.

II. DEVELOPMENT AND DRUG DISPOSITION

Development has been shown to impact upon each of the 'phases' of drug disposition (e.g. absorption, distribution, metabolism and excretion). A better understanding of the various physiological variables regulating and determining the fate of drugs in the body has, in many instances, dramatically improved both the safety and efficacy of drug therapy for neonates, infants, children and adolescents. This understanding has largely resulted over the last 20 years from guided clinical experience in pediatric drug therapy (e.g. application of therapeutic drug monitoring and clinical pharmacokinetics) and also, from carefully conducted pediatric clinical trials designed to characterize the disposition of both old and new drugs. Accordingly, it is most useful to conceptualize pediatric pharmacokinetics by examining the impact of development on those physiological variables that govern drug absorption, distribution, metabolism and excretion.

II.a. Drug Absorption

The rate and extent of gastrointestinal (GI) absorption is primarily dependent upon pH dependent passive diffusion and motility of the stomach and small intestine, both of which control transit time. In term (i.e., fully mature) neonates, the gastric pH ranges from 6 to 8 at birth and drops to 2–3 within the first few hours. After the first 24 hours of extrauterine life, the gastric pH increases to approximately 6–7 consequent to immaturity of the parietal cells. A relative state of achlorhydria remains until adult values for gastric pH are reached at 20–30 months of age. In the neonate, GI transit time is prolonged consequent to reduced motility and peristalsis. Gastric emptying is both irregular and erratic, and only partially dependent upon feeding. Gastric emptying rates approximate adult values by 6–8 months of age. During infancy, intestinal transit time is generally reduced relative to adult values consequent to increased intestinal motility. In the neonate and young infant, additional factors may play a role in intestinal drug absorption. These include relative immaturity of the intestinal mucosa leading to increased permeability, immature biliary function, high levels of β-glucuronidase activity and variable microbial colonization.

The developmental changes in GI function or structure in the newborn period and early infancy produce alterations in drug absorption which are quite predictable. In general, the oral bioavailability of acid-labile compounds (e.g. β-lactam antibiotics) is increased while that of weak organic acids (e.g. phenobarbital, phenytoin) is decreased. For orally administered drugs with limited water solubility (e.g. phenytoin, carbamazepine), the rate of absorption (i.e. t_{max}) can be dramatically altered consequent to changes in GI motility. In older infants with more rapid rates of intestinal drug transit, reductions in residence time for some drugs (e.g. phenytoin) and/or drug formulations (e.g. sustained-release theophylline) can reduce the extent of absorption (i.e. decreased bioavailability). Finally, as illustrated by investigations of the antiviral agent pleconaril, the extent of bioavailability of extremely lipophilic drugs and, in some instances, certain prodrugs (e.g. chloramphenicol palmitate) can be reduced in neonates consequent to reductions in intraluminal enzyme (e.g. lipase) content and activity. As well, developmental immaturity in other intestinal enzymes (e.g. CYP3A4) and/or transport proteins (e.g. *p*-glycoprotein) whose activities can be rate-limiting for the presystemic clearance of specific drug-substrates may translate into altered drug bioavailability in the neonate and young infant.

In the newborn and young infant, both rectal and percutaneous absorption is highly efficient for properly formulated drug products. The bioavailability of many drugs administered by the rectal route (e.g. diazepam, acetaminophen) is increased not only consequent to efficient translocation across the rectal mucosa but also, reduced presystemic drug clearance produced by immaturity of many drug metabolizing enzymes in the liver. Both the rate and extent of percutaneous drug absorption is increased consequent to a thinner and more well-hydrated stratum corneum in the young

Table 1. Summary of drug absorption in neonates, infants and children

	Neonate	Infants	Children
Physiological alteration			
Gastric emptying time	Irregular	Increased	Slightly increased
Gastric pH	>5	4–2	Normal (2–3)
Intestinal motility	Reduced	Increased	Slightly increased
Intestinal surface area	Reduced	Near adult	Adult pattern
Microbial colonization	Reduced	Near adult	Adult pattern
Biliary function	Immature	Near adult	Adult pattern
Muscular blood flow	Reduced	Increased	Adult pattern
Skin permeability	Increased	Increased	Near adult pattern
Possible pharmacokinetic consequences			
Oral absorption	Erratic-reduced	↑ rate	Near adult pattern
I.m. absorption	Variable	Increased	Adult pattern
Percutaneous absorption	Increased	Increased	Near adult pattern
Rectal absorption	Very efficient	Efficient	Near adult pattern
Pre-systemic clearance	<adult	>adult	>adult (↑ rate)

Direction of alteration given relative to expected normal adult pattern.
Adapted from Morselli, 1983.

infant. As a consequence, systemic toxicity can be seen with percutaneous application of some drugs (e.g. diphenhydramine, lidocaine, corticosteroids, hexachlorophene) to seemingly small areas of the skin during the first 8–12 months of life.

In contrast to older infants and children, the rate of bioavailability for drugs administered by the intramuscular route may be altered (i.e. delayed t_{max}) in the neonate. This developmental pharmacokinetic alteration is the consequence of relatively low muscular blood flow in the first few days of life, the relative inefficiency of muscular contractions (useful in dispersing an intramuscular (i.m.) drug dose) and an increased percentage of water per unit of muscle mass. Generally, i.m. absorption of drugs in the neonate is slow and erratic with the rate dependent upon the physicochemical properties of the drug and on the maturational stage of the newborn infant.

Developmental differences in drug absorption between neonates, infants and older children are summarized in Table 1. It must be recognized that the data contained therein reflect developmental differences which might be expected in healthy pediatric patients. Certain conditions and disease states might modify the function and/or structure of the absorptive surface area(s). GI motility and/or systemic blood flow can further impact upon either the rate or extent of absorption for drugs administered by extravascular routes in pediatric patients.

II.b. Drug Distribution and Plasma Protein Binding

During development, marked changes in body composition occur. Alterations in the total body water (TBW), extracellular water (ECW) and body fat 'pools' are illustrated in Fig. 1. The most dynamic changes occur in the first year of life with the exception of total body fat which in males is reduced by approximately 50% between 10 and 20 years of life.

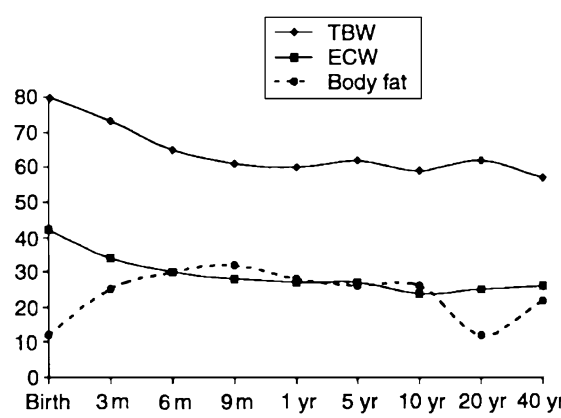


Fig. 1. Developmental changes in body water and fat content (from Ritschel WA and Keams GL, 1999, reproduced by permission from the *Handbook of Basic Pharmacokinetics*, 5th edn. © 1999 by the American Pharmaceutical Association).

Table 2. Plasma protein binding and drug distribution

	Neonate	Infants	Children
Physiological alteration			
Plasma albumin	Reduced	Near normal	Near adult pattern
Fetal albumin	Present	Absent	Absent
Total proteins	Reduced	Decreased	Near adult pattern
Total globulins	Reduced	Decreased	Near adult pattern
Serum bilirubin	Increased	Normal	Normal adult pattern
Serum free fatty acids	Increased	Normal	Normal adult pattern
Blood pH	7.1–7.3	7.4 (normal)	7.4 (normal)
Extracrainial adipose tissue	Scarce	Reduced/Generally reduced	
Total body water	Increased	Increased	Near adult pattern
Extracellular water	Increased	Increased	Near adult pattern
Endogenous maternal			
Substances (ligands)	Present	Absent	Absent
Possible pharmacokinetic consequences			
Free fraction	Increased	Increased	Slightly increased
Apparent volume of distribution			
Hydrophilic drugs	Increased	Increased	Slightly increased
Hydrophobic drugs	Reduced	Reduced	Slightly decreased
Tissue/plasma ratio	Increased	Increased	Slightly increased

Direction of alteration given relative to expected normal adult pattern.
Adapted from Morselli, 1983.

In females, this reduction is not as dramatic, decreasing from approximately 28–25% during this same period. It is also important to note that adipose tissue of the neonate may contain as much as 57% water and 35% lipids, whereas values in the adult approach 26.3% and 71.7%, respectively. Finally, despite the fact that body fat content during the first 3 months of life is low relative to the other periods of development, the lipid content of the developing central nervous system is quite high; thus having potential adverse implications for the localization of lipophilic compounds (e.g. propranolol) administered early in life during critical periods of brain growth.

In addition to age-related alterations in body composition, the neonatal period is characterized by certain physiologic alterations which are capable of reducing the plasma protein binding of drugs (Table 2). In the neonate, the free fraction of drugs which are extensively (i.e. $>80\%$) bound to circulating plasma proteins is markedly increased, largely due to lower concentrations of drug binding proteins (i.e. a lower number of binding sites), reduced binding affinity (e.g. lower binding affinity for weak acids to fetal albumin, presence of acidic plasma pH and endogenous competing substrates such as bilirubin, free fatty acids). This is exemplified by phenytoin, a weak acid that is 94–98% bound to albumin in adults (i.e. free fraction = 2–4%) but only 80–85% bound in the neonate (i.e. free fraction = 15–20%). Consequent to developmental immaturity in the activity of hepatic microsomal enzymes that are responsible for phenytoin biotransformation, compensatory clearance of the increased free fraction does not occur, thereby producing an increased amount of free phenytoin in the plasma and CNS. Consequently, this particular age dependent alteration in drug binding functionally reduces the total plasma phenytoin level associated with both efficacy and toxicity in the newborn, as compared to older infants and children where phenytoin protein binding is similar to that observed in adults. Reduced plasma protein binding associated with absolute and relative differences in the sizes of various body compartments (e.g. total body water, extracellular fluid, composition of body tissues) frequently influences the apparent volume of distribution for many drugs and also, their localization (i.e. both uptake and residence) in tissue. As illustrated by the examples contained in Table 3, the apparent volume of distribution of small molecular weight compounds which

Table 3. Examples of age-related differences in pharmacokinetics

Drug	$V_{d\ ss}$ (l/kg)			Elimination $t_{1/2}$ (h)		
	PT	T	Infant	PT	T	Infant
Ampicillin	0.7	0.65	0.6	4–6	2–3	0.8–1.5
Cefotaxime	0.7	0.6	0.5	5–6	2–3	1.1–1.5
Vancomycin	0.9	0.7	0.6	6–10	4–6	2.5–3
Gentamicin	0.5	0.45	0.35	4–12	3–4	2–3
Chloramphenicol	1.2	0.8	0.5–0.7	20–24	10–12	1.5–3.5
Digoxin	5–7	8–10	10–15	60–170	34–45	18–25

Abbreviations include: PT, preterm neonate; T, term neonate; $V_{d\ ss}$, apparent steady state volume of distribution and $t_{1/2}$, half-life.

are not extensively bound to plasma proteins (e.g. ampicillin, cefotaxime, gentamicin) corresponds to age-related alterations in the total body water space and extracellular fluid pool (Fig. 1). In contrast, the apparent volume of distribution for digoxin, a drug extensively bound to muscle tissue, does not decrease during the first years of life but rather increases to values (i.e. 10–15 l/kg for infants) which exceed those reported for adults (e.g. 5–7 l/kg); alterations that reflect both age-related changes in body composition and the affinity of digoxin for its binding sites.

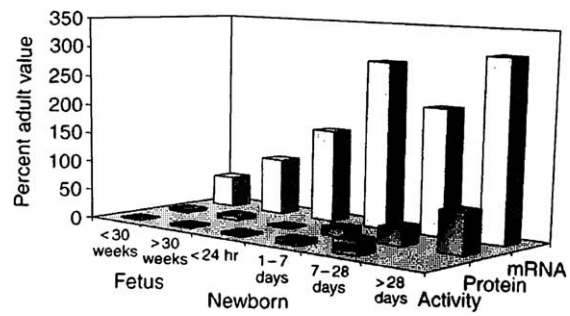


Fig. 2. Ontogeny of CYP2D6 in the fetus and neonate (adapted from Treluyer et al., 1991).

II.c. Drug Metabolism

In general, most of the enzymatic activities responsible for metabolic degradation of drugs are reduced in the neonate. Certain phase I biotransformation reactions (e.g. hydroxylations) appear to be more compromised than others (e.g. dealkylation reactions). This is reflected by prolonged clearance of compounds such as phenytoin, phenobarbital, diazepam, lidocaine, meperidine and indomethacin, during the first 2 months of life. Phase II reactions are also unevenly reduced with sulfate and glycine conjugation activities present at near adult levels during the first month of life as opposed to glucuronidation (i.e. the activity of specific UDP glucuronosyltransferase isoforms) which is reduced as reflected by prolonged elimination of chloramphenicol (Table 3) in the neonate.

It must be recognized that developmental differences in hepatic drug metabolism occur consequent to reductions in the activity of specific drug-metabolizing enzymes and their respective isoforms. For most enzymes, the greatest reduction of activity is seen in premature infants where immature function may also reflect continued organogenesis. This is illustrated by examining data concerning the ontogeny of cytochrome P450 (CYP) 2D6; a polymorphically expressed enzyme which comprises only 2–3% of all drug-metabolizing CYPs in human liver but regulates the biotransformation of over 50 therapeutically used drugs (e.g. captopril, amitryptyline, codeine, fluoxetine, dextromethorphan, paroxetine, flecanide, haloperidol, propranolol, timolol, thioridazine, imipramine). As shown in Fig. 2, the CYP2D6 mRNA at approximately one to four weeks of postnatal life far exceeds the normal values observed in adults while the concentration of CYP2D6 protein is only a fraction of that observed in adults. Also, a marked discordance is evident between the activity of the enzyme and the amount of protein in the first week of life. Finally, as postnatal development ensues, the 'pattern' of CYP2D6 activity increases over time in proportion to the amount of protein such that by 6–8 months of life, the CYP2D6 activity approximates adult levels.

As reflected by an examination of the ontogeny of important drug metabolizing enzymes as summarized in Table 4, it is apparent that maturation

Table 4. Developmental patterns for the ontogeny of important drug metabolizing enzymes in man

Enzyme(s)	Known developmental pattern
Phase I enzymes	
CYP2D6	Low to absent in fetal liver but present at 1 week of age. Poor activity (i.e., 20% of adult) by 1 month. Adult competence by 12 months of age.
CYP2C19, CYP2C9	Apparently absent in fetal liver. Low activity in first 2–4 weeks of life with adult activity reached by approximately 6 months. Activity may exceed adult levels during childhood and declines to adult levels after conclusion of puberty.
CYP1A2	Not present in appreciable levels in human fetal liver. Adult levels reached by approximately 4 months and exceeded in children at 1–2 years of age. Adult activity reached after puberty.
CYP3A7	Fetal form of CYP3A which is functionally active (and inducible) during gestation. Virtually disappears by 1–4 weeks of postnatal when CYP3A4 activity predominates, but remains present in approximately 5% of individuals.
CYP3A4	Extremely low activity at birth reaching approximately 30–40% of adult activity by 1 month and full adult activity by 6 months. May exceed adult activity between 1–4 years of age, decreasing to adult levels after puberty.
Phase II enzymes	
NAT2	Some fetal activity by 16 weeks gestation. Poor activity between birth and 2 months of age. Adult phenotype distribution reached by 4–6 months with adult activity reached by 1–3 years.
TPMT	Fetal levels approximately 30% of adult values. In newborns, activity is approximately 50% higher than adults with phenotype distribution which approximates adults. Exception is Korean children where adult activity is seen by 7–9 years of age.
UGT	Ontogeny is isoform specific. In general, adult activity is reached by 6–24 months of age.
SULT	Ontogeny is isoform specific and appears more rapid than that for UGT. Activity for some isoforms may exceed adult levels during infancy and early childhood.

Abbreviations include: CYP, cytochrome P450; NAT2, N-acetyltransferase-2; TPMT, thiopurine methyltransferase; UGT, glucuronosyltransferase and SULT, sulfotransferase.
Adapted from Leeder and Kearns, 1997.

of activity is enzyme, and in some cases, isoform-specific. It is also important to note that for enzymes which are polymorphic in their expression (i.e. more than one phenotype for activity), development *per se* may produce a discordance between the phenotype and genotype. This is exemplified by N-acetyltransferase-2 (NAT2) where reduced enzyme activity results in over 80% of infants being classified as the poor-metabolizer phenotype during the first 2 months of age.

As denoted in Table 4, the activity of selected phase I and phase II enzymes in young infants can exceed that for adults. The potential pharmacologic implications of this particular developmental alteration in drug metabolism is exemplified by examining the impact of age on the predicted steady state plasma concentrations of theophylline (a predominant CYP1A2 and xanthine oxidase substrate) from a fixed dose of the drug (Fig. 3). In the first 2 weeks of life, the activity of all of the cytochromes P450 and other enzymes (e.g. xanthine oxidase) responsible for theophylline biotransformation is markedly diminished; leaving renal excretion of unchanged drug and *trans*-methylation of theophylline to caffeine as the predominant clearance pathways. By 3–6 months of postnatal age, CYP1A2 ontogeny results in activity of the enzyme which can exceed adult levels, thus increasing the plasma clearance of theophylline to maximum values at 16–48 months of age as reflected by steady-state theophylline concentrations illustrated in Fig. 3. Despite emerging information on isoform-specific developmental differences in the activity of several important drug metabolizing enzymes, there is little or no evidence that clearly describes the regulatory events at a cellular or molecular level that are responsible for producing these differences. While it was commonly believed that age-dependent differences in hepatic size (relative to total body size) in children was in part responsible for the apparent increased activity of many drug metabolizing enzymes during childhood, Murry et al. demonstrated that liver vol-

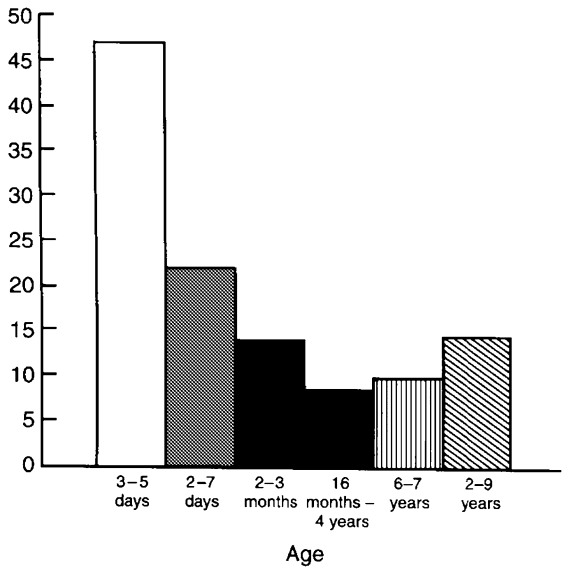


Fig. 3. Impact of development on theophylline plasma concentrations (from Ritschel WA and Kearns GL, 1999, reproduced by permission, from the *Handbook of Basic Pharmacokinetics*, 5th edn. © 1999 by the American Pharmaceutical Association).

ume in children was not associated with changes in the normalized (i.e. to weight and/or body surface area) plasma clearance of lorazepam, antipyrine or indocyanine green. Thus, increased clearance of pharmacologic substrates for selected phase I and II drug-metabolizing enzymes observed in infants and children appears to be the consequence of developmentally dependent increases in enzyme activity as opposed to amount of enzyme.

Finally, it is possible that neuroendocrine determinants of growth and maturation may, in part, be responsible for observed developmental differences in the activity of certain drug-metabolizing enzymes. As recently postulated, the biological effects of human growth hormone expressed during development may account for observed differences in the activity of specific drug-metabolizing enzymes. Support for this assertion was drawn from evidence that human growth hormone can modulate the effect of many general transcription factors, the demonstrated regulatory role for growth hormone in the expression of CYP2A2 and CYP3A2 in rats, the documented effects of human growth hormone treatment on the alteration of the pharmacokinetics for pharmacologic substrates of selected P450 cytochromes, and also, evidence of altered CYP1A2 activity which appears to correlate with the pubertal height spurt.

As expected, age-related differences in the activity of drug-metabolizing enzymes can have dramatic clinical implications for dose and dose interval selection. An understanding of the basic clinical pharmacology of a given drug (often available from studies conducted in older children or adults), the ontogeny of drug-metabolizing enzymes (Table 4) and of the other physiological alterations that occur during development that potentially impact hepatic drug metabolism can enable prediction of the possible pharmacokinetic consequences as summarized in Table 5. Determination of the developmental 'break points' for the activity of drug-metabolizing enzymes can also enable effective guidance of drug dosing and/or the study of new drugs by eliminating arbitrary age-based categories (e.g. infant, child and adolescent) which may or may not have anything to do with the competence of a specific drug-metabolizing enzyme.

II.d. Renal Drug Excretion

At birth, the kidney is anatomically and functionally immature. The acquisition of renal function depends, more than any other organ, on gestational age and postnatal adaptations. In the preterm infant, renal function is dramatically reduced, largely due to the continued development of functioning nephron units (i.e. nephrogenesis). In contrast, the acquisition of renal function in the term neonate represents, to a great degree, recruitment of fully developed nephron units. In both term neonates and preterm infants who have birth weights > 1500 g, glomerular filtration rates increase dramatically during the first 2 weeks of postnatal life (Fig. 4). This particular dynamic change in function is a direct result of postnatal adaptations in the distribution of renal blood flow (i.e. medullary distribution to corticomedullary border), resulting in dramatic recruitment of functioning nephron units. In addition, there is a situation of glomerular–tubular imbalance due to a more advanced maturation of glomerular relative to tubular function. Such an imbalance may persist for up to 6–10 months of age where both tubular and glomerular function approach normal values for adults. The ontogeny of renal function and the potential pharmacokinetic consequences which occur during development are summarized in Table 6.

The fact that the ontogeny of renal function has been the most well characterized of any organ responsible for drug elimination makes it possible

Table 5. Drug metabolism in the neonate, infant and child

	Neonate	Infants	Children
Physiological alteration			
Liver/body weight ratio	Increased	Increased	Slightly increased
Cytochromes P450 activity	Reduced	Increased	Slightly increased
Blood esterase activity	Reduced	Normal (by 12 mo.)	Adult pattern
Hepatic blow flow	Reduced	Increased	Near adult pattern
Phase II enzyme activity	Reduced	Increased	Near adult pattern
Possible pharmacokinetic consequences			
Metabolic rates	Reduced	Increased	Near adult pattern*
Pre-systemic clearance	Reduced	Increased	Near adult pattern
Total body clearance	Reduced	Increased	Near adult pattern*
Inducibility of enzymes	More evident	Slightly increased	Near adult pattern*

Direction of alteration given relative to expected normal adult patterns.

*denotes assumption of adult pattern of activity after the conclusion of puberty. The activity of all drug metabolizing enzymes is generally higher before vs. after puberty.

Adapted from Morselli, 1983.

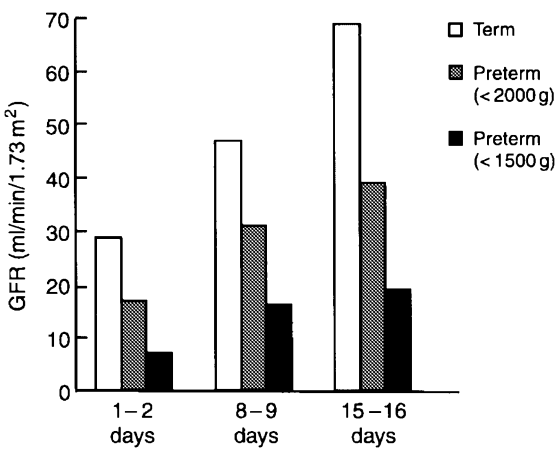


Fig. 4. Ontogeny of glomerular filtration in the neonate (from Ritschel WA and Kearns GL, 1999, reproduced by permission, from the *Handbook of Basic Pharmacokinetics*, 5th edn. © 1999 by the American Pharmaceutical Association).

to accurately predict the potential impact of development on the elimination characteristics of drugs which are predominantly excreted by the kidney. This is well illustrated by a study by James et al. of famotidine, an H_2 receptor antagonist which in older children and adults is approximately 80% excreted unchanged in the urine. As illustrated by the data (Table 7), the renal clearance of famotidine in children was approximately fivefold higher than that observed in neonates; populations where the average glomerular filtration rates would be expected to be approximately 100 and 20 ml/min/1.73 m^2, respectively. Also, correlations between postnatal age, renal function status (i.e. glomerular filtration rate and tubular secretory capacity) and drug clearance have been demonstrated for aminoglycoside antibiotics, vancomycin, β-lactam antibiotics and ranitidine; all of which are predominantly excreted via renal mechanisms.

III. IMPACT OF PHARMACOGENETICS ON PHARMACOKINETICS AND PHARMACODYNAMICS

Pharmacogenetics plays a role in ontogeny through its influence on drug disposition and/or action. Several important drug-metabolizing enzymes which, to some degree, demonstrate a dependence upon development for their activity are polymorphically expressed in man. Therapeutic implications of genetic polymorphisms are illustrated by the following examples. CYP2C9 is polymorphically expressed with point mutations giving rise to three allelic variants (CYP2C9*1, 2 and 3). Inheritance of the CYP2C9*2 and/or CYP2C9*3 allele convey reduced enzyme activity as reflected by a 5.5- and 27-fold reduction, respectively, in catalytic activity towards S-warfarin, a CYP2C9 substrate. Ibuprofen, a CYP2C9 substrate, shows a relationship between clearance and age that is linear and in part, may be influenced by the CYP2C9 polymorphism. Additionally, the disposition of phenytoin, another CYP2C9 substrate, has

Table 6. Renal function in the neonate, infant and child

	Neonate	Infants	Children
Physiological alteration			
Kidney/body weight ratio	Increased	Increased	Near adult values
Glomerular filtration rate	Reduced	Normal (by 12 mo.)	Normal adult values
Active tubular secretion	Reduced	Near normal	Normal adult values*
Active tubular reabsorption	Reduced	Near normal	Normal adult values
Proteins present in urine	Present (30%)	Low to absent	Normally absent
Urinary acidification	Low	Normal (by 1 mo.)	Normal adult activity
Urine output (ml/h/kg)	3–6	2–4	1–3
Urine concentration	Reduced	Near normal	Normal adult values
Possible pharmacokinetic consequences			
Active drug excretion	Reduced	Near normal	Normal adult pattern
Passive drug excretion	Reduced to increased	Increased	Normal adult pattern
Excretion of basic drugs	Increased	Increased	Near normal

Direction of alteration given relative to expected normal adult patterns.
*Denotes slight increase in excretion rate for basic compounds.
Adapted from Morselli, 1983.

Table 7. Famotidine pharmacokinetics in neonates and children

Patient group	$t_{1/2}$ (h)	Cl (l/h/kg)	Cl_{renal} (l/h/kg)
Children ($n = 12$, 1.1–12.9 yr)	3.2	0.70	0.45
Neonates ($n = 10$, 936–3495 g)	10.9	0.13	0.09

Abbreviations include: $t_{1/2}$, elimination half-life; Cl, total plasma clearance and Cl_{renal}, renal clearance.
Data expressed as mean values (from James et al., 1998).

been shown to vary considerably based on the specific CYP2C9 genotype, with the presence of certain alleles (e.g. CYP2C9*3) having an apparent dramatic influence on the dose versus plasma concentration relationship and potentially, the therapeutic index for this drug.

III.a. Practical Clinical Applications of Pharmacogenetics

Advances in technology (e.g. commercially available gene chip assays for *CYP2D6, CYP2C9, CYP2C19, UGT1A1*) are bringing the introduction of pharmacogenetics into the process of clinical therapeutics ever closer. As illustrated by the examples contained in Table 8, there are a host of polymorphically expressed genes with currently validated assays which, when properly applied, can provide important information that can be used to profile patient risk for adverse drug events (e.g., *NAT2, VKORC1, CYP2C9, CYP2D6, TPMT*), guide dose selection (e.g., *VKORC1* and *CYP2C9* for warfarin dosing) and direct drug selection by providing an indication of susceptibility for a given therapeutic target (e.g., *Bcr-abl* for Glivec treatment of chronic myelogenous leukemia). Despite the apparent great potential of pharmacogenomics to permit precise individualization of drug therapy and thereby, improve safety

Table 8. Examples of gene polymorphisms of potential clinical utilityin therapeutic decision making

- NAT2 – hydralazine-associated SLE
- VKORC1 & CYP2C9 – warfarin-associated hemorrhage
- UGT1A1 – irenotecan
- G6PD – primaquine-associated hemolysis
- HERG – quinidine-associated arrhythmia
- CYP2D6 – codeine, tramadol, antidepressant-associated efficacy and AE, taxol
- *Bcrlabl* – glivec treatment of CML
- HER2 – herceptinefficacy in breast cancer
- TPMT – 6MP and azathioprine-associated anemia

and efficacy, many of the purported 'achievements' have heretofore, been disappointing with respect to their ability to significantly improve drug therapy for large numbers of patients.

In view of the apparent complexity of pharmacogenetics and its integration into clinical therapeutics, there are some general, practical queries which merit consideration. These are summarized as follows:

Are the genes chosen for examination of quantitative importance to drug disposition and/or action? As illustrated by Fig. 5, the regulation of drug disposition and action is, in most instances, polygenically determined. Thus, selection of a single genotyping test may not provide a sufficiently complete picture of the phenotypic consequences (e.g. altered drug clearance, drug transporter function, receptor expression) for specific allelic variants in a given gene. A relevant example resides in the use of pharmacogenetics as a tool to aid in the selection of warfarin dose for anticoagulation. Recent information illustrates that polymorphic expression of both CYP2C9 (the enzyme primarily responsible for catalyzing biotransformation of the S-enantiomer of warfarin) and VKORC1 (the enzyme responsible for bioactivation of vitamin K) when considered in combination markedly improve the ability to accurately predict warfarin dose requirements as compared to *CYP2C9* genotype alone.

Does the drug display a narrow therapeutic range? In the case of drug metabolizing enzymes where genotyping is currently used clinically, the results (i.e., implied phenotype) are most often directed at either explaining an apparent drug-associated adverse event or alternatively, preemptive dose adjustment (based on presumed phenotype) to avoid toxicity (e.g., *VKORC1* and *CYP2C9* to prevent warfarin-associated hemorrhage by *a priori* dose selection; *UGT1A1* to individualize irinotecan dosing; *CYP2D6* to individualize dose of atomoxetine in children with attention deficit hyperactivity disorder; TPMT genotyping for dose selection of 6-mercaptopurine and azathioprine). The aforementioned examples illustrate that the concern is not only that with drugs that are known to have a narrow therapeutic index in the general population (e.g., warfarin) but also, compounds that in a segment of the population (e.g., patients with a poor-metabolizer phenotype for a polymorphically expressed enzyme) may also exhibit a small difference

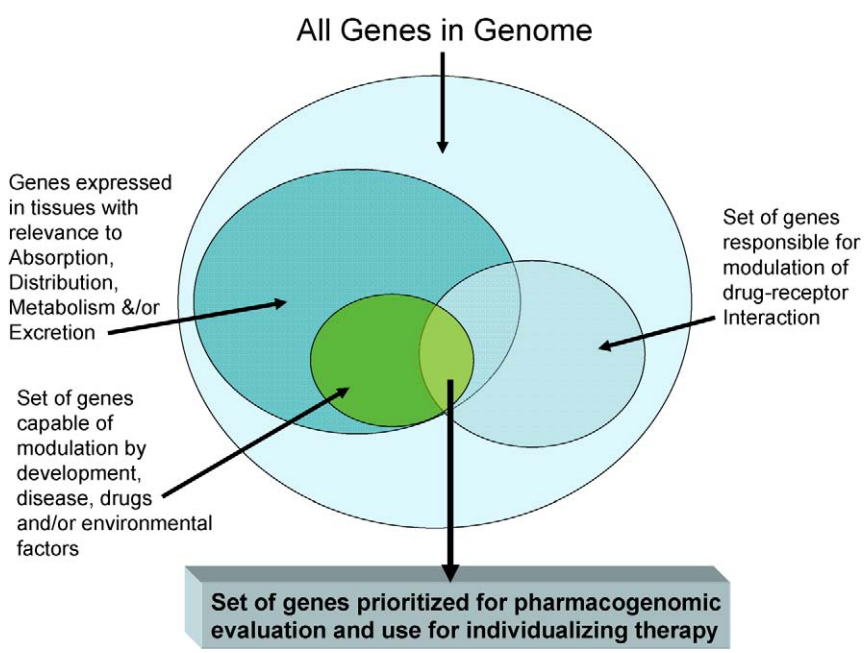


Fig. 5. Selection of 'candidate genes' for selection in a either a study examining the role of pharmacogenomics in drug disposition and/or action or alternatively, use as a clinical tool to individualize drug therapy. Those genes prioritized for inclusion should be those shown to contribute markedly to drug pharmacokinetics and/or dynamics.

between therapeutic and toxic dose. While drug toxicity always represents an adverse drug effect and demands that the available scientific 'tools' of pharmacokinetics, therapeutic drug monitoring and pharmacogenetics be used in an effort to prevent or minimize its occurrence, it is also important to recognize that pharmacogenetic determinants of drug efficacy also exist. This is exemplified by consideration of the dose–concentration–effect relationship for the proton pump inhibitors; all of which are substrates for the polymorphically expressed enzyme CYP2C19. When treating infections caused by *H. pylori*, both omeprazole and lansoprazole demonstrated a gene-dose effect for CYP2C19 that correlated with treatment success when standard doses of the drugs were used.

Can the genotype be translated into a quantitative reflection of protein activity capable of accurately predicting function? The clinical utility of pharmacogenetics is largely the result of being able to accurately infer phenotype for a drug metabolizing enzyme and/or transporter from genotype. In those instances where genotype–phenotype concordance is present, discernment of genotype can enable assignment of an individual to one of several phenotypic groups (e.g., extensive (wild-type), ultrarapid, intermediate and poor metabolizers (variant alleles)). While such an approach permits a form of functional categorization that in some instances, can profile risk of an adverse event and/or enable *a priori* dose selection so as to 'correct' for phenotypic differences, it has rarely provided clinicians with an accurate prediction of either a pharmacokinetic (e.g., plasma drug clearance) or pharmacodynamic variables that can be used to individualize drug treatment. A notable exception to this general dictum appears to reside with genotyping for *CYP2D6*. When one considers previous studies that used pharmacologic probe substrates (e.g., debrisoquine, dextromethorphan) to assign CYP2D6 phenotype, the difference between the extremes of the frequency distribution for individuals classified as 'extensive metabolizers' is greater than one order of magnitude. With the elucidation of 60 different *CYP2D6* alleles and examination of their association with CYP2D6 activity as reflected by dextromethorphan biotransformation, it is now possible to assign 'activity scores' to specific genotypes. The utility of this approach in a pediatric population has been demonstrated by a recent study which examined the impact of ontogeny on dextromethorphan biotransformation during the first year of life.

Can the genotyping be performed accurately and in quasi-real time? Over the past 25 years, the development of sensitive and specific methods for quantifying drugs from blood and other biological fluids and their subsequent translation to the clinical laboratory setting has enabled the development of Therapeutic Drug Monitoring (TDM). Without question, TDM has proven to be a clinically useful tool to individualize drug therapy. At its clinical inception, TDM was generally used as a retrospective approach to assess the adequacy of treatment. With advances in pharmacokinetics (e.g., Bayesian estimation, population pharmacokinetic analyses) and automated bioanalytical techniques which make results virtually available to the clinician within a few hours after a sample has been obtained, TDM has evolved into a more prospective therapeutic approach. This is not presently the case for pharmacogenetics despite the marketing of chip- and bead-based technologies which enable the accurate performance of an increasingly wide variety of genotyping assays; the majority of which focus on polymorphically expressed drug metabolizing enzymes of quantitative importance in human therapeutics (e.g., *CYP2C9, UGT1A1, CYP2D6*). As the value of incorporating pharmacogenetic information into therapeutic decision making increases, the demand for tests with proven clinical utility will continue to drive technology and thus, the availability of genotyping. The result will likely follow the pattern of TDM with regard to the increased availability of accurate, reliable, timely and cost-effective testing in the clinical arena.

What information is needed to interpret pharmacogenetics data in the context of therapeutic decision making? Like TDM, the true utility of clinical pharmacogenetics will reside with the systematic evaluation of its ability to markedly contribute to the outcome of drug therapy by making it safer and more effective. In order to accomplish this overarching goal, a synthesis of information is required so as to enable the effective interpretation and use of pharmacogenetic information. Several examples of the kind of information that must be available and considered are as follows:

- Accurate genotyping information for all relevant genes (Fig. 5)
- Complete access to the patient's medical information (i.e., the medical record)

- Full access to the patient so that an appropriate history (e.g., medical/disease history, diet history, concomitant medications, evidence of use for alternative medicines, etc.) can be taken
- Comprehensive knowledge of the clinical pharmacology (e.g., concentration–effect relationships, pharmacokinetic and pharmacodynamic profile, information related to altered drug disposition and/or action consequent to development, disease, concomitant drug therapy) for the drug(s) of interest
- Ability to integrate medical, pharmacologic and genetic information in a clinical "systems biology" (i.e., whole patient) context

What professional expertise is needed to effectively translate pharmacogenetics information into effective therapeutic decisions? When one considers the palate of information required to integrate pharmacogenetic information into therapeutic decision making, it arguably may not fall to any one healthcare discipline. As is the case for effective use of TDM, a team approach will likely be required to effectively realize the potential of 'clinical pharmacogenetics'. The complimentary expertise provided by professionals in clinical laboratory medicine, nursing, clinical pharmacy and medicine represent the collective skill set which encompasses the information domain described above. Accurate and timely information coupled with effective, dynamic communication between members of the therapeutic team is required to convert translational science into an effective tool with the potential to individualize drug therapy.

What cannot be effectively explained solely by pharmacogenetics? Human development represents a continuum of biological events which culminate in producing a human of reproductive potential. Facets of normal human development (e.g., somatic growth, maturation of organ function, psychosocial development) have been clearly shown to be capable of modulating both drug disposition and action. As illustrated by Fig. 6, genetic constitution generally (with the possible exception of epigenetic events) represents the only 'constant' throughout development with genotype being determined at birth. In contrast, development represents more of a continuous variable. During the first weeks and months of life, discordance between genotype and phenotype for some drug metabolizing enzymes exists as a function of maturation in activity. This has been demonstrated in a recent study which examined the ontogeny of CYP1A2 and CYP2D6 activity by assessing the biotransformation of caffeine and dextromethorphan, respectively, in healthy infants during the first year of life. In the case of dextromethorphan, concordance between CYP2D6 genotype and phenotype was evident by two weeks of postnatal age and after 1 to 2 months, CYP2D6 activity did not change appreciably over the first year of life. In contrast, maturation of CYP1A2 activity was more dramatic over the first six months of postnatal life.

While development and pharmacogenetics constitution may account for a substantial amount of predictive variability during the first decade of life, other intermittent 'factors' during this time can further impact drug disposition and effect. As illustrated in Fig. 6, these may include environmental

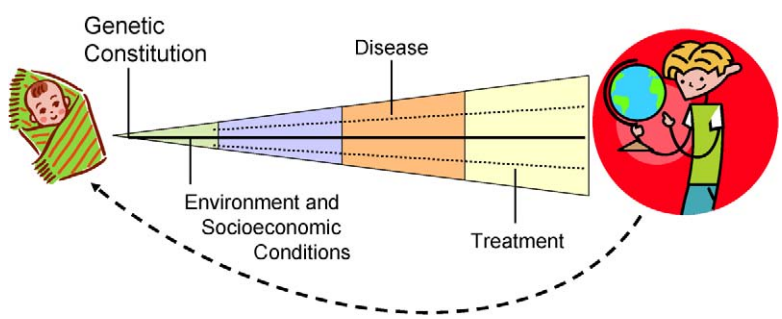


Fig. 6. Human development represents a continuum with distinct facets associated with somatic growth, maturation of organs and organ systems, and psychosocial development. The net result is a physiologically mature human, capable of reproduction. In the context of therapeutics, it must be recognized that genetic constitution, environment (including diet), concomitant disease state(s) and their treatment cut across the continuum of development indifferential dimensions and as a result, may modulate drug disposition and/or action.

exposures, the impact of concomitant diseases and their treatment(s) and nutrition (i.e., composition of the diet, malnutrition, over-nutrition). The impact of diet composition on caffeine biotransformation (a surrogate for CYP1A2 activity) during infancy was recently demonstrated where profound differences in caffeine elimination were found between breast-fed and formula-fed infants.

IV. THE PHARMACODYNAMIC–PHARMACOKINETIC INTERFACE

The dramatic impact that development can have on the pharmacokinetics of a drug may also be associated with its pharmacodynamics. For example, a single intravenous dose of famotidine in neonates produced a sustained increase in gastric pH over a 24-hour period; a finding not seen in older infants and children where gastric pH returned to baseline (i.e. pre-dose) levels at approximately 8–12 hours following a single intravenous dose. In the case of neonates, the sustained response to famotidine was attributed directly to the impaired clearance of the drug which occurred consequent to developmental immaturity in glomerular filtration. Thus, an apparent age-dependent difference in the pharmacodynamics of famotidine appeared to have a pharmacokinetic basis. In contrast, recent data from Scott et al. failed to demonstrate an association between reduced morphine plasma clearance in premature neonates (presumed to be associated with reduced glucuronosyltransferase activity) and analgesic effect as reflected by use of the Neonatal Facial Coding System.

Finally, developmental differences in pharmacodynamics can be observed in the absence of age-associated changes in the dose versus plasma concentration relationship. Marshall and Kearns demonstrated developmental differences in the pharmacodynamics of cyclosporin. In this study, the IC_{50} for interleukin-2 (IL-2) expression observed in peripheral blood monocytes obtained from infants less than 12 months of age and exposed *in vitro* to cyclosporin was approximately 50% of the value observed for older children. In this particular example, the pharmacodynamic differences appeared not to be the consequence of developmental dependence on pharmacokinetics but rather, in the true drug–receptor interaction.

V. A PRACTICAL APPROACH FOR THE INITIATION AND MANAGEMENT OF PHARMACOTHERAPY IN CHILDREN BY USING TEN GUIDELINES

V.a. Introduction

Optimum individualized drug therapy first requires that prescribers understand the general principles of drug disposition and effect. Next, the physician should choose the most effective drug and its correct dosage, formulation, and route of administration, all the while aware of its toxicity, contraindications, drug interactions and side effects. Since children can demonstrate age-related pharmacokinetic characteristics that alter drug disposition, prescribing medications for pediatric patients requires an even greater knowledge of the drug's profile. It is imperative that prescribers keep in mind the pharmacokinetic differences between adults and children as summarized in Sections I–IV of this chapter. Emerging data on developmental differences in pharmacodynamics must also be recognized.

Simply writing a prescription can have a profound impact; in the past, courts have declared that it is the responsibility of the physician to ensure that orders are clear and unmistakable. One study evaluating medication errors in two children's hospitals demonstrated a frequency rate of approximately 5 errors per 1000 medication orders. In addition, approximately 80% of those errors were due to either overdosing or underdosing medications. Pediatrics is the second most frequently implicated medical specialty in legal actions based on drug-related events, with the wrong drug or wrong dose being the most common claim. Written or computer assisted documentation of both the order and administration of the drug is essential for evaluation of pharmacotherapy. Remedial action to ensure compliance by the patient and drug delivery system can only be undertaken with data from such evaluations.

The practice of medicine requires decisions that are both practical and evidence based; until recently, lack of data regarding drug effectiveness in pediatric patients has made this difficult. In the USA, recent congressional legislation and FDA action have encouraged the pharmaceutical industry to perform an increased number of studies leading to pediatric drug labeling. These studies are gradually correcting the previous estimation that 78% of drugs listed in the Physicians Desk Reference were without sufficient pediatric use information. Presently, available

information regarding drugs and their pharmacology must be balanced with circumstances and conditions unique to the location of the prescriber, and also to the patient, such as endemic diseases, socioeconomic issues, and access to medical care. With these caveats, we offer guidelines in the form of a checklist (Table 9) for initiation and management of pharmacotherapy in children.

V.b. Background

Is pharmacotherapy indicated? Under some conditions drug therapy is inappropriate, unnecessary, and possibly harmful. For example, though antibiotics are not indicated in the management of uncomplicated viral upper respiratory infections, many parents request – even demand – a prescription for these drugs. A few moments of explanation about the inefficacy of antibiotics in such situations may save families time and expense while avoiding potentially serious side effects and encouragement of resistant strains of bacteria. Likewise, many parents eagerly and aggressively treat perceived fever unnecessarily, risking potentially serious side effects from needless and often excessive doses of antipyretics. The practitioner who views these situations as an opportunity for educating and empowering parents about the use – and misuse – of medications can impact powerfully and positively on the families in his care.

What are the criteria to start therapy? The decision to begin drug therapy assumes that the practitioner has evaluated the patient, formulated a differential diagnosis, selected a probable working diagnosis, and developed a treatment algorithm based on the potential risks and benefits of proposed drug therapy. Also considered is drug cost which may limit access to the drug. Even though many medications are available as a generic product that would typically provide the patient with the same therapeutic benefits at a reduced cost, newer and more effective drugs which do not have available generic alternatives continue to appear on the market. If the medication is not affordable, then the patient will not obtain the drug and unbeknown to the physician, the drug is not taken and disease goes unabated.

After making a probable diagnosis and determining that pharmacotherapy is indicated, the clinician then chooses an appropriate drug. This choice requires knowledge of the patient, the disease entity to be treated, and the drug itself. Patient-related factors include the patient's age, whether neonate, infant, child, adolescent or adult; medication allergies; and the presence of other chronic medical problems, such as renal or hepatic disease that may impact drug clearance.

Often overlooked is initiation of drug therapy that interferes with either making a diagnosis or evaluation of treatment effects. For example, if a patient is admitted for agitation, prescribing a sedative may not be the most appropriate choice. The patient's history may reveal head trauma or other CNS conditions that certain drugs may mask. An antipyretic may mask symptoms of an infection, and use of an anti-inflammatory drug for pain, rather than acetaminophen, may mask inflammatory signs essential for diagnosis of rheumatoid arthritis. Thus, a drug may confound efforts to make a diagnosis.

Simple but crucial issues such as the patient's ability to chew, swallow, or inhale the drug must be considered. Children frequently require liquid or chewable medications, and are often dosed by weight; consequently, it is important to choose a drug that is available in a strength that makes the dosing volume manageable. Children also freely reject medications that they find distasteful; finding a formulation that they are willing to swallow improves compliance. Medication cost is always an issue, particularly when dealing with third party payment; generic formulations, while often less costly, may not be as efficacious. All these factors must be weighed when designing a treatment regimen.

Social issues, as well, are important in drug selection: Is the treatment regimen complicated, requiring multiple doses of different drugs? Is the family's literacy level marginal, making the use of printed instructions problematic. The caregiver's ability to read prescription labels and to measure doses accurately is crucial, yet often never evaluated by the prescriber. Davis and others have noted that 21% of American adults are functionally illiterate, and that another 27% have only marginal literacy skills. Additionally, Davis and colleagues concluded that many FDA-approved, consumer-directed medication guides currently in use are not likely to be useful to patients with limited literacy. Finally, and critically, is the drug compatible with the family's moral, ethical, cultural, or religious mindset? All these issues may weaken compliance with the therapeutic plan.

Unique management requirements of the disease are also important. Is the condition to be treated

appropriately managed in the inpatient setting, the outpatient setting, or a combination of both? Is treatment best accomplished orally, intravenously, topically, or via inhalation? For example, tuberculosis typically requires treatment with multiple drugs for several months. Conversely, appropriate therapy for streptococcal pharyngitis may require a one-time injection or a 10-day course of oral therapy. Treatment of asthma may require both acute and chronic inhalation therapy, as well as oral medications. Successful drug treatment requires communication with the patient and family so that treatment goals, expected duration of therapy, drug discontinuation procedures and desired outcomes of treatment are understood.

Medication allergies are potentially life threatening, and should be elicited in medical and family histories taken by the clinician. Charting and substantiating such information is also crucial. For instance, is there an actual allergy, such as anaphylaxis to previous penicillin exposure? Or is the reported allergy really an intolerance, such as nausea or diarrhea? Careful questioning and documentation of these issues are essential when designing a treatment regimen.

The therapeutic index and potential drug toxicity are critical factors in drug selection. Following the admonition of Hippocrates to "first, do no harm", it is important to choose the safest, most efficacious drug for each clinical situation. No order should be written until knowledge of a drug's possible side effects, both intrinsic and dose-related, have been considered and weighed. For example, prior to the development of third-generation cephalosporins, chloramphenicol was drug of choice for several life-threatening bacterial infections, despite the possibility of "gray baby" syndrome. The availability of safer alternative antibiotic choices and understanding of drug clearance in the infant have made the "gray baby' syndrome a clinical rarity today. Even though a specific drug may be recommended for a disease state, that drug may not be appropriate for every patient in every situation. For example, aminoglycoside therapy for a urinary tract infection may not be the best drug if renal failure coexists, because the potential for drug toxicity is increased.

What is the appropriate dosing regimen? Determining the appropriate dosing regimen – dose amount, dosing interval, and route of administration – is as important as deciding upon the appropriate drug, and incorrect dosing can result in serious consequences ranging from suboptimal treatment to toxicity. For best results, the dose is individualized for each patient. In pediatrics, it is appropriate to consider the diagnosis, any concomitant medications and conditions, patient age and body size, and developmental maturity of organ systems responsible for drug elimination. Today, most pediatric patients are dosed according to body weight with further adjustments as needed for age differences in drug clearance. Neonates, for example, are dosed based on gestational or postnatal age as well as body weight because of the need to consider the maturation of drug elimination routes. In the case of obese children, all too common in the United States, lean body mass may be a more appropriate basis for dose calculation.

With some drugs, particularly those with a long half life, a loading dose may be useful in order to achieve a therapeutic level more rapidly. For example, the half-life of phenobarbital in the neonate is long, approximately 120 hours, with steady-state concentrations achieved in two to three weeks. A slowly-infused loading dose can be efficacious in achieving seizure control within minutes, typically followed by maintenance infusion and subsequent transition to oral therapy daily.

Dosing interval, which may vary with patient age, is a function of the drug's half-life, which is the time required for the concentration of the drug in the plasma to decrease by one-half. The half-life determines the frequency of dosing, and varies both among drugs and patients. Drugs with short half-lives must be administered more frequently; drugs with long half-lives may be administered less often. The half-life for nifedipine is approximately 3–5 hours with a typical dosing interval of every 6–8 hours. For a drug with a short to intermediate half-life (20 minutes–8 hours), the therapeutic index and convenience of dosing should be considered. A drug with a high therapeutic index may only be administered once every one to three half-lives whereas a drug with a low therapeutic index must be given every half-life or more frequently in order to avoid peak levels associated with toxicity. For a drug with a long half-life (8–24 hours), the dose may be given every half-life to achieve a convenient, compliant and desirable regimen. The same scheme holds true for drugs with a very long half-life (greater than 1 day). The drug may be administered once daily for convenience and to increase patient compliance. The

dosing interval for a drug is not always the same between a neonate, child and adult. For example, theophylline may be administered to an adult three times a day whereas for a young child the typical dosing interval is four times a day. On the other hand, theophylline may be administered to a neonate less frequently. The differences in the dosing interval with this agent are due to the slower clearance seen in adults and an even slower clearance in neonates. The average half-life of theophylline is 4–5 hours for a child, 8 hours for nonsmoking adult and greater than 10 hours for a neonate. It is crucial to select a dosing interval that is patient-friendly, so that compliance is maximized. For example, common dosing intervals include every 6, 8, 12, or 24 hours. Using uncommon dosing intervals, such as every 18 or 36 hours, may be problematic for some parents and impractical for others; regimens that interrupt sleep or school performance typically decrease compliance.

Which route of administration is optimum? Choosing the optimum drug administration route takes into account the specific circumstances of each individual case. For example, can the patient tolerate oral medications, or is intravenous administration required? Does the patient have venous access? For how long can it be maintained? Is intramuscular administration a possibility? In many clinical situations, the available formulation determines the route of administration. Antibiotics are a prime example of this phenomenon; ceftriaxone, for example, is available only for parenteral administration while amoxicillin is administered orally.

Even if a medication is available in multiple formulations and dosage forms, the prescriber must consider the absorption and distribution differences between adult and pediatric patients. Blood supply at injection or infusion site, available blood supply for unit muscle mass, and skeletal muscle mass relative to body mass vary with patient age and size, causing drug absorption to vary, as well. A rapid intravenous bolus in a pediatric patient might result in acute toxicity; a slow intravenous infusion, often required in neonates, can cause erratic, unreliable drug delivery in an older child. In addition, the volume of fluid tolerated for intravenous delivery varies significantly with the age and size of the patient. The blood supply and blood flow to and from the injection site are of prime importance since a gradual decrease in blood supply per unit muscle mass is seen with maturation. In addition, the skeletal muscle mass relative to body mass is smaller in infants compared to adults. These few examples clearly identify the depth of understanding required to understand the dosing differences between neonates, infants, children, and adolescents.

Is therapeutic drug monitoring required? Therapeutic drug monitoring (TDM) can be vital in assessing a patient's response to treatment, especially in cases involving the administration of drugs with narrow therapeutic windows, such as aminoglycosides, antiepileptic agents, and digoxin. Serial monitoring of serum drug levels provides data that are useful in evaluating both therapeutic efficacy and adverse effects; distinguishing disease effects from consequences of non-compliance or drug toxicity; and adjusting dosage regimens in patient subgroups with variable or rapidly changing drug disposition. However, like all data, drug levels must be considered in context and evaluated with an understanding of several factors in play in each clinical situation. It is important to realize that the 'normal' therapeutic range reported is a guideline; not all patients are expected to be included in this so-called 'normal' range. Some may respond to lower drug levels with efficacy or toxicity, and higher levels may be required for efficacy in other patients. Each set of values must be considered individually for the changing drug disposition inherent in children as well as the drug level-response relationship. Modify drug dose according to patient status and plasma drug level, and not just the drug level alone.

Serum drug concentrations can vary according to sample timing, route and technique of drug administration, and time of initiation or change in drug dose. Ideally, samples should be drawn at steady state, typically five half-lives after the dose. Samples obtained at trough levels, just before the next scheduled dose, minimize the effects of absorption rate and typically yield minimum concentration levels at steady state. A change in dose resets the time to achieve steady state levels.

Pediatric patients require other special considerations when prescribing a drug that requires therapeutic monitoring. Simply obtaining blood samples can be difficult, depending on the age, developmental maturation, and hydration status of the child. In some clinical settings, a lack of personnel comfortable with pediatric phlebotomy makes sample collection even more difficult, or even hazardous. As well, some facilities lack on-site laboratories for

processing specimens, making it almost impossible to get important data in a timely manner. Once obtained, drug levels must be evaluated in light of unique aspects of pediatric pharmacology, such as potential problems with drug administration, drug absorption, and changing drug clearance.

How will drug efficacy be assessed? Prior to the initiation of drug therapy, it is important to determine criteria for efficacy of treatment. Why was drug treatment begun, and when and why should it be stopped? Is the therapeutic goal a clinical cure, improved quality of life, disease remission or a change in laboratory value (i.e. a surrogate marker of clinical outcome)? Sometimes efficacy is difficult to assess in the pediatric patient, who may be too young to answer questions like, "Do you feel better?". The pediatrician learns to rely on his patient's actions, such as going to the playroom, instead of remaining quietly in bed. Tools have been devised to help older children articulate their symptoms, such as numbered or pictorial pain scales which correspond to the level of pain at a particular time. These provide the physician with estimates of analgesic drug efficacy. Always, it is important to interview caregivers about the patient's activity level, appetite, and behavior; those who spend time at the bedside have valuable information about the child's response to drug therapy.

How will adverse effects be evaluated? Knowing the common and severe adverse effects of all drugs prescribed, as well as their frequency, severity, and management, facilitates evaluation of signs and symptoms and hence their possible relation to drug therapy. In general, a practical "rule of three" approach suggests that physicians should know the three most common and the three most severe adverse effects of every drug they prescribe. This empirical but practical approach helps to avoid polypharmacy when dealing with adverse effects; rather than adding a medication (an anti-nausea or anti-pruritic drug, perhaps), it makes possible other management options. For example, the adverse effect may resolve if the dose is lowered, or its administration route changed (perhaps given with food). Or perhaps the drug is no longer needed, and can be discontinued. Some medications may cause adverse effects early; the transient sedation common in the early course of antiepileptic therapy is a prime example. Therapeutic drug monitoring can implicate a drug connected with an adverse effect.

What drug interactions are possible? Drug interactions can range from clinically irrelevant to fatal, and it only takes two drugs to cause a significant reaction. When prescribing a new medication, it is essential for the physician to be aware of all other drugs that the patient takes concurrently, including over the counter (OTC) products, nutritional products, and recreational drugs. A data base on current drug interactions is often available at the local or hospital pharmacy. Diet–drug interactions are not uncommon and seldom suspected.

How will compliance be assessed? Evaluating drug compliance in pediatric patients can be complex and requires assessment of both patient and parent behaviors. Among the factors affecting compliance are number of drugs taken, dosing interval(s), adverse effects, drug cost, patient or parent educational level, and effectiveness of communication among pharmacist, physician, patient, and parent. Children frequently do not comply when the taste of the medication is unpleasant. Parental noncompliance is often attributed to forgetting to give a dose, discontinuing medication when the symptoms have cleared, misunderstanding dosing instructions, or ineffectiveness or side effects (perceived or actual) of the medication. Additionally, children who resist being dosed or who deny the presence of symptoms or illness are often successful in avoiding drug treatment. Iatrogenic compliance failure in the hospital setting is often unrecognized. To detect this each link in the chain of events for drug delivery must be inspected. This begins with the physician order and ends with a query of the patient. Compliance in hospitalized patients in not guaranteed.

When and how should a medication be discontinued? A plan for discontinuing medication should be established when therapy is initiated. At the conclusion of the planned treatment period, it is appropriate to re-evaluate the patient and to decide if the initial criteria for drug efficacy have been met. Ideally, the patient's condition should have reached a defined endpoint, such as resolution of symptoms in acute disease processes, or return to baseline status in a chronic illness. Some drugs, such as anticonvulsants, steroids, and some antidepressants, require a plan for tapering doses and gradual weaning to avoid exacerbation of the disease.

V.c. Guidelines for Individualized Drug Use

Table 9 shows a checklist for rational drug therapy of children. The ten fundamental guidelines for pharmacotherapy are both comprehensive and practical. With few exceptions, these guidelines apply to drug therapy of most diseases throughout the world. Consideration of each item on the checklist stimulates *a priori* considerations for drug initiation and continued use. (A concise pocket size summary of Table 9 is included in the Appendix.) In addition to the fundamental principles described in this chapter, the reader is encouraged to consult the following publications that were used for the guidelines seen in Table 9 (from Robertson and Shilkofski, 2005; World Health Organization, 2005; Bradley and Nelson, 2006; Yaffe and Aranda, 2004; Kearns and Reed, 1989; Jacqz-Aigrain and Morselli, 1989).

V.d. Application of the Checklist

Two case reports demonstrate application of the checklist in Table 9 to short and prolonged drug use in diseases frequently seen in children. A natural application incorporates the checklist without need for categorical recitation.

Case 1

A four-year-old male presents to an emergency room at a small community hospital in the southeastern United States with history of fever to 103 F, vomiting, and increasing irritability. The emergency room physician notes meningismus and makes a clinical diagnosis of acute bacterial meningitis.

Clinical signs and symptoms and the confirmatory spinal tap are sufficient criteria for initiation of drug therapy because serum, urine, and CSF specimens have been submitted for immunologic and bacteriologic evaluation, drug administration will not interfere with further diagnostic evaluation. The physician consults a standard text and determines that a third generation cephalosporin is drug of choice in his locale. The physician orders an intravenous loading dose of ceftriaxone at 75 mg/kg to

Table 9. Checklist for rational drug therapy

Criteria to start therapy	Diagnosis or likely working diagnosis
	Does initiation of drug therapy interfere with making the diagnosis?
	Drug of choice (e.g. cost, resistance, allergy)?
Dose	Body weight adjusted
	Age adjusted
	Adjust for absorption at route chosen
	Adjust for organ of elimination: (Is it normal (?))
	Dose load or not
Dose interval	A function of $t_{1/2}$ or that in the label
	Adjust for individual schedule of administration
Route	Relates to speed and extent of absorption
	Availability of formulation often determines route
Use of TDM (Therapeutic Drug Monitoring)	(*When* to measure plasma levels of drug and *What* to do with them) $t_{\text{css}} = 5 \times t_{1/2}$. Valuable time for obtaining blood sample is at t_{css}
	Normal or desired therapeutic range is assessed with plasma level
	Obtain plasma sample just before next dose to decrease effect of drug absorption
Criteria for efficacy	Define objectives of treatment before initiation of a drug
Objective and subjective Common AEs to monitor	Note frequency and severity for a drug
	Dependant on age, disease, and individual patient factors
Drug interactions (note frequency and severity)	Include drug action, absorption, elimination, and protein binding
	Are they clinically significant?
	Include OTC drugs, illegal drugs, and list drug interactions
Compliance	Is the patient getting the drug as ordered?
	Weakened by number of drugs, frequency of dosing, side effects, denial of illness, cost
Criteria for drug discontinuation	How long to treat – objective end point identified at initiation of therapy
	When and how to discontinue the drug

be followed by a maintenance dose of 100 mg/kg divided q 12 h for 10 days, in accordance with CDC (United States Center for Disease Control) guidelines. The physician notes that therapeutic monitoring of drug levels is not indicated with ceftriaxone. He informs the parents that he will monitor the child closely for decreasing fever and discomfort, improved responsiveness, and a gradual return to normal appetite and activity levels. Changes in laboratory values will be followed.

Over the course of treatment, the physician monitors the patient for local reactions at the IV site (redness or swelling), diarrhea, and hypersensitivity rash (three common side effects of ceftriaxone). He also follows serum renal and liver functions and blood counts for evidence of organ damage or abnormal hematologic indices. The physician also follows the child's fever curve closely; remembering that prescribed antipyretic/analgesic drugs may mask a febrile response to infection. Nurses' notes are read to ensure that no doses of antibiotic are missed, even though IV access must be re-established every third day. On day eleven, after all treatment goals have been met and the child's laboratory findings are normal, the physician discharges the patient home with his parents.

Case 2

A tearful new mother brings her one-month-old daughter to the pediatrician for a routine visit, distraught because the baby "throws up all the time" and is "always fussy". As the pediatrician is talking with the mother, he notes that the baby frequently arches backward, grimacing as if in pain. At this point, the pediatrician makes a presumptive diagnosis of gastroesophageal reflux disease (GERD).

After discussing conservative measures for managing GERD in infants, the pediatrician elects to begin drug therapy. Since infant GERD is most often diagnosed clinically, he believes that drug administration will not interfere with any further diagnostic evaluation. He prescribes an H-2 receptor antagonist, because there are drugs of this type available in palatable, easy-to-administer liquid formulations; additionally, there are published studies documenting the drug's safety and efficacy in infant GERD.

The pediatrician calculates the dose based on the infant's weight, choosing the infant dose recommended in a pediatric pharmacology reference text. He prescribes a maintenance dose, given q.i.d. by mouth prior to scheduled feedings, and advises the mother to contact him immediately for GI disturbances and altered sleep patterns, the most common side effects of the drug. He tells the mother that no laboratory work or drug levels are indicated at this time. At the follow-up visit, mother reports that the baby is sleeping "much better", and less fussy, especially after feeding. She reports that the child still spits up occasionally, but does not appear to be uncomfortable. The physician notes that the baby has gained weight, and that both mother and child appear more rested. Subjective clinical criteria for drug efficacy are appropriate in this case. After cautioning the mother to report any other illnesses or medications, the pediatrician advises that the medication will likely be continued for several months, based on the baby's symptoms. He also informs the mother that the dose will probably be increased periodically, as the infant's weight increases. Both symptoms and age of the child will give a basis for discontinuation of the drug.

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APPENDIX: CHECKLIST FOR RATIONAL DRUG THERAPY

- Criteria to start therapy
- Dose
- Dose interval
- Route
- Use of TDM (Therapeutic Drug Monitoring)
- Criteria for efficacy
- Objective and subjective Common AEs to monitor
- Drug interactions (note also OTC and illicit drugs and diet)
- Compliance
- Criteria for drug discontinuation

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Chapter 13

Drug Therapy in Older Persons

Barry Cusack, James Branahl

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I. SUMMARY

Drug use in older patients generally is similar to that in younger adults. There are however, unique challenges that make drug use more complicated in the older population. These include altered physiology that can change pharmacokinetics and drug sensitivity with age. In addition, multiple diseases are common in older patients and this leads to multiple drug therapy. In turn the risk of drug–drug interactions and drug–disease interactions increase with age. These problems are discussed in this chapter in addition to discussion of therapeutics of important disorders in the older population.

II. INTRODUCTION

Effective treatment of older patients poses many unique challenges. Age-related changes in body composition and physiology, by altering drug handling (pharmacokinetics), can affect dose requirements. Similarly changes in drug action (pharmacodynamics) can alter the extent or on occasions the quality of drug response. Added to these changes are those due to diseases that affect organ function, a common occurrence in older persons. Multiple diseases prompt multiple drug use, raising the risk of drug–drug and drug–disease interactions. In addition, some older patients experience difficulties with drug adherence, reducing the potential for successful treatment. To compound the problem, there has been a relative neglect of instruction of age-related pharmacology to medical and other health care students and trainees. Older age groups traditionally have been underrepresented in clinical pharmacology research studies, even for drugs used mostly in older age groups. In this chapter, these problems will be discussed, emphasising the principles that improve the safety and effectiveness of drug therapy and also reviewing therapeutics of common important conditions in older patients. Many other recent reviews are available.

III. DRUG USE AND ADVERSE DRUG REACTIONS

The elderly comprise an increasing section of the population with a disproportionately high rate of drug consumption. For example, in the US those more than 65 years comprise about 12% of the population and account for about 25% of drug use. Drug use is especially increased in older patients in hospitals and in nursing homes. This high rate of use, although likely of therapeutic benefit in many cases,

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may be inappropriate in other cases, leading unnecessarily to an increased risk of adverse drug reactions. Many reports describe an age-related increase in adverse drug reactions among both community dwelling and hospitalised patients. While this suggests increased susceptibility to adverse drug reaction in older patients, further analysis suggests that this relationship may be more complex. When disease severity and the number of drugs used are included in the equation, it appears that the apparent age-related relationship is abrogated. The rate of adverse drug events (ADEs) is increased with age in many, but not all studies. However polypharmacy has a much stronger relationship than ageing with ADEs; with an increase in the number of drugs taken concurrently the risk of ADEs increases exponentially (Fig. 1). Many adverse reactions can be serious; about 7% of hospital admissions in the UK are related to adverse drug reactions, more common in older adults and 9 and 63% of these were classified as definitely or possibly avoidable, respectively. Based on a large meta-analysis, it was estimated that 76,000 or more hospitalised patients died in 1994 in the US from adverse drug reactions. Many adverse reactions are considered preventable; one metaanalysis estimated that 88% of ADE hospitalizations were preventable in older adults compared to 24% in young adults. Thus, great care must be taken to reduce the risk of adverse drug reactions. It is important to minimise the number of drugs used, to screen for potential drug–drug interactions, to consider the risk of adversely affecting a patient's condition by adding or stopping a medication, and to quickly recognise developing adverse reactions. Common reactions include pruritus, nausea, vomiting, rash, confusion/lethargy, diarrhoea, unsteadiness, dizziness, falls, and incontinence. Serious reactions include GI hemorrhage, intracranial hemorrhage, renal failure, electrolyte disturbance, heart block and fractures. Errors in prescribing, transcribing, dispensing, and drug administration must be avoided carefully. Computerised prescribing systems may help with this when available. Medications

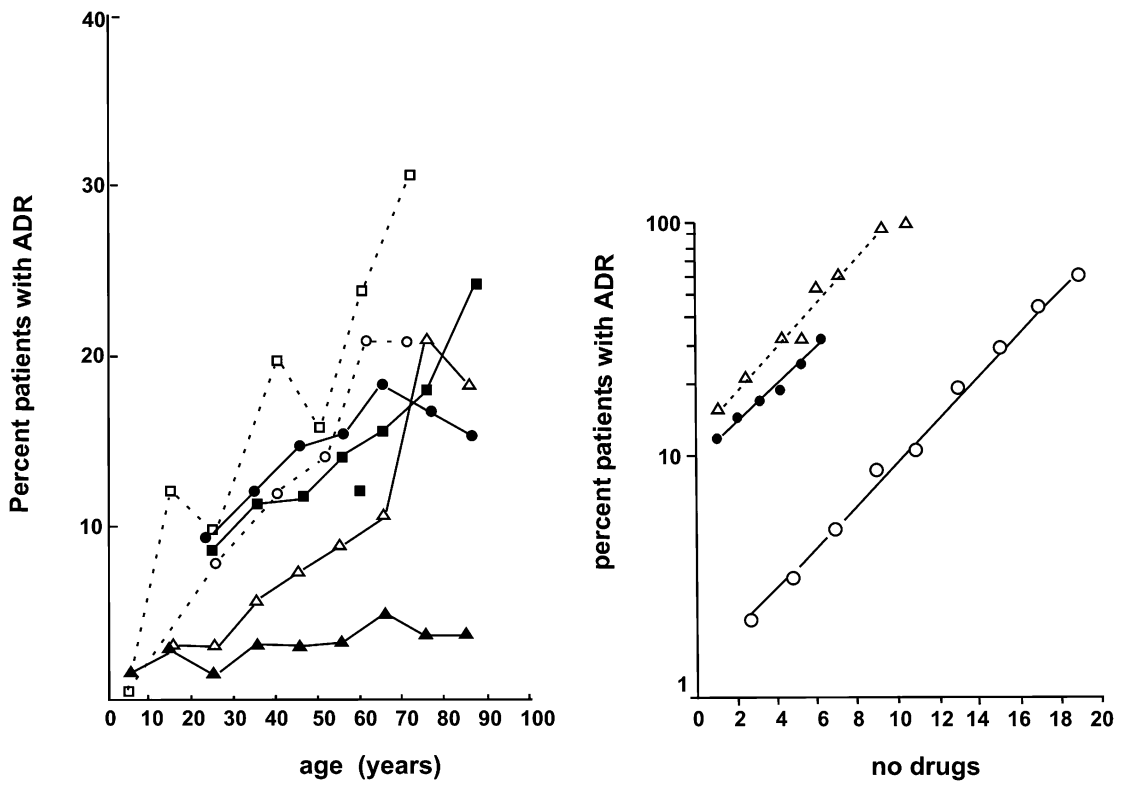


Fig. 1. Incidence of adverse drug reactions in relation to age (left panel) and relationship between the number of drugs taken concurrently and the incidence of adverse drug reactions (right panel). From Nolan and O'Malley, 1988; used with permission.

should be included as an important aspect of patient education. Care must be taken to enhance compliance by use of reminder systems, use of simple regimens, use of medication multidose containers and by providing assistance at home with drug administration.

IV. PHARMACOKINETICS

The magnitude of drug effect is related to the concentration of a drug achieved at the site of action and to the sensitivity to the drug at the site of action. The former is determined by pharmacokinetics characteristics and the latter by pharmacodynamics processes. Physiological changes, alterations in homeostatic regulation, and disease modify pharmacokinetics and drug response in older patients (Table 1).

IV.a. Absorption

There are some changes with ageing that have an effect on drug absorption. Prolonged gastric emptying may delay absorption of some drugs in older persons. The rate of absorption of some drugs such as digoxin, and acetylsalicylic acid is delayed in older subjects. Delayed absorption may prolong the time to peak effect after a single dose of drug, of importance when rapid onset of action is required as in the case of hypnotics or analgesics, for example. Otherwise it is of little clinical consequence. The extent of absorption is related to the absorptive surface in the small bowel; there is such a large reserve that the age-related reduction is not of significant importance. Studies have shown that, overall, there is little change with age in the extent of drug absorption.

IV.b. Bioavailability and Presystemic Extraction

Following absorption in the small bowel, many drugs undergo metabolism in the intestine or in the liver prior to entering the systemic circulation. This lessens the amount of drug that becomes bioavailable. Whether ageing is associated with alterations in intestinal metabolism is not yet well established. However, the bioavailability of nifedipine, a drug that is metabolised by CYP3A4 in the intestine, is increased in older subjects, suggesting reduced intestinal extraction. The effect of P-glycoprotein (P-gp), an efflux transporter located on the membrane of small bowel enterocytes on bioavailability of substrate drugs in relation to aging in man has not been well characterized. Ageing is associated with a decrease in presystemic liver metabolism, with

Table 1. Effect of aging on drug disposition

Pharmacokinetic parameters	Physiologic changes of aging	Clinical significance
Absorption	Elevated gastric pH; reduced small-bowel surface area	Little change in absorption with age (i.e., no clinical significance)
Distribution	Reduced total body water; reduced lean body mass; increased body fat	Higher concentration of drugs that distribute in body fluids; increased distribution and often prolonged elimination half-life of fat-soluble drugs
	Reduced serum albumin	Increased free fraction in plasma of some highly protein-bound acidic drugs. Free drug clearance of such drugs is better indicator of dose requirements than total clearance
	Increased α_1-acid glycoprotein	Small decreases in free fraction of basic drugs bound to α_1-acid glycoprotein
Hepatic metabolism	Reduced hepatic mass; reduced hepatic blood flow. Often decreased metabolizing isoenzyme activity. Pseudocapillarization of hepatic sinusoids	Often decreased first-pass metabolism; decreased rate of biotransformation of many, but not all drugs; marked interindividual variation in rate of hepatic metabolism
Renal elimination	Reduced renal plasma flow; reduced glomerular filtration rate, altered tubular transport function	Decreased renal elimination of drugs and metabolites; marked interindividual variation

Adapted from Vestal, 1979; used with permission.

increased bioavailability of some drugs with high hepatic extraction, such as verapamil, labetalol and propranolol.

IV.c. Distribution

Because fat as a proportion of body mass is increased with age, the volume of distribution of fat-soluble drugs may be increased in older persons. The increased volume of distribution also prolongs the elimination half-life. For example, diazepam elimination half-life is prolonged in older subjects due to the increased volume of distribution, despite the fact that systemic clearance is unaltered (Fig. 2). Conversely, lean body mass declines with age and the volume of distribution of water-soluble drugs often is decreased in older patients. The extent of distribution of a drug is one determinant of the concentration achieved in the plasma or other tissues after a single dose. Thus, the loading dose of water-soluble drugs such as digoxin or alcohol is decreased in older patients due to a decreased volume of distribution. This may be one reason why older persons are at increased risk of acute intoxication from alcohol.

Distribution of some drugs including fexofenadine, cyclosporine and verapamil is also determined by activity of membrane bound transporters such as P-glycoprotein, a 170-kd ATP dependent efflux transporter member of the multidrug resistance associated protein (MDR) family. This is sited at the blood side of the brain capillary endothelial cells. Substrates that pass the blood–brain barrier (BBB) can then be extruded by this glycoprotein transporting mechanism. Recent studies of verapamil, a P-gp substrate, uptake into the brain demonstrated increased uptake in older compared to young adults, consistent with an age-related decline in P-gp activity at the BBB. This has possible significant implications for age-related effect of P-gp transport substrate drugs on brain function.

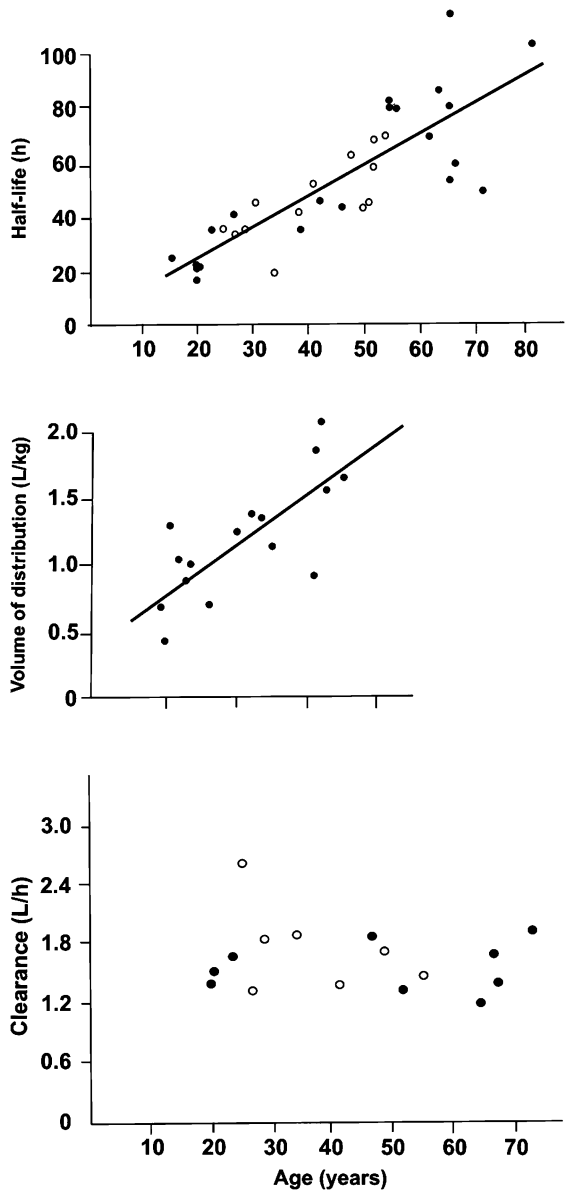


Fig. 2. The relationship between age and the elimination half-life (upper panel), volume of distribution (middle panel) and plasma clearance (lower panel) of diazepam in healthy volunteers. From Klotz et al., 1975; used with permission.

IV.d. Plasma Protein Binding

There are small changes in serum albumin concentration with age, with concomitant small effects on protein binding of some highly bound drugs such as naproxen, salicylate, and warfarin. For such drugs the free concentration rather than the total plasma concentration is a better predictor of drug dose requirements, particularly for drugs with low therapeutic index (difference between the therapeutic and toxic plasma concentration) such as phenytoin. Overall this effect is minor and likely of little clinical importance for drugs with a high therapeutic index. Likely of more importance are greater disease-related alterations in serum albumin. Acute stress, surgery, infections and other hypercatabolic conditions can cause rapid reductions in serum albumin

so that protein binding of highly bound drugs can fall, increasing free fraction of drug available for distribution to the site of action. Age-related increases in the concentration of the alpha-1 acid glycoprotein increase the binding of some basic drugs such as lignocaine (lidocaine) in older patients. In cases where the carrier protein for highly bound drugs such as phenytoin is reduced, the total drug concentration also may appear to be low since the amount of bound drug is decreased. In such cases, when possible, the therapeutic concentration should be determined by assay of the free drug concentration.

IV.e. Hepatic Metabolism

Many drugs are eliminated by metabolism, which occurs mainly in the liver. The rate of metabolism depends on the rate of drug delivery to the liver, liver mass, and the amount and activity of drug metabolising enzymes. Age-related changes in the liver may alter the rate of drug metabolism. Liver blood flow declines by about 40% with age. This causes a decrease in the rate of metabolism of highly extracted drugs such as lignocaine, verapamil, morphine and labetalol following parenteral administration. For other, less extensively extracted drugs, the rate of metabolism depends more on hepatic enzyme activity. Earlier studies suggest that the activity and content of hepatic P450 enzymes did not change with age. It was noted that liver volume reduced by about 25% in old compared to young individuals. This has been offered as an explanation for reduced hepatic metabolism in older patients. More recent studies indicate that there may be specific alterations in *in vitro* activity of some but not all of the cytochrome P450 subfamilies with ageing. Studies *in vivo* in humans also have demonstrated variable findings. One review found decreases in almost all CYP 450-mediated drug elimination, whereas another review found two of eight pathways studied were unchanged. For example, while clearance of substrates of CYP2D6 such as propranolol is not age-dependent, the rates of elimination of erythromycin (measured by the erythromycin breath test) and nifedipine are reduced, suggesting a decline in activity of CYP3A4. A further explanation for a reduction in drug metabolism is pseudocapillarization of hepatic sinusoids that occurs in rat and also in human liver with advanced age, impairing oxygen delivery for phase one drug metabolism (see McLean et al., 2003).

Other drugs are metabolised by Phase II synthetic reactions, catalysed typically by non-microsomal enzymes. Processes include acetylation, sulphation, glycine conjugation and methylation. Phase II reactions may be affected less frequently by ageing. Thus according to some studies, the elimination of isoniazid, rifampicin (rifampin), paracetamol (acetaminophen), valproic acid, salicylate, indomethacin, lorazepam, oxazepam, and temazepam is not altered with age. However, other studies have demonstrated a reduction in metabolism of lorazepam, paracetamol (acetaminophen), ketoprofen, naproxen, morphine, free valproic acid, and salicylate, indicating that the effect of age on conjugation reactions is variable.

Although the effect of ageing in causing reduced hepatic clearance of many drugs is important, it is unpredictable and is one of many factors that influence biotransformation in older patients. Other factors include interindividual variation, ethnic background, drug polymorphism, liver disease, acute disease states, nutritional status, tobacco smoking, and other drugs that can cause induction or inhibition of drug metabolism. Since hepatic drug clearance, when reduced, is so by about 30% on average, the daily starting dose of a metabolised drug should be reduced by 30% or more in older patients, particularly in very old, frail individuals. The dose can then be adjusted cautiously according to clinical response.

IV.f. Renal Drug Elimination

It is well known that both glomerular and tubular renal functions decline with age in at least one third of individuals. As a result there is greater variation in renal function in older subjects. Glomerular filtration rate can be predicted by creatinine clearance, which can be estimated based on measured serum creatinine ($\mathrm{Ser_{Cr}}$) concentration. One such formula is the Cochrane and Gault formula in which

$$\mathrm{Cl_{Cr}\ (ml/min)} = \frac{\{150 - \text{age (y)}\} \times \text{body weight (kg)}}{\mathrm{Ser_{Cr}\ (\mu mol/l)}}.$$

In males add 10%, and in females subtract 10% from the value obtained.

The effect of age on the renal elimination of some drugs is shown in Table 2. In general, the dose can be guided by the estimated or measured creatinine clearance. This should be performed in particular

Table 2. Examples of medications with reduce renal elimination

Amantadine
Amikacin
Amiloride
Ampicillin/sulbactam
Bumetanide
Captopril
Chlorpropamide
Cimetidine
Ciprofloxacin
Digoxin
Enalapril
Furosemide
Gabapentin
Gentamicin
Hydrochlorothiazide
Levofloxacin
Lisinopril
Lithium
Methotrexate
N-Acetylprocainamide
Oxipurinol (active metabolite of allopurinol)
Procainamide
Quinapril
Ranitidine
Streptomycin
Tobramycin
Triamterene
Vancomycin

for drugs with a low therapeutic ratio with reduced renal clearance in older persons. Such drugs include aminoglycosides, vancomycin, lithium, digoxin, and procainamide. Subsequent dose adjustments can be made depending on clinical response or therapeutic monitoring. Anticipation of the effect of decreased renal function is important, since the risk of adverse drug events due to water soluble drugs excreted by the kidney is increased in elderly patients with unrecognized renal dysfunction.

V. PHARMACODYNAMICS

In many instances, drug sensitivity (pharmacodynamics) is altered in the elderly (Table 3). This may be a result of altered receptor numbers, post-receptor changes, alteration in membrane channel behaviour or in homeostatic counter-regulation. For example, β-adrenoceptor sensitivity appears decreased with age. Early studies indicated that the chronotropic effect of isoprenaline (isoproterenol) and its inhibition by propranolol declined with age, suggesting reduced β-adrenoceptor sensitivity to both stimulation and inhibition with advancing age. Consistent with this were observations of reduced cyclic AMP response to β-adrenergic stimulation perhaps related in part to the decreased binding affinity of receptors and to changes in post-receptor events, as have been shown in human lymphocytes. However more recent studies of the cardiac chronotropic effect of isoprenaline in humans indicate that the decrease in response with advancing age may not be simply due to decreased β-adrenergic responsiveness but rather to alterations in sympathetic and parasympathetic response, an example of altered counter-regulation with ageing.

Several studies have suggested increased sensitivity of older persons to effects of benzodiazepines (Table 3). For example, midazolam, widely used for rapid sedation for procedures, requires lower doses to reach defined end points of sedation that is attributable to a 59% reduction in the EC_{50} (the concentration that produces 50% of the maximum effect) and not to changes in pharmacokinetics, as shown in Fig. 3. The reasons for this increased sensitivity are not known. Animal studies have not shown any difference in brain benzodiazepine receptor density or affinity or effects on the associated chloride channel function with ageing. In any event, benzodiazepine doses should be reduced in older patients.

Natiuretic response to diuretics including frusemide and bumetanide is reduced as a result of decreased renal tubular secretion of diuretic Thus, age-related changes in renal tubular function may influence not only pharmacokinetics but also drug action on the kidney (pharmacodynamics).

Altered homeostasis in older persons can lead to important and common adverse drug effects; the less robust homeostatic milieu may be stressed by drugs, causing adverse effects. Examples include orthostatic hypotension due to antihypertensives and other agents that cause α-adrenergic blockade (e.g. terazosin, doxazosin, tricyclic antidepressants and phenothiazines) in those with baroreceptor dysfunction. Diuretics can cause hyponatraemia or hypokalaemia in older patients, whereas ACE inhibitors and NSAIDs can cause hyperkalaemia.

Table 3. Effect of aging on drug response

Drug	Action	Effect of aging
Analgesics		
Aspirin	Acute gastroduodenal mucosal damage	Ö
Morphine	Acute analgesic effect	↑
Pentazocine	Analgesic effect	↑
Anticoagulants		
Heparin	Activated partial thromboplastin time	Ö
Warfarin	Prothrombin time	↑
Bronchodilators		
Salbutamol/albuterol	Bronchodilation	Ö
Ipratropium	Bronchodilation	Ö
Cardiovascular drugs		
Adenosine	Minute ventilation and heart rate response	Ö
Benazepril	Acute antihypertensive effect	↑
Diltiazem	Acute antihypertensive effect	↑
Enalapril	Acute antihypertensive effect	↑
Isoproterenol	Chronotropic effect	↓
Phenylephrine	Acute venoconstriction; acute hypertensive effect	Ö
Prazosin	Chronotropic effect	↓
Timolol	Chronotropic effect	Ö
Verapamil	Acute antihypertensive effect	↑
Diuretics		
Bumetanide	Peak and extent of natriuretic effect	↓
Furosemide	Latency and size of peak diuretic response	↓
Psychoactive drugs		
Alprazolam	Psychomotor function	↑
Diazepam	Acute sedation	↑
Diphenhydramine	Psychomotor function	Ö
Haloperidol	Acute sedation	↓
Midazolam	EEG activity, sedation	↑
Temazepam	Postural sway, psychomotor effect, sedation	↑
Triazolam	Psychomotor activity	↑
Others		
Levodopa	Dose limitation due to side effects	↑
Methylprednisolone	Acute adrenal suppression	↑
Tolbutamide	Acute hypoglycemic effect	↓
Zolmitriptan	Increase in systolic BP	↑

↑ = increased; ↓ = decreased; Ö = unchanged.
Adapted from Cusack, Vestal, 1986; used with permission.

VI. DRUG–DISEASE INTERACTIONS

Because of the frequent co-existence of multiple disease and polypharmacy, the potential for drug disease interactions is an extremely important aspect of drug therapy in older patients. Hepatic and renal disease, by altering drug clearance, can affect dose requirements. Other diseases leave the patient at risk of significant adverse effects (Table 4). The prescriber should consider the possibility of a drug–disease interaction prior to adding any new drug.

VII. TREATMENT OF IMPORTANT DISORDERS IN OLDER PATIENTS

Some disorders, because of their frequency, clinical impact and responsiveness to therapy, are important to discuss in older patients. Appropriate drug ther-

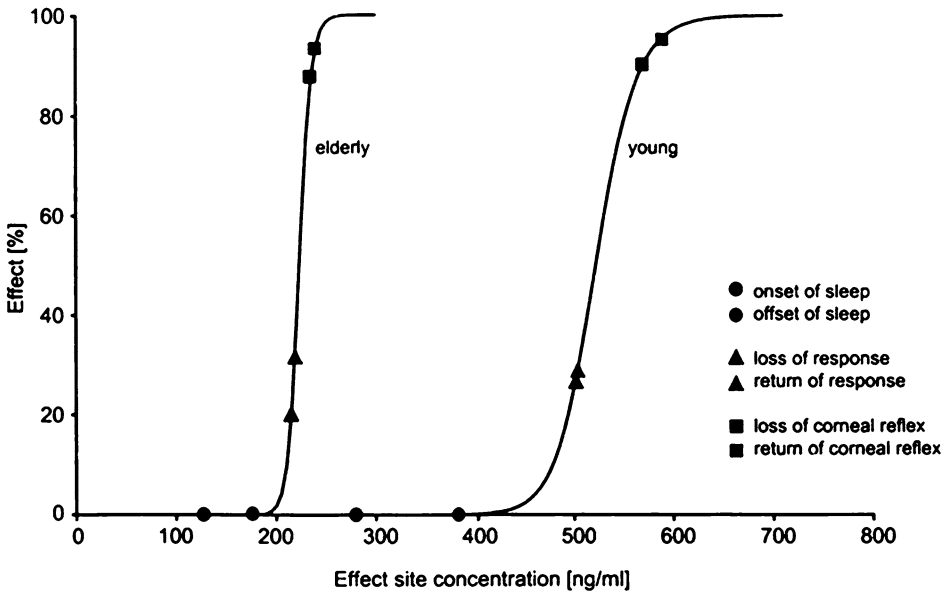


Fig. 3. Concentration–response curves and clinical end points for young and elderly subjects following intravenous infusion of midazolam. The effect is expressed as a percentage of the maximum effect measured with the EEG median frequency related to the concentration in the effect compartment. From Albrecht et al., 1999; used with permission.

Table 4. Important drug–disease interactions in older persons

Disease or disorder	Drugs	Adverse reactions
Cardiac conduction disorders	β-Blockers, digoxin, diltiazem, verapamil, tricyclic antidepressants	Heart block
Chronic obstructive pulmonary disease	β-Blockers Opioids	Bronchoconstriction Respiratory depression
Chronic renal failure	NSAIDs, radiocontrast agents, aminoglycosides	Acute renal failure
Constipation	Anticholinergics, opioids	Faecal impaction
Congestive heart failure	β-Blockers, diltiazem, verapamil, disopyramide, NSAIDs, rosiglitazone	Worsening of heart failure
Dementia	Opioids, antiepileptics, levodopa, antiparkinsonism drugs, psychotropic drugs, anticholinergics	Increased confusion, delirium
Diabetes	Corticosteroids, diuretics	Hyperglycemia
Depression	Alcohol, benzodiazepines, β-blockers, centrally-acting antihypertensives, corticosteroids	Precipitation or worsening of depression
Glaucoma	Anticholinergics	Exacerbation of glaucoma
Hypertension	NSAIDs	Increase in blood pressure
Hypokalaemia	Digoxin	Cardiac toxicity
Orthostatic hypotension	Antihypertensives, diuretics, antipsychotics, tricyclic antidepressants, levodopa, dopamine agonists, α-blockers	Dizziness, falls, syncope
Osteoporosis	Corticosteroids	Fracture
Peptic ulcer disease	NSAIDs, anticoagulants	Upper GI bleeding
Peripheral vascular disease	β-Blockers (non-selective)	Intermittent claudication
Prostatism	Anticholinergics, α-agonists	Urinary retention
Unsteady gait	Long-acting benzodiazepines, tricyclic antidepressants, SSRIs, anti-psychotics	Falls, injuries

Adapted from Cusack, 1989; reproduced with permission.

apy of these conditions significantly improves outcomes, while inappropriate use of these drugs can reduce benefit or add the burden of adverse drug reactions. The following discussions attempt to highlight areas of importance in treating elderly patients. More complete discussions of individual drugs are presented in specialist chapters.

VII.a. Hypertension

Hypertension can be defined as a systolic blood pressure $\geqslant$ 140 mmHg and a diastolic blood pressure $>$ 90 mmHg. Isolated systolic hypertension (BP $\geqslant$ 140 mmHg with a diastolic blood pressure $<$ 90 mmHg) is even more common in older persons. It is now recommended to treat blood pressure in excess of these thresholds in older persons. Both the risk of complications from hypertension, and benefits of treatment increase with age. A meta-analysis of 8 placebo-controlled trials observed that active treatment of isolated systolic hypertension decreased strokes (30%), coronary events (23%), cardiovascular deaths (18%) and total deaths by 13%. The authors reported that the number of patients needed to treat for 5 years to prevent one major cardiovascular event was lower in men than women (18 vs. 38), at or above age 70 compared to those under 70 (19 vs. 39). Whether there is an upper age limit at which the benefit of treating *uncomplicated* hypertension declines is not known. Current evidence suggests that benefit extends beyond the age of 80 years. On balance, the systolic blood pressure is better than diastolic blood pressure as a method of stratifying risk and as a target for treatment in older hypertensives. It is now recommended that treatment should not be withheld in patients with a systolic blood pressure between 140 and 159 as well as those with more severe systolic hypertension. Treatment should be based on an average of 3 readings, ensuring that the patient is resting for at least 5 minutes and that "white coat" or pseudohypertension is excluded. Before and during treatment, one should check for development of symptoms and signs of orthostasis which is increased in frequency in older patients.

Non-pharmacological life-style modifications, including salt restriction, adequate potassium, calcium and magnesium, weight loss and exercise, should be considered in older patients. These interventions constitute a feasible, effective, and safe nonpharmacologic treatment of hypertension in older patients.

Older hypertensives tend to have lower renin levels than younger persons and based on this principle, *thiazide diuretics* and dihydropyridines calcium channel blockers may be preferred and may be used initially. Thiazides are inexpensive, safe in low doses (e.g. 12.5–25 mg hydrochlorothiazide daily) and are effective in improving cardiovascular outcomes. Effects on other cardiovascular disease risk factors such as glucose, lipid and potassium concentrations generally are mild. In outpatients, the risk of hypokalaemia, and hyponatraemia, increases with age, mandating monitoring of electrolytes soon after starting and later in follow up after commencing thiazide therapy.

Longer-acting dihydropyridine *calcium channel blockers* such as felodipine, amlodipine, nitrendipine and long-acting nifedipine improve cardiovascular outcomes, including multi-infarct dementia, in older hypertensives, with either diastolic or isolated systolic hypertension. Nitrendipine has been found beneficial in reducing cardiovascular outcomes in patients with systolic hypertension, including patients with diabetes. Other drugs recommended for treatment of hypertension in older patients include *ACE inhibitors*, and *angiotensin II inhibitors*.

Beta-blockers can no longer be considered as first line monotherapy for uncomplicated hypertension in older patients since some studies suggest they are less effective than diuretics and no better than placebo in reducing cardiovascular outcomes. Their use in elderly with hypertension probably should be confined to those with other indications such as angina, following myocardial infarction or with heart failure.

VII.b. Diabetes Mellitus

Older patients have predominantly Type 2 diabetes mellitus, which shares with Type 1 the risk for retinopathy, nephropathy and neuropathy, but carries a greater risk for macrovascular complications such as coronary artery disease, stroke and peripheral vascular disease. Many such patients have associated obesity, hypertension and hyperlipidemia, compounding the risk of cardiovascular disease. The goals of treatment of DM in the elderly are to decrease symptoms related to hyperglycaemia and to prevent long-term complications. Treatment of type 2 DM can improve prognosis. In the UKPDS trial, sulphonylureas, insulin, and metformin were all associated with a reduction in diabetes-related

endpoints of microvascular complications and development of nephropathy. It should be noted that clinical trials have shown that it takes about 8 years to demonstrate reduction in microvascular complications with drug therapy of hyperglycemia whereas only 2–3 years are needed to obtain benefit from good blood pressure and lipid control. Thus, attention to control of blood pressure and dyslipidemia is of paramount importance in treating older patients with diabetes. Evidence from the UKPDS and other sources support the goal of tight blood pressure control in type 2 diabetes. In the HOT study that included patients up to age 80, there was a 51% reduction in major cardiovascular events in the group with a goal of <80 mmHg compared to the group with a target <90 mmHg in diastolic blood pressure. In the UKPDS 38 report, those with a tight blood pressure control (mean 144/82) had clinically meaningful reductions in diabetes related deaths, complications and retinopathy compared to the less tightly controlled group (mean BP 154/87) (13). Different agents were used in these trials, suggesting that blood pressure reduction, rather than the choice of drug, was the explanation for benefit. Clearly, aggressive blood pressure reduction should be employed in selected older patients with diabetes. Similarly, because of the increased risk of myocardial infarction and known outcome benefit in older diabetic patients, control of hyperlipidaemia is highly important, with a goal of reducing LDL to 100 mg/dl or less. Older diabetics should also be offered low dose aspirin 75–325 mg daily for prevention of macrovascular complications.

Older diabetic patients are a heterogenous group and treatment needs to be individualized. Treatment approaches and the goals of treatment of hyperglycaemia should be discussed with the patient. Ideally, in younger healthy elderly, a goal of reduction of HbA1c to 7% is a reasonable target (the mean HbA1c in the UKPDS trial was 7% in the intensive treatment arm). This goal may have to be modified in individual patients depending on treatment-related side effects, risks of hypoglycaemia, severity of disease, comorbidity and life expectancy. For reasons discussed above, in patients with a limited life expectancy of less than 5–10 years, careful control of blood sugar to prevent microvascular complications is of secondary importance. Finally, it should be remembered that the patients in the UKPDS trial had a mean age of 55. Whether the data can be extrapolated to older patients is not known.

Life-style changes are an important component of blood sugar control. Diet, weight loss, and regular aerobic exercise reduce insulin resistance. These life-style approaches to blood sugar control should be strongly encouraged even in older, frailer diabetics. At the same time it is prudent to understand limitations to these approaches in frail persons with limited exercise ability or limited financial resources to provide an appropriately balanced diet. If a trial of diet and exercise does not provide adequate blood sugar control, then one should consider oral agents. An increasing array of oral hypoglycaemic agents is available as shown in Table 5.

Sulphonylureas act by increasing release of insulin from pancreatic β cells, reducing serum

Table 5. Oral hypoglycaemic agents

Class	HbA_{1c} reduction	Name	Dose range (mg/day)	Comment
Sulphonylureas	1–2%	Chlorpropramide	100–750	Avoid in elderly
		Tolbutamide	250–3000	
		Glibenclamide (glyburide)	2.5–20	Increased risk of hypoglycaemia
		Glypizide	5–30	
		Glimepiride	1–4	
Biguanides	1–2.0%	Metformin	500–1700	Avoid with renal impairment, CHF
Thiazolidinediones	0.5–1.0%	Rosiglitazone		Can worsen CHF
α-Glucosidase inhibitor	0.5–1.0%	Acarbose	75–300	Take with meals
		Miglitol	150–300	Flatulence, abdominal pain
Non-sulphonylurea insulin secretagogue meglitinides	0.5–1.0%	Repaglinide	1–16	Taken before meals to reduce postprandial hyperglycaemia
		Nateglinide	180–360	

glucagon levels, and potentiating the action of insulin on target tissues. They are inexpensive and are mainstays of oral therapy in older patients, especially in non-obese patients. The more potent agents such as glipizide are preferred in older persons. Chlorpropramide and glibenclamide (glyburide) share an increased risk of prolonged hypoglycaemia and are not recommended in elderly patients. Sulphonylureas have a rather flat dose-response curve so that there is commonly little further to gain by increasing the dose above the half-maximal dose. Older patients may have impaired counterregulatory response to blood sugar reduction and are at increased risk of hypoglycaemia. Other factors that predispose to hypoglycaemia include renal impairment, liver disease, alcohol, and poor food intake.

Metformin, the only available biguanide, has an effect on both fasting and postprandial blood sugars, perhaps by increasing peripheral glycolysis and reducing hepatic gluconeogenesis. Metformin does not cause hypoglycaemia or weight gain and is useful in particular for obese patients. It can be used alone or in combination with other agents. Metformin should be taken with meals, initially in low doses, to avoid common GI side effects. Lactic acidosis is a rare but serious adverse effect. The drug should be avoided in those with an elevated serum creatinine above the normal range for age. It is less clear that old age per se is an absolute contraindication to use of metformin. Other risk factors for lactic acidosis include hepatic dysfunction, alcohol abuse, NYHA class 3 or 4 heart failure, severe lung disease and a history of lactic acidosis.

Thiazolidinediones such as rosiglitazone or pioglitazone decrease hepatic glucose output and increases insulin-dependent glucose disposal in skeletal muscle. They can be used in combination with oral agents or insulin. They should be given with meals. They do not cause hypoglycaemia. These agents can cause sodium retention and hepatic toxicity and are contraindicated in those with uncontrolled heart failure and active liver disease or abnormal transaminase levels. Interestingly, rosiglitazone provides more durable long term glycaemic control compared to metformin or glyburide monotherapies in older as well as in middle aged diabetics. Recent studies have raised concern that rosiglitazone may increase the risk of cardiovascular complications.

Acarbose and miglitol are α-glucosidase inhibitors of carbohydrate digestion in small intestine brush border, thereby reducing postprandial hyperglycaemia. They are usually prescribed in addition to other agents to help further improve glycaemic control. They have their greatest effect if taken before high carbohydrate meals. Due to sugar malabsorption they cause flatulence, diarrhoea and abdominal pain. Symptoms may be reduced by very slow titration of dose. *Repaglinide and nateglinide*, which are meglitinides that function as pancreatic β-cell insulin secretagogues with rapid absorption and short duration of action, help to reduce post prandial blood sugars. There is no evidence to date of altered efficacy or risk of adverse events of these effective but expensive agents in older patients. *Exenatide*, which stimulates hyperglycemia sensitive pancreatic β cell insulin release, with interesting potential benefits including weight loss and low risk of hypoglycemia, is very expensive and as yet has not been evaluated well in older diabetics.

Insulin can be added to improve glycaemic control in those whose blood sugar is not adequately controlled on oral agents. Although insulin clearance may decline with ageing, this is not of great importance in determining insulin dose in older diabetic patients with variable degrees of obesity and insulin resistance. The goal is to use sufficient amounts of insulin to achieve target HbA_{1c} levels with least risk of hypoglycaemia. Different methods are employed. Some experts advocate initial evening doses of a longer acting insulin such as NPH or glargine, often in addition to oral agents. If lunch, afternoon or evening blood sugars are too high, insulin can be given twice daily in motivated, reliable older patients. Obese patients may have very high insulin requirements and may be candidates for addition of metformin, or in some cases, rosiglitazone. There is some evidence that metformin and insulin provide effective lowering of HbA1c with less weight gain and fewer hypoglycaemic events than insulin alone Clearly, insulin administration has to be tailored according to the individual older patient's needs, capabilities, and motivation to maintain careful glycaemic control while avoiding hypoglycaemia.

VII.c. Coronary Artery Disease

Compared to 50 year olds, the incidence of CAD rises fourfold in men and ten-fold in women aged 85–94. Thus the incidence increases with age, especially in older women so that the male to female ratio declines to unity in those over 85. Moreover,

the risk of death from CAD rises with age. Therapies for treatment of stable angina, unstable angina and myocardial infarction are similar in older and young adults. The major questions are whether the risk/benefit ratio and pattern of use are age-related.

VII.c.1. A Stable Angina

Angina pectoris occurs when oxygen supplies are insufficient to meet heightened demands that occur, for example, during exercise or emotion. Treatment is aimed at improving tissue perfusion or decreasing oxygen demands. *Nitrates* are the primary drugs for treatment. They act by causing vasodilatation in arteries and veins, thereby reducing both afterload and preload, respectively. This requires an initial step in conversion of nitrates to nitric oxide, a step that requires reduced sulphydryl groups. Continuous administration can lead to tolerance, considered due to sulphydryl depletion. Preparations include sublingual nitroglycerin, oral preparations (isosorbide mono- and dinitrate), transdermal nitroglycerin and intravenous nitroglycerin. These agents remain effective in older patients. Adverse effects include hypotension due to vasodilation, and headaches. Elderly patients should be evaluated for orthostatic hypotension before and during treatment. It is not known whether nitrate pharmacokinetics, including absorption, changes with ageing. The effect of nitrates on human hand vein dilation and on systemic cardiovascular physiology does not change with ageing. It is not known whether older persons are more susceptible to nitrate tolerance. A drug-free interval of at least 12 hours, typically overnight, is recommended daily during chronic use to help prevent this developing.

Beta-adrenoceptor antagonists cause reduction in heart rate, myocardial contractility and in blood pressure, thereby reducing myocardial oxygen demands. Cardioselective β_1-agents such as metoprolol, atenolol and bisoprolol are best used for treatment of angina in older patients because of the high prevalence of interacting co-morbidity such as obstructive airways and peripheral vascular disease. Small studies suggest that the plasma levels of metoprolol are unaltered but concentrations of an active metabolite are increased in older subjects. Although the systemic clearance of atenolol is not age-dependent, dose requirements are likely reduced in older patients with impaired renal function. Pharmacodynamics of β-blockers may be altered by ageing, however, as evidenced in one example where the negative chronotropic effect of propranolol on heart rate declined with age. In practice one should be cautious in older persons, starting with lower doses (e.g. metoprolol 12.5–25 mg bid or atenolol 25 mg daily) and increasing the dose according to the response. Important adverse reactions in this age group include fatigue, symptomatic bradycardia, heart block, worsening of airways disease and possibly, acutely, worsening of congestive heart failure.

Calcium channel blockers are also used in angina with beneficial effects on oxygen demands and supply due to afterload reduction, negative inotropism and coronary vasodilation. Calcium blockers used for angina include verapamil, diltiazem, and dihydropyridines such as long-acting nifedipine, felodipine and amlodipine. The clearance of some of these drugs is lower in older persons than in young adults, necessitating initial dose reduction. Increased susceptibility to conduction delay mandates careful dose adjustment of verapamil or diltiazem.

Aspirin is of benefit in atherothrombotic disease because, at low doses, it inhibits cyclooxygenase in platelets, decreasing formation of thromboxane A_2, which is involved in platelet aggregation and coronary vasoconstriction. In men with a mean age of 64 years, suffering from chronic angina, aspirin in low doses reduced the risk of myocardial infarction from 13% to 4% over an average of 5 years. Aspirin (80–325 mg/day) therefore should be used in older persons with chronic angina. Some studies, however, that included elderly subgroups, indicate a dose-related risk of significant bleeding of about 20–50 events per 1000 patients per year.

Unless contraindicated, lipid lowering with *HMGCoA reductase inhibitors* (statins) should be used to treat hyperlipidemia for prevention of cardiovascular complications and are effective and well tolerated in those at least up to 80 years with coronary disease.

VII.c.2. Acute Coronary Syndrome

Drug therapy of acute coronary syndromes including unstable angina and non-Q-wave myocardial infarction includes use of aspirin, heparin and antiischaemic drugs and is similar in older patients to other age groups. Activation of platelet thromboxane production in the coronary circulation has been demonstrated in unstable angina. The risk of myocardial infarction or death is reduced by approximately 50% by early *aspirin* therapy in recommended doses of 160–325 mg per day and continued

indefinitely. *Heparin* also is beneficial, and when used in addition to aspirin, the risk of major complications is reduced by 50% compared to aspirin alone for the duration of heparin treatment. Heparin is given as an i.v. bolus and infusion with a goal of maintaining an APTT of 46 to 70 sec. Despite these well-known benefits, older patients often do not receive aspirin and heparin therapy. More recently, *low molecular weight heparins* such as enoxaparin and dalteparin have been proven as good as or better than unfractionated heparin and, although more expensive, are easier to use. These may make use of heparin more widespread in older patients. *Glycoprotein IIb/IIIa inhibitors* such as tirofiban, abciximab and eptifibatide may add incremental benefit in addition to aspirin and heparin in patients including those over 65 years. Their role in older patients is not yet well established. Studies have shown that clopidogel, another antiplatelet agent that acts by inhibition of a platelet ADP receptor required for platelet activation, was beneficial in patients with acute coronary syndromes including unstable angina, over half of whom were over 65 years old. Benefit in reducing composite risk of cardiovascular death, myocardial infarction and stroke was seen in all risk groups and increased in higher risk individuals for a period of 12 months. *Clopidogrel* is recommended in older patients with unstable angina who are not immediate candidates for bypass surgery without bleeding or thrombocytopenia.

Nitrates are required for symptomatic relief of chest pain; they are not proven to improve hard outcomes such as MI or death. Nitrates should be given initially sublingually or by spray, followed by oral or transdermal routes if pain is relieved. Lack of pain relief mandates i.v. administration. *Beta-blockers* such as metoprolol are used and may reduce the risk of subsequent MI. *Calcium channel blockers* such as diltiazem, verapamil, or long-acting dihydropyridines can be added for symptom control if nitrates and beta-blockers do not suffice; they do not improve outcomes. In fact, they may worsen outcomes in the presence of left ventricular dysfunction or CHF in acute coronary syndrome.

VII.c.3. Myocardial Infarction

While the survival of older patients with ST elevation MI has improved in the last 20 years, it still remains much higher than in younger adults. Thus, the potential of treatments to improve outcomes in absolute terms is greater in older patients. Despite the potential for a significant impact on outcomes, the effective therapies have not been well studied and are often underused in older patients. Important treatments include antiplatelet agents, beta blockers, thrombolytic therapy and ACE inhibitors. *Aspirin* should be given to all patients unless allergic in which case an alternative antiplatelet agent such as *clopidogrel* may be used. Acute and continued aspirin can reduce adverse outcomes by over 20% in older patients. *Beta-blockers* have antiarrhythmic, antiischaemic and antihypertensive properties that can reduce pain, wall stress and infarction size. Early short-term use of beta blockers such as metoprolol and atenolol is an important measure that reduces mortality from myocardial infarction by 15% in patients at large and notably by 23% in those aged 65–74 years. Longer-term use for up to 33 months also significantly reduces mortality. Despite this, beta-blockers are underused in older patients, especially those with systolic dysfunction who also benefit. In one large study only 50% of patients discharged after myocardial infarction were on beta-blockers. These patients, after adjustment for confounders, had a 14% less mortality at one year compared to non-treated patients. Every effort should be made to use beta-blockers following myocardial infarction. Contraindications include significant cardiac failure, pulmonary oedema, asthma, hypotension, bradycardia and greater than first degree heart block.

In a large metaanalysis including 58,000 MI patients, *thrombolytic agents* were associated with significant absolute reductions in 35 day mortality of 30 per 1000 in those treated within 0–6 h, and 20 per 1000 within 7–12 h of presentation. Mortality reduction was significant in patients aged 65–74 at 27 per 1000 and was insignificant at 10 per 1000 in those over 75. The modest risk of haemorrhage, including stroke is increased in older patients. Thus the current data support use in carefully selected patients under 75 but do not provide definitive support for those $\geqslant$75. The use of thrombolytic therapy is reduced in older patients, even when allowing for contraindications perhaps due to concern about bleeding or delayed diagnosis. *Heparin*, used without thrombolytics, is considered beneficial following myocardial infarction, but in older patients it may not be effective in reducing early mortality. *ACE inhibitors* decrease blood pressure, ventricular wall stress and ameliorate left ventricular remodelling. Large studies have shown that ACE inhibitors

such as captopril and lisinopril, administered within 24 hours for up to 42 days, reduce absolute mortality by 4–5 lives per 1000 treated. Absolute benefit is much greater in those with anterior MI with either asymptomatic or symptomatic left ventricular dysfunction (EF < 45%). Older subjects were included in these studies. Trandolapril therapy has increased the life expectancy of patients, including those over 65 years, with reduced LV function post myocardial infarction. The time when 50% mortality was reached was prolonged by 15.3 months (27%). Based on these data older patients with myocardial infarction should be treated with an ACE inhibitor (typically captopril initially due to short half-life and less cost), for 6 weeks and if there is evidence of left ventricular dysfunction therapy should be continued indefinitely.

VII.d. Chronic Congestive Heart Failure

The prevalence of CHF increases and prognosis worsens with age. Some studies demonstrate that age markedly influences all follow-up events, including total mortality, and mortality or hospitalisation related to CHF. Some studies suggest that physiological changes occur in CHF with ageing; with an age-related increase in systemic vascular resistance and circulating noradrenaline (norepinephrine) concentrations and a decrease in renal function.

Drugs of known benefit in CHF are the same in older and younger adult patients. *Diuretics* remain important to reduce or eliminate sodium retention and oedema. They can reduce ventricular diastolic pressure, thereby decreasing diastolic ventricular wall stress and promoting subendocardial perfusion. Once oedema is controlled, diuretic use should be reduced to avoid excessive neurohormonal activation or volume depletion. Motivated, co-operative patients can adjust the diuretic dose to maintain a consistent body weight. Loop diuretics such as frusemide (furosemide) are most often used. The response to frusemide is reduced in older persons because of decreased presentation of frusemide to the site of action in the renal tubule. Although interesting, this not important clinically, since the dose of frusemide is adjusted according to the response. One should be particularly cautious in older patients to avoid volume depletion, hypokalaemia or orthostatic hypotension. Thus, initial doses of loop diuretics such as frusemide, bumetanide and ethacrynic acid should be low and treatment monitored by careful evaluation of volume status and electrolyte levels. Thiazide diuretics can be used for treatment of milder CHF in patients with preserved renal function. The renal clearance of hydrochlorothiazide decreases with age.

Digoxin increases myocardial contractility by inhibition of sarcolemmal Na^+/K^+-ATPase and also causes impairment of conduction (negative dromotropic effect). Digoxin is of benefit for patients with systolic dysfunction with an ejection fraction of 0.45 or less. Patients on digoxin (mean age 63 ± 11 years) in addition to diuretics and ACE inhibitors had fewer hospitalisations for heart failure compared to those on placebo (63.5 ± 11 years). Digoxin appears to be of most benefit in those with worst ventricular function (EF < 0.25). However, digoxin did not alter mortality in the DIG trial. The target plasma level should be around 1.0 nmol/l (c. 0.75 ng/ml), the mean level in the DIG study. Since digoxin clearance declines with age, digoxin maintenance dose requirements are reduced in older patients. The other main indication for digoxin is for control of ventricular rate in atrial fibrillation, particularly in the presence of cardiac failure. The plasma level of digoxin required for control of resting ventricular rate in atrial fibrillation is unaltered in older persons. Older patients may be at increased risk of adverse effects including anorexia, nausea, vomiting, visual disturbances, and cardiac toxicity, characterised by arrhythmias and conduction disturbances.

Angiotensin converting enzyme inhibitors (ACEIs) reduce peripheral resistance and improve cardiac output in patients with CHF by blocking production of the highly potent vasoconstrictor, angiotensin II, and perhaps by inhibiting bradykinin breakdown, in the circulation and the heart. The sensitivity of circulating converting enzyme to ACE inhibition is unaltered with ageing. Since most of these drugs, excepting fosinopril and trandolapril, are cleared by the kidney, doses required in older patients may be reduced due to decreased renal function. These drugs are important in treatment of congestive heart failure. They improve symptoms, reduce hospitalisation and decrease mortality. Patients over 65 years have been included in several studies with benefit observed in those up to 95 years of age. Despite their proven benefit, ACEIs often are underused in older patients with CHF and dosage frequently may be inadequate. Older patients, especially the very elderly, should be started on very conservative doses (e.g. captopril 6.25 mg daily) after correction of volume depletion and hyponatraemia. One should titrate very carefully to achieve

doses equivalent to those used in successful studies (e.g. captopril 150 mg/day or enalapril 20 mg daily). However, some patients may only tolerate lower doses, due to impaired drug clearance or other factors. Limiting outcomes to dose titration in older persons include symptomatic hypotension, increase of serum creatinine by more than 20%, and hyperkalaemia.

In patients who cannot tolerate ACE inhibitors for reasons such as cough, *angiotensin II type 1 receptor antagonists* such as losartan should be prescribed. These agents reduce afterload, improve cardiac output and symptoms in heart failure patients. Several studies in patients with class II to IV heart failure demonstrated benefit including significant reduction in death and hospitalization in elderly including those over 85. Benefit appears similar to ACE inhibitors. In the ELITE study in elderly patients with CHF with systolic dysfunction, losartan 50 mg daily was associated with similar improvement in NYHA class and mortality rate compared to captopril 50 mg tid. The patients generally tolerated losartan as well or even better than captopril.

Beta-adrenergic blockers are effective in treatment of CHF with systolic dysfunction in older patients. Beta-blockers can improve cardiac function, left ventricular remodelling, and exercise capacity. They reduce symptoms, hospitalization rate for heart failure and death when used in addition to diuretics, digoxin and ACE inhibitors. These trials showed benefit in patients over 65 years Further studies specifically in patients $\geqslant$70 years, one third of whom had EF $>$ 35%, showed a reduction in mortality or cardiovascular hospitalization with treatment with nebivolol that appeared unaffected by age, EF or gender. As with ACE inhibitors, the starting dose in older patients has to be low (e.g. carvedilol 3.125 mg bid; metoprolol 6.25–12.5 mg daily) and the dose slowly titrated to target doses if possible, watching for evidence of hypotension and bradycardia. In the MERIT-HF study the target dose of metoprolol was 200 mg daily, and in the COPERNICUS study the target dose was 25 mg bid for carvedilol. Many elderly patients may not be able to tolerate these doses, however. *Aldosterone inhibitors* such as spironolactone and epleronone, help reduce mortality in patients with advanced heart failure. Electrolytes and renal function should be closely monitored especially in old patients and these drugs should be used with great caution if at all in those with renal dysfunction.

Older patients with CHF may be faced with multiple therapies of diuretics, ACE inhibitors/angiotension II blockers and beta-blockers. This puts them at risk of hypotension, orthostatic hypotension, azotaemia and electrolyte imbalance. Drugs should be added carefully, starting at low dose and patients should be monitored for volume depletion and changes in serum creatinine and electrolyte concentrations.

Patients with CHF and a normal ejection fraction are considered to have *diastolic dysfunction.* The frequency of CHF with diastolic dysfunction increases with age. Such patients benefit from treatment of the underlying cause such as hypertension or ischaemia. Inotropic agents such as digoxin should be avoided. Diuretics, β-blockers, ACE inhibitors can be used. Aldosterone inhibition, using spironolactone or epleronone, may be beneficial. Carvedilol improves diastolic dysfunction in diastolic CHF. However the long-term benefit of different drug therapies has not yet been defined.

VII.e. Alzheimer's Disease and Related Disorders

Dementia is a common, age related disorder in older people, affecting about 5% of those over 65 years with a prevalence of 30% in those over 80 years. The most common causes include Alzheimer's disease (up to 60% of cases), vascular dementia, dementia with Lewy bodies, and frontotemporal dementia. The natural history of most dementias is that of inexorable decline in cognitive function. Complications of dementia are common, including depression, behavioral disturbances, psychotic features and sleep disturbances. Comprehensive guidelines for pharmacotherapy have been developed by many societies. *Acetylcholine esterase inhibitors* such as donepezil, galantamine and rivastigmine are approved for treatment of mild to moderate Alzheimer's dementia – they increase acetylcholine neurotransmission, which is decreased in Alzheimer's dementia. These agents appear to have similar efficacy in producing a modest improvement in cognitive function and in global function in those with mild to moderate dementia. Assessment of progress should be performed on a regular basis, using a cognitive testing instrument in addition to careful evaluation of the patient and obtaining a history from caregivers. Side effects include nausea, abdominal discomfort, diarrhoea and

bradycardia. *Memantine*, an NMDA receptor antagonist works by a different mechanism and is modestly effective in treatment of moderate to severe Alzheimers dementia either alone or in addition to a cholinesterase inhibitor. Other possible therapies such as *vitamin E*, *selegiline and Ginkgo biloba* are less well proven.

Behavioural disturbances are very common with agitation, hyperactivity, aggression, wandering and psychotic features such as delusions, paranoia and hallucinations. It is important to attempt behavioural approaches initially, including environmental adaptations and specific techniques such as distraction, exercise, behavioural management or group socialisation therapies that have demonstrated benefit. These behaviour disturbances often resolve spontaneously. It is most important to try to diagnose any precipitating cause such as infection, medications, pain, constipation or dehydration. If behavioural approaches fail to achieve a tolerable level of disturbance and there is distress or risk of injury to the patient or caregivers, drug therapy should be considered.

Antipsychotic agents are modestly effective in improving behavioural symptoms and for psychotic disturbances. They should be used at the lowest effective dose (Table 6). Since the long-term safety and efficacy of these drugs is not established, dose reduction or drug cessation on improvement of symptoms should be attempted. Since it is not clear that there are differences in efficacy, the adverse affect profile should be considered in drug selection. *Traditional antipsychotics* such as haloperidol can be used in low doses, but carry the risk of producing parkinsonism, akathisia, orthostatic hypotension, falls, and drowsiness. In addition, older patients are particularly susceptible to the complication of tardive dyskinesia. Drugs with significant anticholinergic activity, such as thioridazine, should be avoided as a rule. Newer *atypical antipsychotics* including risperidone, quetiapine and olanzapine are much more expensive, but appear moderately effective according to initial studies. Although they carry a lower risk of extrapyramidal side effects than traditional agents, adverse effects such as sedation may offset their benefit. They appear to be associated with a small but definite risk of death, an effect, however, that may be shared with conventional antipsychotics such as haloperidol. Metabolic side effects such as weight gain and increase in blood sugar and lipids appear modest in older patients treated with relatively moderate doses of atypical antipsychotics and their importance in this age group has yet to be determined. The risk/benefit of antipsychotic drugs should be discussed prior to use. Use should be limited in duration with attempts to wean the patient off the antipsychotic agent. Antidepressants, including trazodone, benzodiazepines, anxiolytics (e.g buspirone), trazodone and anti-epileptic agents (carbamazepine, valproic acid) have also been studied in small trials for dementia-related behavioural disorders with variable and unconvincing benefit. Sleep disturbance is common. Usual sleep hygiene measures should be attempted. Trazodone is often recommended for hypnotic purposes in demented patients.

VII.f. Depression

Depression is relatively common in older persons; about 3% of those over 65 suffer from major depression and up to 15% have clinically significant

Table 6. Usual recommended doses and common side effects of neuroleptic agents used for psychosis or behavioral disorders in dementia in the elderly

Drug	Starting dose	Maintenance dose	Comments/Adverse effects
Haloperidol	0.25–0.5 mg qd	0.5–2 mg bid	OH, EPS, and TD are problematic
Aripiprazole	2.5–5 mg qd	10–20 mg qd	Little experience in elderly
Risperidone	0.5 mg qd	0.5–1 mg bid	OH, EPS at higher doses
Olanzapine	2.5 mg qd	5–10 mg qd	Sedation, OH
Quetapine	12.5–25 mg qd	37.5–75 mg bid	Sedation, OH
Ziprasidone	10–20 mg bid	20–40 mg bid	Mild QT prolongation, limited experience in elderly
Clozapine*	12.5 mg bid	50–75 mg bid	Agranulocytosis, OH

EPS = extrapyramidal symptoms; OH = orthostatic hypotension; TD = tardive dyskinesia. These doses represent usually effective doses but individual patients may respond to lower or higher doses. *Should be used rarely due to risk of bone marrow depression.

Table 7. Antidepressant drugs often used in the elderly

Drug	Initial dose (mg/day)	Dose range (mg/day)	Active metabolite	Comment
Desipramine	10–25	25–100	None	Less sedating
Nortriptyline	10	20–100	10-hydroxy	More sedating, less orthostasis
Fluoxetine	10	10–50	Nor	Long half-life, increased plasma levels
Sertraline	25	50–150	desmethyl	Diarrhoea common; less effect on CYP 450
Fluvoxamine	25	50–200	None	Nausea and vomiting are frequent
Paroxetine	10	20–40	None	Anticholinergic effects; increased plasma levels
Citalopram	10	20–40	desmethyl	Highly specific inhibitor of serotonin
Escitalopram	5–10	5–15	s-desmethyl	More potent than citalopram
Nefazodone	100	100–400	Hydroxy	Short half-life,[1] hepatotoxicity
Buproprion	100	150–300	None	Short half-life;[1] seizure risk
Venlafaxine	50	50–225	*O*-desmethyl	Short half-life;[1] increases blood pressure
Duloxetine	20	20–60		Increases BP, urine hesitancy
Mirtazepine	7.5–15	15–45		Sedating; rare blood dyscrasias

[1] Short half-life necessitating two or three daily doses; slow-release formulations available.

symptoms. Prevalence is much higher in the medically ill and in institutionalised elderly. Depression causes much suffering, affects cognitive function, and increases the risk of mortality from medical illness and suicide. The risk of suicide is greater in older patients with depression, particularly in males. Drug treatment can be effective, with the goal of remitting symptoms, and, equally importantly, sustaining the remission from depression. When possible, pharmacotherapy should be combined with psychotherapy for most effective results. Available medications include tricyclics, selective serotonin uptake inhibitors (SSRIs), serotonin–noradrenaline reuptake inhibitors (SNRIs), monoamine oxidase inhibitors (MAOIs) and other atypical heterocyclic agents as shown in Table 7. *Tricyclic antidepressants* are well documented as effective in treatment of depression in late life and are as effective as SSRIs in older persons. They are less expensive than other choices. Their usefulness is limited by side effects, including sedation, anticholinergic symptoms (such as dry mouth, urine retention or cognitive impairment), orthostatic hypotension, falls, and, most seriously, cardiotoxicity and lethality in overdose. Pretreatment EKGs are required to detect conduction disorders than can be worsened by tricycyclics. Of the tricyclic antidepressants, the secondary amines nortriptyline and desipramine are preferred, due to less anticholinergic potency and orthostasis (nortriptyline) with goal plasma concentrations of 60–120 μg/ml and >115 μg/ml, respectively. *Selective serotonin reuptake inhibitors* (SSRIs) such as fluoxetine, fluvoxamine, sertraline, paroxetine, citalopram and escitalopram have less affinity for histamine, acetylcholine and adrenergic receptors and cause fewer side effects. Because of relative safety in overdose in this at risk population, they are preferred, when financially feasible, to tricyclic antidepressants. The SSRIs are structurally heterogeneous and have different pharmacokinetic properties, CYP 450 inhibition and adverse effect profiles in elderly subjects. Fluoxetine has a very long half-life in elderly patients (330 h for norfluoxetine, an active metabolite). Its use may be problematic in older patients for that reason. Other agents have shorter half-lives than fluoxetine but in some cases plasma levels are higher than in younger patients, suggesting use of lower starting doses.

Side effects, mainly due to serotonin reuptake inhibition include GI upset, nervousness, and sexual dysfunction. SSRIs are associated with an increased risk of falls. Hyponatraemia due to SIADH is an uncommon, but important side effect in elderly patients. *Selective serotonin and norepinephrine reuptake inhibitors* (SSNRIs) such as venlafaxine and duloxetine are also useful in older patients. Other heterocyclic antidepressants of importance in older patients because of relative safety include buproprion and mirtazepine. They are reserved for patients with resistance to or intolerance of SSRIs. Currently, trazodone is used mostly for sleep disturbance in depression in doses of 50–100 mg at bedtime. The *monoamine oxidase inhibitors* phenelzine,

tranylcypromine, and moclobemide are effective in many forms of depression but should be prescribed only by mental health specialists. Orthostasis can be troublesome in older recipients. The benefit of *amphetamine-like agents*, such as methylphenidate, although only documented in small clinical trials, can, in the author's experience, be very useful to expedite recovery in frail, medically ill, older patients with severe depression and poor oral intake. They are typically used in addition to conventional antidepressants.

VII.g. Osteoarthritis

Osteoarthritis, or degenerative joint disease, is an age-related disorder in the older population. The methods of treatment include important non-pharmacological approaches such as exercise to increase range of motion and contiguous muscle strength, such as quadriceps exercises for knee osteoarthritis. The goal of pharmacotherapy is relief of pain to permit functional use. Analgesics are of central importance. *Paracetamol* (acetaminophen) is widely used since studies have shown it causes similar relief of pain in osteoarthritis compared to ibuprofen (1200 or 2400 mg daily) when used in relatively high doses of 4 g daily. The effect of aging on biotransformation of paracetamol by sulphate and glucuronate conjugation is variable according to small studies performed to date. Paracetamol appears well tolerated in older patients but doses in excess of 4 g daily are not recommended due to the risk of hepatotoxicity. Alcohol ingestion and poor diet are additional risk factors for hepatotoxicity. Drug doses should be halved in hepatic disease. The combination of paracetamol and a NSAID at lower dose may also be more beneficial than a high-dose NSAID. *NSAIDs* are among the most widely used drugs in older patients. They inhibit cycloxygenase (COX), both type 1 that is expressed constitutively in many tissues including GI mucosa, kidney, and platelets and type 2 that is induced in inflammatory tissues. Inhibition of COX type 2 is considered to mediate the anti-inflammatory effects of NSAIDs. Pharmacokinetics in older persons show modest changes, with often a reduction in protein binding, and clearance may be reduced especially for parent drugs or active metabolites excreted by the kidney. Overall, pharmacokinetics is not markedly different, but in cases with high protein binding (e.g. naproxen) free drug clearance is reduced. There is not much difference in general in the effectiveness of these drugs in the treatment of osteoarthritis, but individuals respond to a variable extent to specific agents. Response should be monitored and, if no appreciable benefit is seen, the agents should be stopped. NSAIDs are generally well tolerated, but some adverse effects are of concern in the elderly. A study in the UK indicated that 3% of admissions in older patients were due to conditions either caused (GI toxicity) or aggravated (renal impairment or CHF) by NSAIDs. They can produce a further decrement of GFR function in older persons with baseline renal impairment. Renal function should be monitored during treatment. NSAIDs also may be an independent risk factor for hypertension, and can increase the risk of hospitalisation with CHF in older patients. However, gastropathy is the most serious adverse outcome of NSAIDs, claiming over 16,000 lives in the US in 1997. Increasing age is an independent risk factor for gastrointestinal toxicity, such as gastritis or ulceration or ulcer complications including bleeding or perforation. Risk of gastropathy or complications is further compounded in patients with a history of peptic ulcer, concomitant corticosteroid use, higher dose of NSAID, or use of anticoagulants. Strategies to reduce the risk of such events such as prescribing lower doses of NSAIDs and employment of lower risk NSAIDs should be considered in the elderly. Less gastric toxicity allegedly is found with diclofenac, nabumetone, etodolac and, in particular, non-acetylated salicylates such as salicylsalicylic acid (salsalate). Initial dosage of salsalate is 500–750 mg bid in older patients and is a less expensive choice. Agents such as celecoxib and rofecoxib that are *selective COX-2 inhibitors* and thus may cause less gastropathy, either have been withdrawn or have become unattractive options due to the risk of cardiovascular complications. Older patients, especially with another of the risk factors for gastropathy as mentioned above, should receive concomitant therapy with high-dose H_2 receptor blockers (e.g. ranitidine or famotidine), or a proton pump inhibitor (omeprazole or lansoprazole), or the prostaglandin misoprostol. The latter two choices appear more effective than H_2 blockers in peptic ulcer prevention.

There are some additional choices in patients with refractory arthritis despite the use of NSAIDs or paracetamol (acetaminophen), alone or in combination. *Narcotics* can be used with little risk of addiction, but with the caveat that they can cause cognitive changes, constipation, urine retention and respiratory depression (see section on analgesics). Codeine

or tramadol are reasonable initial choices, avoiding propoxyphene due to less favourable risk/benefit ratio in elderly. More potent choices may be required such as hydrocodone, oxycodone, morphine or methadone. *Intra-articular corticosteroid injection* of large accessible joints such as the knee may provide benefit. This can be used no more that 2–3 times per year to avoid further cartilage breakdown. Local applications of topical capsaicin may help reduce pain. Some patients receive benefit for several months from a course of intra-articular injections of *hyaluronate*, but this is an expensive approach. Arthroscopic surgery can provide additional benefit until arthroplasty is finally indicated.

VIII. CONCLUSION

The treatment of disease in older persons is a challenge to the prescriber's knowledge and judgement. Although age-related physiological changes are important determinants of drug disposition and effect, disease, drug–drug interactions, and problems with compliance often complicate drug therapy. In addition, it is not unusual that quality, evidence-based approaches to therapy are marred by lack of data in the older population. Prescribing practices may limit potential benefit to the elderly due to underuse of effective therapies or overuse of agents with less clear-cut risk/benefit ratio. But the situation is improving, with the advent of newer, often safer drugs, and increasing evidence of therapeutic benefits in this population. The prescriber must be vigilant in ensuring that drug use is appropriate and based on a sound knowledge of geriatrics therapeutics principles.

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Chapter 14

Adverse Drug Reactions

Ralph Edwards, Chen Yixin

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I. INTRODUCTION

Adverse drug reactions constitute a major morbidity, causing deaths in some cases. About 6% of all hospital admissions are related to ADRs and about half of these are avoidable. There is also a substantial diagnostic problem since there is a limited way in which the body may respond patho-physiologically. This means that ADRs often masquerade as other diseases. Commonly reported ADRs are given in Table 1.

In some instances ADRs may be more specifically related to drug or chemical exposure: some examples of these are shown in Table 2. From this latter table note that there are some very common problems with a relatively lower drug relatedness at the bottom, but these constitute a numerically higher public health risk.

It follows from this that practising clinicians must always consider adverse drug reactions as part of their clinical diagnosis. The causal relationship of a drug to a clinical event may be far from easy to distinguish from other (disease) candidates in the differential diagnosis.

There are some general points for any doctor to bear in mind before prescribing, related to safety:

- The skill of therapeutics is to anticipate, and then use drugs in a way that minimizes risk.
- Drugs are capable of modifying fundamental biological processes profoundly, and their use is associated with the risk of adverse drug reactions.
- Always consider the risks and benefits of using any drug. Think also about all of the costs of using that drug. Compare it with other treatments for the same indication. Then decide which is best to use for your particular patient.
- Remember that it is the patient stands to gain the benefits, but also runs the risks! The benefit of your specialised knowledge of both the patient and the drug must be shared as completely as possible.
- All drug effects are the result of complex interaction between the drug, the patient and the illness. Extrinsic factors, such as speed of administration intravenously, diet, chemical exposures (including other drugs) and many other factors, can also modify drug response.
- Important general predisposing factors to adverse reactions include an excessive amount of the drug due to non-individualised dosage, altered responsiveness to drugs at extremes of age, previous history of allergy or reaction to drugs.

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Table 1. Most reported adverse reactions in the WHO database

Adverse reaction term	System organ class	Number of reports	% of total
Rash	Skin and appendages disorders	147,663	4.2
Pruritus	Skin and appendages disorders	96,636	2.7
Urticaria	Skin and appendages disorders	93,843	2.6
Fever	Body as a whole – general disorders	87,509	2.5
Nausea	Gastro-intestinal system disorders	83,740	2.4
Headache	Central and peripheral nervous system disorders	71,225	2.0
Vomiting	Gastro-intestinal system disorders	70,801	2.0
Rash erythematous	Skin and appendages disorders	61,089	1.7
Dizziness	Central and peripheral nervous system disorders	59,166	1.7
Diarrhoea	Gastro-intestinal system disorders	50,822	1.4
Rash maculo-papular	Skin and appendages disorders	47,919	1.4
Abdominal pain	Gastro-intestinal system disorders	46,305	1.3
Dyspnoea	Respiratory system disorders	45,622	1.3
Death	Body as a whole – general disorders	39,713	1.1
Pain	Body as a whole – general disorders	35,276	1.0
Hypotension	Cardiovascular disorders, general	33,972	1.0
Injection site reaction	Application site disorders	31,302	0.9
Somnolence	Psychiatric disorders	31,189	0.9
Paraesthesia	Central and peripheral nervous system disorders	30,744	0.9
Face oedema	Urinary system disorders	30,403	0.9
Thrombocytopenia	Platelet, bleeding and clotting disorders	28,971	0.8
Confusion	Psychiatric disorders	28,168	0.8
Fatigue	Body as a whole – general disorders	28,013	0.8
Hepatic function abnormal	Liver and biliary system disorders	27,769	0.8
Convulsions	Central and peripheral nervous system disorders	27,370	0.8
Allergic reaction	Body as a whole – general disorders	25,093	0.7
Tachycardia	Heart rate and rhythm disorders	24,783	0.7
Vision abnormal	Vision disorders	23,997	0.7
Tremor	Central and peripheral nervous system disorders	23,630	0.7
Malaise	Body as a whole – general disorders	22,362	0.6

Table 2. Selected diseases with a high drug related fraction

Disease (or trauma)	Overall annual incidence (/10^5)	Drug related fraction (%)*
Toxic epidermal necrolysis	0.04–0.012	80
Aplastic anaemia	0.2	20
Agranulocytosis	0.35	70
Erythema exudativum multiforme	0.12–0.6	50
Anaphylaxis	1	45
Uraemia (chronic)	10	10
Gastrointestinal haemorrhage	50	30
Pancreatitis (acute)	50–150	<10
Traffic accidents (hospital admissions)	77	2–6
Falls (requiring medical treatment)	2700	7
Asthma	5000	10

*This table gives some idea of the actual figures only.

- Pregnancy and labour are also times of altered drug responsiveness: the fetus has special susceptibility to some adverse drug reactions though may be immune to others, for example due to the drug not passing the placenta.
- The incidence of adverse reactions increases with the number of drugs. A minority of adverse effects of drugs can be attributed to drug interaction, but some important adverse interactions are predictable and can be avoided. In the WHO global database of individual case safety reports (ICSR), only about 0.7% of possible adverse events which might be due to interactions between drugs known to share the same CYP enzyme are recorded as possibly due to interaction by the reporter, therefore missing a possible important signal. It should be noted, however, that many interactions have been reported in the literature without much evidence (see Chapter 15).
- Adverse drug reactions should be avoided, managed by dose reduction or withdrawal of the offending drug, replacement with another if necessary, but not treated by with other drugs unless essential.
- The clinician has a responsibility to recognise the possibility of an adverse drug reaction and include it as part of the differential diagnosis or problem list.
- The clinician must report clinically important adverse drug effects to a committee or registry, which have responsibility for deciding on drug formularies (local or national) and for advice on therapeutics.

II. BACKGROUND

When a drug is first placed upon the market, exhaustive toxicological and safety testing has been done in addition to investigating its pharmacology and efficacy. On the other hand pre-marketing human exposure to drugs is in typically 3000–5000 volunteers and patients: sometimes the number is much less depending on the type of drug. Statistically, this does not allow for the sure recognition of even a severe reaction occurring in less than 1 in 1000 patients. It will be also clear that finding a single case gives almost no useful indication to the clinician about range of severity, outcome of the reaction, and what management of the reaction is required. Such information can only be found from gathering considerable post-marketing experience, from large clinical studies, meta-analysis, and reports by clinicians of adverse experiences to national and international data collections agencies.

National and international agencies and a number of hospital-based and other local programmes have been established for monitoring the occurrence of reactions by collecting ICSR, collating the data, and then providing information and warnings to health professionals. The aim has been to promote awareness of possible adverse reactions in all therapeutic fields and to assist in early recognition of reactions.

Complementary to the ICSR data is pharmacoepidemiology, which provides confirmation of the suspicions raised by ICSR, by controlled studies (often observational) and also gives quantification (incidence or rate), not possible by collections of ICSR because there is no reliable exposure information Other important information comes from pathological and other investigations into possible mechanisms of adverse reactions, improving our understanding of the processes underlying the adverse drug reactions (clinical toxicology).

It will be clear from the above that drug safety information changes as more information is gathered, particularly on newly marketed drugs. Prescribers should keep up-to-date on drug safety information, and use central drug information services when in doubt. Bulletins issued from such authorities on drug safety should always be read and considered carefully. Web sources are increasingly used and useful. There are many of them, and not all are reliable. It is best to use information from summaries of product characteristics (SPC or package inserts), from government agencies, or quality assured sites such as www.hon.ch which has other medical information as well.

Drug abuse (except insofar as dependence may result from therapeutic use), accidental or suicidal self-administration, and homicidal use of drugs do not come under the heading of ‘adverse drug reactions’, but the wise clinician needs to bear these in mind as well. However, as noted above, adverse effects of prescribed drug regimens that are inappropriate for a particular patient do. There is a strengthening view that we have neglected the area of medical error in relationship to drug safety. Medical errors, which are essentially avoidable adverse reactions to treatment, form about half the adverse drug reactions leading to hospital admissions (see Pirmohamed et al., 2004). There are many reasons

for medical error ranging from outright negligence to mistakes made by conscientious doctors who are too tired or pressured or distracted. The ultimate causes may be multilayered and can only be fully evaluated by tracing back to the ultimate causative factors: a long process, but which may be very important in order to discover system errors which can be managed and avoid problems in the future. Such 'reporting and learning' is the cornerstone of wider patient safety work and is promoted globally by the WHO World Alliance on Patient Safety. Simple examples of such an approach might be improved working hours to avoid tiredness and stress or double checking interpretation of prescriptions prior to dispensing, to avoid errors due to misread handwriting.

II.a. Definitions

There are some definitions that will help in understanding of drug safety jargon. The list is taken from those adopted by National Centres participating in the WHO International Drug Monitoring Programme, September 1991. Unfortunately there are others which differ, some slightly, others in important ways. Definitions change with time but these have wide international use.

Side effect: Any unintended effect of a pharmaceutical product occurring at doses normally used in man which is related to the pharmacological properties of the drug.

Adverse event/adverse experience: Any untoward medical occurrence that may present during treatment with a pharmaceuticalproduct but which does not necessarily have a causal relationship with this treatment.

Signal: Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously. Usually more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information.

Adverse reaction: A response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophyxis,diagnosis,or therapy of disease, or for the modification of physiological function.

Unexpected adverse reaction: An adverse reaction, the nature or severity of which is not consistent with domestic labeling or market authorization, or expected from characteristics of the drug.

II.b. Causality Assessment of Suspected Adverse Reaction

Certain: A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.

Probable/Likely: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfil this definition.

Possible: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.

Unlikely: A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.

Conditional/Unclassified: A clinical event, including laboratory test abnormality, reported as an adverse reaction, about which more data is essential for a proper assessment or the additional data are under examination.

Unassessible/Unclassifiable: A report suggesting an adverse reaction which cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified.

In addition to the above there is also widespread agreement on the definition of *seriousness* and *severity* of a reaction. A *serious* adverse reaction is:

- Any untoward medical occurrence that at any dose:
  - results in death
  - requires inpatient hospitalisation or prolongation of existing hospitalisation
  - results in persistent or significant disability/incapacity
  - is life threatening.

- Any cancers and congenital anomalies or birth defects should also be regarded as serious.
- Medical events that would be regarded as serious if they had not responded to acute treatment should also be considered as serious.
- The term '*severe*' is often used to describe the intensity (severity) of a medical event, as in the grading 'mild', 'moderate' and 'severe': thus a 'severe' skin reaction is not usually 'serious'.

A newer set of definitions is published by Lindquist (see Lindquist, 2007) and includes some additional useful terms.

III. PHARMACOLOGY OF ADRs RELATED TO THERAPY

Adverse reactions may relate to the known pharmacology of the drug but perhaps be of surprising degree (Type A) but many are allergic or idiopathic in origin (Type B) and unpredictable. Some are the result of true cytotoxic effects of the drug or active metabolite. Some do not fit easily into the two main categories above but may result in cancer, congenital malformations, genetic effects causing birth defects, or even second generation effects. Other reactions may be to the pharmaceutical form of the product such as oesophageal damage caused by a hard tablet, or an allergic reaction to a colouring agent or other excipient.

The information we usually have about a drug is detailed pharmacology and toxicology, plus information from studies on relatively small groups of selected patients in controlled studies. From these studies, and from non-interventional observational studies, we know that drugs are not effective in all patients and cause harm in some. In practical therapeutics the emphasis must be on the individual patient and his or her disease. With a knowledge of the pharmacological characteristics of a particular drug (i.e. its actions, physicochemical and pharmacokinetic properties), and understanding the possibility of special susceptibility of an individual patient under specific circumstances (by taking a very good clinical case history), many drug reactions may be avoided or at least reduced. A very important judgement a health professional has to make on prescribing a drug is to decide whether his/her individual patient fits the general pattern of patients previously studied and how and why their patient might be different. More than that, it is the responsibility of the prescriber to follow-up the patient to ensure that the desired, and agreed, outcome for the patient is achieved.

Most drugs are remarkably non-toxic but at times serious and even life-threatening reactions can occur. A few drugs have a small margin between the effective and toxic dose. The indication for the use of such 'low therapeutic ratio' drugs must be very sound. In spite of every care taken in therapy adverse reactions will occur that may be difficult to diagnose. This often occurs because of unfamiliarity with the drug in question. With multiple therapy the decision as to which, if any, drug is to blame is compounded by the possibility of drug interaction producing or aggravating the clinical condition.

Some adverse reactions are predictable from knowledge of the basic pharmacology of the drug concerned. Examples are:

- Overdose relative to a particular patient. Adverse reactions may be explained by the way drugs are metabolised in phenotypically different sub-sets the population. There are, for example, differences in the way that some drugs are metabolised by the liver microsomal enzymes (dealt with elsewhere), which alter the kinetics of the drug and its metabolites. Special care must be taken with such drugs and interactions with other drugs.
- Reduction in the ability to eliminate the drug. Liver and kidney disease especially important. Patients with such diseases cannot be safely treated without a complete understanding of the metabolism and kinetics of the drug.
- Drug/food/chemical interactions which enhance action of drug/reduce clearance. Polypharmacy increases the chance of interactions. About 4–5% of prescription drugs used in hospital have the potential for interaction. About 7% of ADRs may be due to interaction, and up to 1% of hospital admissions are due to interaction. The more drugs, the more interactions are likely. With up to 5 drugs, the chance is about 4%. With 16–20 drugs the chance is up to 54%.
- A known side effect of the action of the drug being prominent or problematic because of other disease. As examples, AIDS patients have a propensity to have allergic adverse reactions. Cardiac patients may not tolerate drugs which alter the blood pressure so well since their cardiac reserve is impaired.
- Enhancement of the desired effect or side effect by new clinical or environmental conditions. An excessively hot environment may cause hypotension in someone taking anti-hypertensive drugs.

Some chemical exposures may be hepatic enzyme inducers/inhibitors, altering the effects of drugs like warfarin. Some foods such as mono-amines, will cause reactions in patients given MAOIs: grapefruit juice may interact with terfenadine and some other drugs. New diseases may cause problems: heart failure causing reduced liver blood flow can reduce the metabolism of drugs like warfarin.

- Special at risk groups. An example is warfarin given during pregnancy. In the first trimester of pregnancy the fetus is at risk from developmental malformations. After that, particularly at the end of pregnancy, the fetus is very susceptible to cerebral/cerebellar bleeding. Throughout pregnancy there is a risk of bleeding in the placenta.

The above examples show the great variety of ways in which adverse reactions can be caused. There is one clear message: you must understand the drugs you use, know their pharmacology and think how they will act in your particular patient with his/her set of diseases, social circumstances, occupation and any other 'peculiarities'.

IV. BENEFIT AND RISK IN THERAPY

It follows from the above that the treatment of every patient is an experiment, in the sense that general knowledge about the drug may not be sufficient to cover a particular patient's situation. Whenever a drug is given therefore, the prescriber should have a clear idea of what is to be achieved, the likelihood of success, the chance of doing harm and try to balance these factors. What alternative management is available must also be considered. It is worth stressing that this information should be also used in deciding how and for how long the patient should be followed up.

The benefits and risks of drugs are determined, in a general sense, from available literature, including the enclosure with the drug produced by the manufacturer. It is useful to try to answer the following questions:

For benefit:

- What is the seriousness of the disease and how much will the drug do in reducing the seriousness?
- How long will the disease last, and how much reduction can I expect from the drug?
- In the case of prophylaxis, how prevalent is the disease and what reduction can I expect?

For risk:

- How serious are the adverse reaction(s)?
- How long will it/they last?
- How frequent is/are it/they?

It will be seen that the factors of seriousness, duration and frequency are common to both sides of the benefit–risk balance. This is a help in making a decision about a drug, but there is a problem with adverse reactions, since many are possible with differing seriousness etc. They must be summarised, perhaps best by considering the most serious and most common, and then comparing with the benefit of the drug (see Edwards et al., 1996).

You should do this analysis for all available treatments for the condition you wish to treat (not only drugs) and compare their advantages and disadvantages. Finally, you should apply this knowledge to the patient. In considering the patient not only clinical issues, as above, affect the final decision but also the patients background of knowledge, personality, risk experience and perception, as well as some logistic factors such as the ability and willingness of the patient to be followed up and be monitored.

In many places therapeutic guidelines are available which limit the choices and make some of the above options clearer because they are formulated by clinicians with long experience using sound evidence. On the other hand guidelines are not infallible, and must be used critically.

V. THE DIAGNOSIS AND MANAGEMENT OF ADVERSE DRUG REACTIONS

V.a. Approach to Diagnosis

As with any clinical diagnosis, a good history and examination are essential. In the history great care must be taken to find out about ALL drugs and their details. Patients often overlook drugs that are not prescribed for an illness. This includes over-the-counter drugs, herbal and other traditional remedies, vaccines and oral contraceptives, vitamins and other 'food supplements'. It is even less likely that a patient will admit to taking an illegal drug (narcotic or sports doping drug, for example). The better a physician is able to create a rapport with the patient the more likely it is that the information will be forthcoming. It is very useful to ask about drug use in relationship to other events in the clinical history rather than to take a separate 'drug history'. Use empathy: make sure that you imaginatively try to put yourself in the patients position and think what (s)he might do.

V.b. The Diagnosis of Adverse Drug Reactions

Think of the following:

- Is the patient taking drugs?
  - OTC (Over-the-counter or directly purchased without prescription) drugs
  - Oral contraceptives
  - Herbal/traditional medicines
  - Abused drugs
  - Long term prescription drugs
- Check with medical history.

Once you know about all drugs you will need to know the doses and instructions for use. It is always best to check the written instructions on the container or instruction sheet to ensure no confusion can exist. Be careful when there are multiple dosage forms of a drug that you do not assume that '2 tablets' is equivalent to a certain milligram dose. In fact, make no assumptions unless necessary – always check! This allows you to know whether the right drug has been prescribed in the correct dose and you can check the patient's adherence to the prescription instructions. A check on the amount prescribed, the date of the prescription and the number of tablets etc. left in the container also provide a check on adherence and the timing and duration of therapy. Further considerations are:

- Time relationships?
- Drug has been given before adverse event?
- Timing of drug and reaction?
  - Consider the whether the patient has achieved steady state blood levels of the drug
- Could it be a withdrawal reaction?
- Could this be an allergy
  - Previous exposure? Type?
- Is the patient pregnant
  - At what stage
- If neoplasia is the suspected adverse reaction, is the time relationship plausible.

The timing of start and discontinuation of treatments in relation to symptoms and signs is a crucial aid to diagnosis. Leukaemia starting within a few days of the commencement of a drug is implausible. A rash commencing almost immediately suggests an immediate hypersensitivity/urticaria (check previous exposure to the drug), but a rash at about 10 days is more likely to be part of a serum sickness reaction and other symptoms and signs should be sought. Time relationships are clearly of help where interactions are involved.

Some examples will help:

1. A female patient with 3 young children complains of being tired. She is pale and has iron deficiency anaemia. You will ask her about the closeness of pregnancies and whether she has a good diet. You will want to know about menstruation. But if she tells you that she is constantly anxious and has tension headaches, do not lose the opportunity to ask about possible aspirin intake! Do not leave the questioning there. Patients often say that they are not taking aspirin because they do not know that their particular proprietary drug for headache may contain aspirin. Get them (or relatives) to name the tablets and possibly to bring the tablets or the bottle.
2. A patient is admitted with what looks like extensive first degree burns over nearly the whole body. These have occurred since the patient had been on holiday. You diagnose sunburn and get into a debate with the patient who claims to have been very careful and has never had such a problem before. What you have missed is that the patient had an ear infection on the flight, which caused pain, went to a local doctor and was given tetracycline- a well known cause of photosensitivity.
3. You are on a plane and are asked to see a 65 year old man in response to a request from the cabin crew. The man is sitting, unconscious, pale and sweating with a thready irregular pulse. A very anxious wife says that he had a myocardial infarct 4 weeks previously, and this his first time out and about since then. You ask the wife for more details, and then ask to lay the patient flat in the aisle. Another doctor who has heard the first part of the story claims that you will kill the patient who clearly must have left ventricular failure.

   You do what you think and the patient is awake and recovering in a few minutes. You are able to make such a decision because:

   - The patient had been started on anti-hypertensive therapy in hospital and has not been checked since
   - The patient had a good deal of alcohol with the meal on the flight which is just completed
   - The cabin is very hot.

All of the above make postural hypotension a possibility. Moreover, you can examine the patient better when he is flat, and left ventricular failure is not usually rapidly fatal because the patient is flat for a while, even though they may feel better sitting upright.

The examination of the patient is an equally important aspect of making a diagnosis. The physical presentation of adverse reactions certainly mimic

other diseases, but sometimes a drug may represent the most common cause for a physical condition. Agranulocytosis with fever, gastro-intestinal (incl. mouth) ulceration and infection is such a condition. On the other hand the common morbilliform rash can be the pointer to a number of diagnoses, including measles!

Be a good detective and be particularly alert to the possibility of drug causation when the clinical signs are not quite typical. Again some examples may help:

1. A 75 year old man was examined on a routine visit 1 month after discharge from hospital for a myocardial infarction. No communication had been received from the hospital on the patients stay and management. The patient seemed well but had a few purpuric 1 cm round lesions on his hands. The doctor assessed these as senile purpura. He then noticed that there were several more on both legs. He felt that these were both more extensive than with senile purpura and in an unusual site. He questioned the patient about injury, which the patient denied. On ringing the hospital it was learned that the patient had had a deep venous thrombosis and was treated with warfarin. They apologised for not informing the doctor earlier!
2. A 75 year old man was examined on a routine visit 1 month after being disabled by a stroke. He was very immobile and in bed. He complained of a painful heel, which on examination was inflamed and with a small necrotic centre. A pressure sore was diagnosed and suitable measures taken to manage this. A week later there were further lesions on the other foot but this time on the dorsum of the foot and lower leg. These were not easily explained by pressure necrosis, indeed a closer examination suggested a vasculitis. The cause for this was frusemide which had been prescribed for a mild heart failure apparent at the time of the stroke. It is very easy to accept the "obvious" without careful examination.
3. A 28 year old mother of two children developed jaundice. There were no obvious causes for hepatitis. Investigations did indicate a hepatitis, however, but no viral cause. Further case history found that she was taking an oral contraceptive, which can be a rare cause of jaundice. By then she had had a liver biopsy, which did not show a typical histology. Finally, after much thought and further questioning it was found that she had taken a short course of flucloxaillin 3 weeks prior to the hepatitis. This antibiotic is a rare cause of delayed hepatitis with an unusual histology. This case even more demonstrates the need for care in reaching a diagnosis where drugs are possibly involved.

There are, however, some particular conditions which point to a drug or chemical causation. Hepatitis is one such condition, and it can easily be seen that the liver can be a target because of its part in the metabolism, conjugation and excretion of chemicals. The kidney seems to be at much less risk as an excretory organ alone, nevertheless renal damage by drugs is more common than heart or lungs, for example.

The bone marrow is a rapid turn over tissue and can be damaged by drugs causing total aplasia, and single cell line damage such as agranulocytosis and thrombocytopaenia. This latter can also be caused by the rapid removal of platelets from the circulation in an immune reaction.

Another rapid turn over tissue is the intestine and gastro-intestinal reactions are also quite common, mainly diarrhoea and vomiting, but also life threatening peptic ulceration.

The skin is frequently involved in allergic reactions from drugs including the rare but life threatening Stevens–Johnson syndrome.

A list of some common adverse reactions is given in Table 3 and some commonly causally related to drugs are in Table 2.

Table 3. Some common and serious adverse reactions and their treatments

Adverse reaction	Treatment	Possible problems
Anaphylaxis	Adrenaline	Effect reduced by beta blockade Cardiac arrhythmia
Bleeding from warfarin	Protamine	Hypercoagulability and warfarin ineffectiveness
Convulsions	Possibly phenytoin (better use bezodiazepines first!)	Hepatic enzyme inducer

VI. THE APPROACH TO MANAGEMENT

It can be seen that although one may suspect an adverse drug reaction as a diagnosis, it is not easy to determine a causal relationship, unless there is a special investigation result which is specific. How therefore do you manage a patient with a suspected drug reaction?

- Decide the likelihood of patients condition being drug related
- Consider the of the clinical event frequency related to drug versus the background frequency of the event
- With careful clinical benefit risk judgement, decide to stop relevant drug(s)
  - Consider:
    - Known pharmacology
    - Of single drug
    - Of drug class
  - Known idiosyncracy
    - Of the single drug
    - Of the drug class to which it belongs.

The first principle is exclusion. Look for other causes than drugs and do investigations which will prove their presence or absence. If your suspicion for a drug causality is strong, or if the condition is serious, this may include stopping any suspect drug, which will allow you to see whether the condition improves or goes away entirely, in a way in keeping with what you expect from that condition. This process is called de-challenge. De-challenge must be considered carefully. First, what are the risks of removing the drug? If the drug is essential for the patients well being you may still be able to stop it temporarily, but you will need to consider whether you will be able to assess the improvement of the patient's condition before you must re-commence the drug if that is likely to be necessary. You also need to consider what alternative therapies and what risk/benefit profile they may have, including the possibility of cross sensitivity or other shared reactions of a therapeutic group. Substitution may be the best way forward but be very careful not to confuse the diagnosis by cross activity. Try some options:

- Stop non-essential drugs
  - Consider dose – reduce where suitable
- Consider interactions
- Stop those drugs likely to be causing serious reactions and whose benefit/risk balance in this situation is not good.

The patient's progress after drug has been stopped is clearly important for the diagnosis to be confirmed. You must have a clear idea how the patient should be monitored, for example, by clinical findings or specific investigations. You should have an idea of the suspected time course for improvement. This time relationship, together with the time of exposure to the drug and onset of symptoms are crucial pieces of evidence. None of the above is easy to assess, since adverse reactions are rare and the information on these issues is often to be found scattered in a few case reports on a particular drug and adverse reaction.

It is often possible to reduce the dose of the drug rather than stopping it completely. This is particularly appropriate for pharmacologically induced reactions. In doing this it is particularly important to explain the situation to the patient and to gain their confidence to continue with the drug.

A further complication occurs when several drugs are taken at the same time. Knowing the relative incidence of the reaction related to the drugs is helpful, but again there is very little help from the drug literature on the incidence of adverse reactions to different drugs. A practical approach is to withdraw the least necessary drug first, followed by the others in priority. Some kind of comparison of probability, severity, and benefit of the drug to the patient must be considered, since with the most severe reactions one must stop all likely drugs: with mild reactions it is possible to simply assess the drugs one by one.

There are some diagnostic tests that can be used for adverse reactions. Many of them are simply looking for particular patterns amongst standard tests, for instance of liver function or specific histology. For some drugs there is the possibility of specific drug monitoring to assess whether the drug level in blood, plasma, or other body fluid is at a therapeutic, and not toxic, level. Such monitoring is available for a variety of drugs with a small difference between therapeutic and toxic levels – a "low therapeutic index" – and is particularly relevant to pharmacologically related adverse reactions.

For idiosyncratic, patient related adverse reactions, less confirmatory tests are available but the number is growing. Skin, blood and urine tests are available to confirm acute and chronic allergic reactions. Genetic tests can determine the susceptibility of individuals and includes general tests such as for the porphyrias and sickle cell anaemia, and specific tests for drug metabolism, such as acetylator status

and liver oxidative enzyme status. These tests are very useful in preventing problems with subsequent drug treatment.

The potential for genomic information to be useful in the diagnosis and, more important, prevention of idiosyncratic adverse reactions to drugs is great, but in its early phases. A particular challenge is to understand the factors that affect gene expression before genomic date is of great practical value. Another challenge is the cost–effectiveness of genetic screening for relatively rare phenotypes. There are, however, some examples of the use of genomic data in predicting the safe use of drugs such as the anti/retroviral drug abacavir. Abacavir hypersensitivity reaction is a potentially life-threatening adverse reaction that affects approximately 8% of patients. It has been shown that there is a strong predictive association between this hypersensitivity reaction and HLA-B*5701, indicating that exclusion of HLA-B*5701 positive individuals from abacavir treatment would largely prevent this reaction.

In spite of the use of the above methods to diagnose adverse reactions, uncertainty over causality can remain. A final test which is very helpful is re-challenge with the drug(s). Ethically re-challenge may often not be justified, certainly the severity of the reaction and the need to be certain about the reaction are major considerations.

Finally:

- Reconsider interactions
- Consider re-challenge for drugs which are or will be important to the patient
  - Consider very carefully whether it is ethical to perform a rechallenge
  - Use the same dose (usually, but possible skin testing for allergies)
  - Use the same route
  - Use the same preparation
  - Make sure that you have available all necessary safeguards to prevent a serious outcome.

Many ‘re-challenges’ occur accidentally and do not fulfil the full criteria mentioned above. Re-challenge should only be undertaken when the patient has recovered completely from the first reaction. Re-challenge means that precisely the same drug, in the same formulation, at the same dose is given to the patient again, for as long as is reasonable to re-produce the adverse effect. The aim is to see if the same effect is produced under controlled conditions. It is important to differentiate this from re-exposure. Re-exposure is an accidental event in which any of the above re-challenge requirements is in doubt. For example, a patient who has a rash following amoxycillin and gives a history of a rash following penicillin 30 years before is not to be described as having a positive re-challenge, even though the reaction is likely to be cross sensitivity. Also, the use of a (sometimes rather dangerous) penicillin, or other, skin test to test allergy should not be considered a re-challenge in pharmacovigilance terms. This is because the dose and route do not mimic the way in which the drug was used initially. Note that this does not mean that such tests do not have a place in diagnosis, but their place is limited and not pharmacological re-challenge.

Always one should send in a report with full details of the situation to the national centre for pharmacovigilance.

VII. TREATMENT

It is clear from the above that the treatment of adverse reactions is linked with the diagnostic workup, since the major treatment step is to stop the drug or reduce the dose. This obvious solution is not always sufficient, and patients may need or request additional treatment.

When treating an ADR, important considerations are.

- Do not confuse the picture unnecessarily by using more drugs unless absolutely necessary!
- Have a clear objective
  - Do not treat for longer than is necessary
- Review the patient.

The treatment situations are threefold:

Firstly, the patient may want treatment during a protracted diagnostic phase. This is difficult since the new treatment might well interfere with the diagnostic process, but short term symptomatic treatment, for instance for pruritis is acceptable. The use of other drugs for the treatment of life threatening reactions is naturally essential, but the choice of drugs must take into account potential interactions. In either case the new treatment drugs should be discontinued as soon as possible. Some common and serious adverse reactions and their treatments are given in Table 3.

Secondly, sometimes an adverse reaction will produce long term and even permanent conditions that need treatment. Review of the patient is essential to avoid the treatment drugs being continued unnecessarily.

Thirdly, and even more unusually, it might be necessary to use a second drug to prevent an adverse effect of a primary treatment drug. It should be emphasised that such an approach should be considered very carefully, and an alternative using a single drug may be preferable.

Some examples of treatment of adverse reactions:

- A patient with an amoxycillin skin rash and pruritis, can be treated reasonably and safely with calamine and phenol solution topically. The use of topical steroids is also reasonable treatment.
- Some adverse reactions lead to organ fibrosis for instance in the lungs, peritoneum or of mucous membranes in Stevens–Johnson syndrome. Then other treatments of these conditions may be needed which can include even surgery, for example, to free ureteric obstruction or to correct vaginal stenosis.
- The anti-cancer drug cyclophosphamide causes cystitis. This drug may be essential in the patients treatment so a second drug is always given to relieve or avoid this common reaction.

In general great care must be taken in treating adverse reactions. The patients must be followed up to ensure that the desired outcomes are achieved. New symptoms should usually be managed by stopping all treatment where it is possible (it usually is!) and then taking a new approach: do not fall into the trap of adding third or even fourth drugs to treat new adverse reactions.

VIII. REPORTING ADVERSE DRUG REACTIONS

A good deal of effort and money is spent on drug safety both pre- and post-marketing. It is quite clear that even serious, but still quite common, reactions may not be detected before a drug is used after it is marketed. The rationale put forward for this includes the following:

- Animal toxicology is often not a good predictor of human effects
- Pre marketing human exposure is such that only frequencies of events in the 'per thousand' range are likely to be detected
- Even detected events will be incompletely described and understood since they are too few
- Specially susceptible patients are unlikely to be included in studies and the effects of inter-current disease or medication are little assessed.

The main information on safety of drugs in regular use is obtained from doctors reports of clinical concerns (ICSR) and published case reports from health professionals, post-marketing clinical studies, controlled retrospective or prospective studies, and case series. The studies may or may not have safety issues as their major focus.

It is clear that pharmacovigilance (the study of clinical drug safety and benefit-to-risk analysis) should have four major goals:

- To recognise as early as possible new adverse drug reactions
- To refine and add to information on suspected or known reactions
- To review the merits of the drugs against other therapies
- To communicate the information in a way that improves therapeutics.

Systematic spontaneous reporting of possible drug caused adverse effects began with the "Yellow card system" in the UK in 1964. It was a medium for doctors to report their concerns on marketed drugs, thereby enhancing the limited pre-marketing clinical data on safety. Now 83 countries around the world have similar systems, and many warnings of adverse drug reactions and some deletions from the market have been made on the basis of such reports.

ICSR used to be called 'spontaneous reports' because they arise during a clinician's normal diagnostic appraisal of a patient, the clinician drawing the conclusion that a drug may be implicated in the causality of the clinical event. As with all diagnoses the certainty of attribution will vary with the skill and experience of the doctor, what confirmatory tests may show, the natural history of the clinical event, and the existence of other plausible explanations, but it is clear that anecdotal case reports provide important evidence on the safety of drugs. For an individual clinician there should be great professional interest and challenge in seeing a new or rare reaction, investigating and recording it to the best of his/her ability and reporting and publishing it.

In addition to new reactions to new drugs there is a function of reporting which is even more important to public health. Many adverse drug reactions are avoidable. They may be due to:

- A wrong diagnosis (and therefore wrong treatment!)
- Wrong prescription (either an error in decision making or in writing) which might include dose or dosage frequency as well as which drug is chosen

- Wrong dispensing (misinterpretation of writing, or a practical error, or mis-labelling)
- Failures of patient adherence (due to misunderstanding of or failure to read instructions, misperceptions about drugs, bad taste or even appearance of drug formulation, competing advice e.g., from friends, suicide attempts) as well as some bizarre problems such as suicide pacts and homicide attempts.

Most of these medical errors are regarded as non-systematic problems, in other words, although the individual situation might have been avoided by some other more appropriate action, there is no general advice that can be given. It then follows that there is no need to report an incident. This is not always true: consider the possibility of mistakes in dispensing due to bad hand writing. Firstly, there is some general advice that may be given – write clearly and in upper case, but more than that there are some trade names (and even some generic names) which are easily confused. Reports of where this has happened may be important. Another example is the use of small clear glass ampoules in anaesthetic practice. It was common to find that they were the same size, colour, small writing on the container showing the contents, and the writing was the same colour. Although one can argue that a competent anaesthetist should be aware of this, not every anaesthetist is experienced, has perfect eyesight, or cannot be caught out in an emergency. (The author actually had a report referring to this problem and both notified manufacturers and wrote a letter to all doctors drawing attention to the hazard.) The subject of medical errors in general has been addressed by WHO in setting up the Global Alliance on Patient Safety (see Edwards, 2005).

Under-reporting, reports of known reactions, and false causality attribution are the common criticisms of spontaneous reporting systems. Several studies show that workload, doubt about causal relationship, and doubt about whether it is worth reporting, are the common reasons for under-reporting. It follows that the attribution of causality is at least as good as any other careful clinical diagnosis, often after the exclusion of other disease (because doctors are less likely to report where there is doubt over causality); if under-reporting is due to workload, then there must be a real motivation to send a report.

In a response to an open ended question on why doctors report, the following were given as the main reasons, in order of frequency:

- Motivation to contribute to medical knowledge
- The reaction is previously unknown to reporter
- The reaction was related to a new drug
- The reporter was in the habit of reporting all significant reactions
- There was a known association between drug and reaction
- The reaction was severe.

So, ICSR are reports of genuine, general clinical concerns about a drug and suspected reaction. All must be treated as 'valid', in fact they should be labelled 'clinical concerns' rather than 'spontaneous reports' (a term that has long use) because the label is descriptively more explicit. Other reasons for reporting such as medico-legal considerations and current awareness of a particular drug problem were identified, but were of much less frequent concern to the international reporters surveyed.

Reporting systems around the world are in various states of development, mostly following what the Chinese have called a 'point-line-net' approach, starting with a centre of excellence and moving linearly towards an active network. In many countries there is concomitant development of a legal system to govern the reporting and public health management of drug safety matters. Each country is different in this respect, but an aim should be that health facilities, manufacturers and the public all have risk awareness to a certain extent and risk signals should be identified and managed in a sensitive way on the basis of ensured quality and quantity of information and scientific evaluation. Feedback from the ADR monitoring system primarily to health professionals and to the public is essential. There should be continuous monitoring and audit of the performance of drug safety systems both for the quality and quantity of information processed and for the impact the work has on public health.

There are 83 countries which have systems by which doctors can report adverse drug reactions to an established national authority. These national authorities have the responsibility to evaluate the new data and to recommend further action to their respective governments. Most often the action will be to provide further information about how the drug can be used safely. This is most often incorporated in the drug label, package insert, or summary of product characteristics (SPC) which is usually an agreed document between the regulatory authority in a country and the pharmaceutical company concerned. Sometimes more urgent warnings can be

given by 'Dear Doctor' letters sent to individual health professionals, and a drug may be removed from the market if the relative benefit to risk balance is considered unacceptable. These 83 countries also belong to the World Health Organisation Programme for International Drug Monitoring. In this Programme they exchange regulatory information and any ADR case records they receive are copied to a huge international database in Uppsala, Sweden which analyses the pooled data for new ADR signals that may not be apparent from a single national centre.

In addition to the work of national centres, most pharmaceutical companies monitor the safety of their own products. Consumer groups also monitor safety of drugs and the medical and general media are also alert for drug related stories. It is not surprising therefore that there is often controversy between groups, not only on the interpretation of information, but on the data itself. The aim of the WHO Programme was to have a single international data set, which is clearly in the global public health interest.

A point to note is that different medical systems such as traditional Chinese medicine, Ayurvedic medicine, and traditional African medicine and homeopathic medicine have different standards by which they judge adverse reactions, as compared with Western allopathic medicine. This may lead to controversy and confusion amongst patients and health professionals alike: communications must take this into account.

A mounting challenge in drug safety is the growing use of biopharmaceuticals. Biopharmaceuticals are medical drugs produced using biotechnology. They are proteins (including antibodies), nucleic acids (DNA, RNA or antisense oligonucleotides) used for therapeutic or *in vivo* diagnostic purposes, and are produced by means other than direct extraction from a native (non-engineered) biological source. Since these substances have a profound effect on body function (even having permanent effects in the case of some vaccines) and may vary in quality according to methods of production (see Pichler, 2006). The unique and complex nature of biotechnology-derived pharmaceuticals has meant that it is often not possible to follow the conventional safety testing programs used for chemicals, and hence they are evaluated on a case-by-case basis. Risk management strategies must take this into account, and the careful analysis of clusters of reactions related to specific batches of product undertaken. Pichler also suggests a very useful approach for classifying adverse reactions to biologicals. It is based on the major immunological activity of biological agents and differentiates five distinct types:

- Clinical reactions due to high cytokine levels (type α),
- Hypersensitivity due to an immune reaction against the biological agent (β),
- Immune or cytokine imbalance syndromes (γ),
- Symptoms due to cross-reactivity (δ),
- Symptoms not directly affecting the immune system (ϵ).

Such an approach and classification might help to relate the clinical features of these side effects to individual and general risk factors, and to direct research in this new area.

IX. PHARMACOEPIDEMIOLOGY

Reported suspicions of drug related clinical concerns are mainly hypothesis generating. They cannot be used to give any realistic size of a problem without knowing the population exposed. Various methods can be used to work out an incidence/prevalence of drug related adverse effects, but each has its own strengths and weaknesses. The methods are given briefly below.

In prospective cohort studies a population taking the investigated drug is assembled over time. At the same time matching controls (matching often by age and gender, sometimes by disease, occupation etc.) not taking the drug are followed for a given time period looking for pre-determined ADR end-points. Usually the control group is 2–3 times larger than the treatment group to improve the power of the study. The risk ratio is the proportion of the drug taking group (D) having an ADR (D_{adr}/D), divided by the proportion of the non-drug taking group with the same clinical end-point (C_{adr}/C) or $(D_{\text{adr}} \times C)/(C_{\text{adr}} \times D)$.

Cohort event monitoring, or Prescription event monitoring – PEM – in the UK and IMMP Intensive Medicines Monitoring Programme – IMMP – in New Zealand (see Shakir et al., 2002), is a way of recording all patients exposed to selected drugs. The patients or their doctors can then be approached by questionnaire to record any or selected events. This approach is particularly useful for new drugs and has the advantage of being able to assemble large cohorts over time. It also allows the follow up

Table 4. Epidemiological studies have different strengths and weaknesses

Type of study	Strengths	Weaknesses
Prospective, cohort	Control over variables involved Can look at multiple outcomes Gives incidence Gives the strength of the relationship	Costly Time consuming May be limited in size and power
Retrospective case-control	Can study multiple exposures Gives the strength of the relationship Least costly Useful for rare events	Control of only one variable Recall and other biases and confounding Less certain causality

of exposed patients over a long period. The disadvantage is that controls are usually taken from cohorts made to investigate other drugs that have been monitored previously, though this can be very useful in looking at the comparative merits of drugs for the same indication. Also the information obtained on cases comes from doctors records and no other validation is easy without extensive correspondence. A strength, however, is that the method may detect unexpected benefits of therapy.

Post-marketing studies of cohorts of patients, often assembled by practitioners with the support of the relevant pharmaceutical company, may also be useful in detecting ADRs related to new drugs but they have been criticised for their small size and that they are interventional. These criticisms are supported by the history of some of these studies, but they cannot be seen as intrinsic reasons why the approach is not valid if the studies are carried out properly and to completion.

Special studies on drugs or diseases may yield signals that were unexpected. On the other hand such studies may not be any larger than the premarketing studies and thus have little power to find less common ADR signals. Moreover, they are usually narrowly focussed, involve only a few drugs and are limited in time.

Health care related data bases may be very large and contain both information on prescribed drugs, indications, concomitant diseases and outcomes of therapy. Since the data is collected systematically either data linkage or data base linkages could provide new ADR signals. For this to be used for routine signal detection, there is a need to use 'data mining' algorithms which allow useful associations between drugs and clinical (or other) events to be found. This approach is currently the focus of much attention, since it is a very good way to determine what happens when a drug is used in regular clinical practice, looking for both benefits and harms. Another advantage of data mining is its flexibility. The disadvantages are the fitness for purpose and the quality of the data which is collected during patients management, and not for pharmacovigilance.

The case-control methodology is very useful in the further analysis of signals and the studies may take part within a continuous system of cohort development such as those in large multi-purpose health databases-so-called 'nested studies'. In a case-control study, cases of the investigated outcome (C_a) are found, then a large matched group of controls (C_o) identified. The proportion of the C_a cases using the drug (D_a) within a defined period (D_a/C_a) is then related to the proportion of the controls taking the drug in the same way D_o/C_o. The risk ratio is then $(D_a \times C_o)/(D_o \times C_a)$.

Epidemiological studies have different strengths and weaknesses associated with their design (Table 4) shows some of the strengths and weaknesses of the two main methods of prospective cohort studies and retrospective case-control studies.

Occasionally animal studies and mechanistic pharmacological studies in humans suggest the possiblity of new ADRs, but these are unusual as primary signal detection tools in post marketing drug safety. A final possibility for signal detection is to monitor diseases often caused by drugs or that are important public health problems. This idea (Wiholm,[1] personal communication) has the advantage of continuously monitoring the most important known drug morbidity. Wiholm's proposal is to run

[1] Bengt-Erik Wiholm passed away on July 30, 2005. Wiholm was one of the true leaders of pharmacoepidemiology and pharmacovigilance.

a continuous case control network for the relevant diseases and using continuously enrolled community controls. Whilst this may appear expensive, the approach aims at the bulk of drug related morbidity and certainly monitors in case control studies are often not used continuously and could enrol the community controls.

The way in which studies should be used to investigate signals of adverse reactions from reports of clinical concerns, can be in steps according to the severity of the adverse reaction. This process can start even during the pre-marketing stage where it may be that hints from animal toxicological studies, abnormal laboratory results in human volunteers, perhaps single cases of possible harm seen clinically in humans, or that the drug is in a class with a potential for particular risk suggests that studies should be done in the post-marketing phase. This 'risk management' strategy is becoming the norm for newly marketed drugs, and is also of value when it may be that special risk groups of patients (e.g. children or patients in special disease categories) may be exposed to a drug where there is no pre-marketing experience. Very useful information on risk management can be found on the Web (see Eudravigilance, 2007).

Adverse reactions, particularly of a serious or potentially serious nature, which have not been seen in premarketing studies should be assessed for reporting rates, by using drug sales and other drug exposure data. It should be then possible to work out a strategy for further investigation. Those with reporting rates apparently less than $1/10{,}000$ patients require evaluation for risk factors and expression of the ADR. This situation is usually not urgent and a request for special reporting by practitioners is probably the best tool for this, though careful case control studies may be required if the reaction is potentially serious and if causality is in doubt, for instance, where there is a substantial prevalence of the clinical event due to other causes. Cohort studies are probably not cost effective because of the time it would take to recruit a large enough cohort to study such rare events.

When the reporting rate indicates a frequency of occurrence apparently lying in the range $1/1000$ to $1/10{,}000$, an accurate overall idea of incidence and attributable risk is desirable in addition to qualitatively defining risk factors. It is not easy to generalize about the type of study which would be most informative, but the use of computerized data bases with a 'nested' case control method has the advantage of speed and relative economy. These should only be considered for questions where the data base information is likely to be reliable and complete; the multipurpose data bases are an attractive option. Cohort studies are useful if the event suspected of being a reaction has a high background prevalence in the population.

The comments on reactions where exposure data suggests an apparent incidence between $1/1000$ and $1/10{,}000$, apply even more to new reactions found post-marketing with an incidence greater than $1/1000$. Rigorous, rapid investigation is essential.

One of the problems of drug safety epidemiology, therefore, is that a large number of exposed patients is necessary as a study base, and suitable controls, particularly when the possible ADR has a high background in the community. It is relatively easy to find enough exposed individuals to widely used drugs such as NSAIDS and antihypertensives, but much more difficult in the treatments for ulcerative colitis, for example. From a public health point of view, to know most about the drugs most commonly used in the community is the priority; but from an individual patient's viewpoint they are concerned about their own proposed drug therapy: for them to have reliable, useful information on adverse reactions is as important as for anyone else!

The availability of disease data bases, common drug induced disease monitoring and prescription event monitoring allows for quantitative assessments as well as for signal detection. There are not so many such facilities throughout the world; they should be nurtured. Similar comments could be made for the detailed hospital monitoring of patients for ADR signals. They have been very valuable, even though the patient numbers are relatively small and are a biased selection of the population.

Signal follow up should not be confined to epidemiological studies alone. Much could be learned by thorough checking of existing background pharmacological and toxicological information e.g., from animal experiments, which should be reviewed to see if further laboratory or clinical investigation may help in elucidation of risk or mechanism of the putative reaction. Combined pharmacogenetic and epidemiological studies are a good example of interdisciplinary investigation.

The methods for finding signals are imperfect; those signals that are detected are by no means all investigated; and signals which are subject to studies often result in controversy and more expensive

investigation. Nevertheless, pharmacoepidemiology has lead to a much better understanding of adverse reactions and quantification has put many issues in a perspective that has allowed for more rational decisions to be made about drugs. Drugs like clozapine and metamizole have been re-evaluated when the size of the major risk has been properly appreciated and their merits considered against alternatives.

X. ASSESSMENT OF THE MERITS OF DRUGS

Accepting that there are challenges in finding and investigating drug–ADR relationships, there is a need to put such findings in the context of the benefit (and cost) of the drug concerned. This assessment of the merit of the drug can be in the context of an individual patient or society at large.

A risk–benefit assessment of a drug can be made looking at the risks of the disease being treated, the chance of improvement by the drug, and the risk from the treatment. A risk–benefit assessment can also be comparative between two or more treatments for the same indication and also examine costs to individuals and the community. It is clear that these assessments should have complete contemporary data for all aspects, and that the data should be organised in such a way as to make qualitative and quantitative comparison easy.

Even if the above basic requirements are fulfilled, it is clear that the risk aspects of drugs are likely to contain much incomplete, controversial and anecdotal data compared with the benefit data which mostly comes from controlled clinical trials of efficacy. The latter is usually a prerequisite for drug marketing.

When ADR data on different drugs are compared, and even used in cost and comparative cost estimates, it is easy to see that there is a large potential for error. Common mistakes are comparing old and new drugs (when the experience of drug use and ADRs may be very different) and only considering a part of the ADR profile of the drugs. Cost–benefit–risk estimates are very context dependant and the results only 'transportable' with great care. Although the term 'risk–benefit ratio' is in common use, this is a misleadingly precise concept considering the data and assumptions which are used.

Merit assessments of drugs are used increasingly to decide on which drugs should be available at a local or national level. The basic notion for doing this is laudable but greatly needs the availability of better data. A possible consequence of the consideration of the overall merits of a drug in public health terms alone, is a reduction in the range of drugs available. This seems inevitable if the totality of the benefits and risks of drugs are compared and an attempt is made to reduce the overall drug budget by deleting the more expensive out of otherwise comparable drugs for a specific indication. This may disadvantage minority patient groups and individual patients because possible special benefits, and absence of some risks, to a minority patient group can be hidden. Considering the problems inherent in benefit-risk comparisons and the influences of drug costs, flexiblity to reconsider the overall situation is essential to avoid disadvantaging some patient groups. A useful guideline to thinking about risks and benefits of drugs is a CIOMS publication referenced below.

XI. COMMUNICATION OF INFORMATION

The people who care most about pharmacovigilance results are patients. They want to use the most effective and safe drugs available. Many patients would like to believe that their prescribed or OTC drug is totally safe. Many patients seek and are given drugs for prophylaxis and mild self limiting disorders, when the risk from the disease is small or remote, and the risks of the therapy then loom larger in comparison. Certainly the risk perceptions of patients are enormously variable and certainly influenced by the disease they have.

In China, the development of pharmacovigilance has been done by careful steps following the point-line-net philosophy mentioned above, but the focus is strongly on the needs of the public. As the system has developed and personnel employed, they have been trained with the vision of public health improvement as well as technically: each must see their role as important in the specific Chinese culture and medical situation. China has also used several ways of making sure the public are informed about and actively brought into the network. It is only by such an approach that all those involved in using medicines, naturally including patients, can play a part in their most beneficial and safe use for the good of all.

Pharmacovigilance has resulted in two practical levels of regulatory and pharmaceutical industry activity and communication. One level is simply to

control the availability of drugs, the second is to provide information for their safe use. The information given can be of a mandatory or advisory nature. Pharmacovigilance activity also results in publications which health professionals may read, and also in some output in the public news media.

It is currently assumed that removing a drug with many side effects from the market is in patients' best interests. If it is assumed that doctors and patients cannot make an informed selection amongst alternatives then such an approach is justified: it may also be expedient to withdraw products when they are clearly inferior to several alternative drugs for the same indications. However, the fine differences between individual patients' needs must demand, above all else, that information on the benefits and risks of drugs can be useful in helping them and their doctors to reach the best therapeutic decisions. Recently, much attention has been placed on the development of risk management strategies (see above and see Eudravigilance, 2007). This should lead to the prevention of ADRs, or at least in finding early signals more efficiently, but the value of this development will depend upon the communication and use of the results.

International expert groups have examined some of the important issues to be pursued in achieving this goal, and latest of these is a Manifesto (see Appendix and Hugman et al., 2007), which identifies future challenges.

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APPENDIX: THE ERICE MANIFESTO[2,3] FOR GLOBAL REFORM OF THE SAFETY OF MEDICINES IN PATIENT CARE

Foreword

The science of pharmacovigilance – monitoring and evaluating drug safety issues and communicating them effectively – is a vital activity of worldwide significance in the safeguarding of patient welfare and public health. Its clinical, public health and economic importance has been demonstrated, but it needs to be better understood and appreciated by politicians, the media and the public.

Pharmacovigilance is evolving from being a largely reactive discipline, concentrating on the discovery of harm caused by marketed drugs, to a proactive study of their safety, effectiveness and associated risk factors in normal medical practice and use by patients.

The Erice Manifesto specifies the challenges which must be addressed to ensure the continuing development and usefulness of the science, in particular:

- The active involvement of patients and the public in the core debate about the risks and benefits of medicines, and in decisions about their own treatment and health
- The development of new ways of collecting, analysing and communicating information about the safety and effectiveness of medicines; open discussion about it and the decisions which arise from it
- The pursuit of learning from other disciplines about how pharmacovigilance methods can be improved, alongside wide-ranging professional, official and public collaboration
- The creation of purposeful, coordinated, worldwide support amongst politicians, officials, scientists, clinicians, patients and the general public, based on the demonstrable benefits of pharmacovigilance to public health and patient safety.

Preamble: Reasons for Concern

With much progress already made, the important scientific activity of pharmacovigilance[4] has yet to fulfil its potential to deliver much greater benefits for patients, in terms of the early detection and prevention of unexpected and avoidable harm from medicines, the management of risk, and improvement

[2] This document was drawn up at the international workshop on Future Perspectives in Pharmacovigilance, Ettore Majorana Centre for Scientific Culture, Erice, Sicily, 28 June–2 July 2006. It shares the values of the Erice Declaration on Communicating Drug Safety Information of 1997, and of the Luxembourg Declaration on Patient Safety of 2005, but focuses on new and urgent contemporary issues.

[3] This version of The Erice Manifesto has been produced by the UMC (Uppsala Monitoring Centre) as a service to member countries of the WHO Programme for International Drug Monitoring, and to the international scientific community. The Uppsala Monitoring Centre, Stora Torget 3, SE-753 20 Uppsala, Sweden. Tel.: +46 18 65 60 60; internet: www.who-umc.org

[4] The science and activities relating to the detection, assessment, understanding and prevention of adverse effects ofdrugs, biologics and other medical products, or any other possible product-related problems.

in therapy. A number of factors have inhibited and continue to limit the development of pharmacovigilance:

- despite significant efforts, patient safety and drug safety remain undervalued and under-resourced, resulting in avoidable economic and human cost;
- cautious bureaucratic processes, in the context of a social climate of risk-aversion, sometimes with insufficient concern for assessment of impact on clinical practice and informed patient choice, have displaced the crucial encounter between patient and physician and the decisions made between them as the main focus of attention;
- competing national and regional self-interest has undermined the possibility of productive, open collaboration among all countries for the benefit of humanity as a whole;
- insufficient attention has been paid to the varying needs of countries at different levels of development.

The reform of pharmacovigilance as a whole, and the reassessment of the activities, attitudes and goals associated with it, are urgent and important matters for debate and action by all players.[5] This science should be placed centre-stage and made truly fit-for-purpose in the 21st century.

International recognition that access to quality healthcare is a key human right also requires the safety of medical treatment to be given the same high level of ethical and political importance. *We believe that the following issues represent the highest priorities* on the lengthy agenda of reform.

1. Placing the welfare, safety and concerns of patients at the absolute centre of all thinking, planning and operations, and measuring the value of all activities against those nonnegotiable priorities by:
   - Actively communicating with all players to ensure that drug safety, in the eyes of the people of the world, belongs to the community as a whole and that patients are essential partners to be involved in all aspects.
   - Providing health professionals and patients with accurate, accessible, up-to-date, targeted medicines information and decision-making tools, including emerging safety issues, at the point of need:
     - to facilitate discussion between them, and particularly for comparing the potential benefits and risks of the alternative therapies available;
     - to allow them to learn about the recognition and avoidance of harm, and about effective, early diagnosis and notification of harm when it occurs.
   - Ensuring the availability of openly-assessed choices of therapy, through intelligent risk management processes and information, without over-cautious reduction of options or the erecting of economic barriers limiting access for poorly resourced countries.
   - Encouraging integration of pharmacovigilance and clinical pharmacology in the choices made by public heath programmes, into all clinical practice including primary and hospital care, and in all healthcare training.
   - Developing active and effective education for patients and the general public, including children and young people, in the realities of medical practice, the nature and inevitability of risk, in reasonable expectations of therapy and in the rational and discriminating use of drugs.
2. Transforming medicines regulation from a centralised, sometimes distanced, bureaucratic operation by:
   - All parties being open to audit of decisions in drug safety and their impact on public and individual health.
   - Developing a common vision of ethical and effective regulation and rational legislation.
   - More active collaboration between pharmacovigilance centres (close to practitioners and patients), regulatory authorities, and the pharmaceutical industry and other players.
   - All parties being open to sharing and transferring knowledge and experience, to mutual support and assistance, through open access to research and data and transparency of decision-making.
   - Minimising the demands placed on all stakeholders for burdensome, non-critical, non-essential processes and documentation.
   - Encouragement of the pharmaceutical industry to take a more active, direct, long-term responsibility for the safety of their products and customers, through reallocation of priorities and funds, as part of corporate social responsibility.

[5] Including, but not restricted to, patients and their representatives, consumers, health professionals, researchers, academia, media, pharmaceutical industry, drug regulators, governments and international organisations.

3. Adopting innovative, proactive approaches (including emergent science such as pharmacogenetics and personal informatics) and learning from other social and industrial sectors (such as aviation) where safety is a core aspect of operations, for:
   - The broader conceptualisation and identification of hazard and risk to determine comparative risk and benefit.
   - The earliest possible detection of harm through the vigorous development of spontaneous reporting in every country, the active involvement of professionals and patients in such systems, and the refinement of signal detection methods.
   - The extension of methods for the prediction and prevention of harm (including audit and learning from errors of the past) and the investigation of patients' concerns.
   - The reduction of uncertainty through greater knowledge of the variables in therapy, robust risk management and new methodologies.
   - The development of in-depth pharmacovigilance knowledge (using, for example, emergent population databases):
     - of adverse reactions and side effects of drugs, and drug mechanisms in normal therapeutic use;
     - of the priorities, concerns and behaviour of patients;
     - of the needs, priorities and behaviour of prescribers;
     - of the impact of environmental and all factors related to diagnosis, prescribing and drug use.
   - Broad collaboration in an integrated process to develop truly individualised, personal medicine.
   - The elimination of unsafe practices and inferior or counterfeit products, with strong action against deliberate offenders.
4. Pursuing open, active, altruistic collaboration at all levels and between all parties worldwide by:
   - Recognising that all core patient safety issues transcend national and other boundaries, and that the greatest progress could be achieved under collaborative global oversight and harmonised and co-operative action.
   - Establishing a common baseline for medical data collection and research, and compatibility or bridging mechanisms for all technologies and terminologies for quality assured research in databases and registries.
   - Building on existing knowledge and resources and avoiding duplication and waste.
   - Implementing high ethical and professional standards for all drug safety activities in all countries (including clinical trials and public health programmes) based on transparent, quality assured procedures and guiding safety principles, and including ethical marketing.
   - Maximising the usefulness of all current and emergent methods of drug safety research and intelligence-gathering and exploiting their complementarity.
5. Ensuring that all activities are based on all available, evaluated, transparent evidence and include powerful tools for feedback, impact assessment and review, for shared, global use.

This agenda for reform cannot be addressed by gesture politics, short-term compromise or bureaucratic concession: it demands a transformation of focus, attitudes and goals, and the profound commitment of all players to the single ambition of putting patients' safety, needs, wishes and priorities at the very centre of the global drug safety enterprise; it requires vision, resources, investment, continuous advocacy and local and international champions. We believe such reform has the potential to save lives, prevent injury and illness, and to reduce costs, all on a huge scale, far beyond anything that has yet been achieved or imagined.

Addendum

The Erice Manifesto[6] was developed by a group of 27 experts in pharmacovigilance from 12 developed and emerging countries, meeting strictly in their personal capacities, and expressing their personal views. They bring with them experience in national and international regulation and pharmacovigilance; in the pharmaceutical industry, academic research and medical education; in communications and private sector organisations concerned with drug safety.

The Manifesto was signed by:

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Chapter 15

Drug–Drug Interactions

Karen Baxter, Anne Lee, Ivan H. Stockley

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I. INTRODUCTION

Interactions between drugs were first recognised over 100 years ago. A drug interaction is said to occur when the response of a patient to a drug is changed by the presence of another drug, food, drink, herb or by some environmental chemical agent. The net effect of the combination may be:

- synergism or additive effect of one or more drugs
- antagonism or reduction of the effects of one or more drugs
- alteration of effect of one or more drugs or the production of idiosyncratic effects or toxicity.

Although many recognised interactions are deliberately used with therapeutic benefit, drug interactions are an increasingly important cause of adverse drug reactions (ADRs). Contributing factors include a plethora of new therapeutic agents with complex mechanisms of action and multiple effects, and the increasing prevalence of polypharmacy. Despite rigorous attempts to ensure that the safety profile of these new medicines is as fully defined as possible when they are authorised for marketing, the potential for adverse interactions may not be evident. This was illustrated by the worldwide withdrawal of the calcium channel blocker mibefradil, within months of launch, following reports of serious drug interactions. Recent advances in the drug treatment of HIV infection is another pertinent example; the current treatment approach involves the early use of combination antiviral therapy in an attempt to reduce the plasma viral load markedly. The combinations of drugs used are chosen to have synergistic or additive activity, a good example of beneficial drug–drug interactions. However, some of the drugs used, particularly protease inhibitors, inhibit the cytochrome P450 enzyme system and consequently their potential to cause significant drug interactions is great.

The medical literature contains thousands of reports of adverse drug interactions, of which only a relatively small proportion are clinically important. The importance of drug interactions to the clinician primarily involves knowing or predicting those occasions when a potential interaction is likely to have significant consequences for the patient. When these arise, the clinician should take steps to minimize adverse effects, for example by using an alternative treatment to avoid the combination of risk, by making a dosage adjustment, or by monitoring the patient closely. In order to predict the possible consequences of the co-administration of two or more drugs it is essential that the clinician has a practical knowledge of the pharmacological mechanisms involved in drug interactions, an awareness of the drugs associated with greatest risk, and the most susceptible patient groups. Clinicians must also be alert to the possible involvement of non-prescribed medicines and other substances in drug interactions. There is an increasing tendency for patients to self-treat with medications that can be purchased without a prescription, including herbal medicines. In addition, some foodstuffs, most notably grapefruit juice, have attracted attention as a cause of drug interactions.

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This chapter reviews the main mechanisms of drug interactions. It gives some clinically important examples of these, and suggests how they can be assessed and managed. It focuses on drug interactions that may have an adverse clinical outcome, rather than those that are used to therapeutic advantage. The issues of pharmaceutical incompatibility and drug interactions with food and alcohol will not be covered here.

II. EPIDEMIOLOGY

It is difficult to give an accurate estimate of the incidence of drug interactions mainly because published studies have frequently used different criteria for definition (particularly in distinguishing between clinically significant and non-significant interactions). Some of the early studies uncritically compared prescribed drugs with lists of possible drug interactions without taking into account their potential clinical significance. Already in 1972 the Boston Collaborative Drug Surveillance Program (BCDSP) revealed an incidence of reported ADRs of 3,600 in 83,000 drug exposures (4.3%). Of these, 234 (6.5%) were attributed to drug interactions. Studies in which hospital in-patients' prescribed medication was screened suggest that about 5% were taking combinations of drugs with the potential to interact. However, most potential interactions have no adverse repercussions for the patient. A review of nine studies of the epidemiology of drug–drug interactions in hospital admissions found that the reported incidence ranged from 0 to 2.8%. However, the authors considered all studies reviewed to be flawed to some extent. In the Harvard Medical Practice Study of adverse events, 20% of events in acute hospital in-patients were drug related. Of these, 8% were considered to be due to a drug interaction, suggesting that interactions are responsible for less than 2% of adverse events in this patient group (see Leape et al., 1991). An Australian study found that 4.4% of all ADRs which resulted in hospital admission were due to interactions. Few studies have attempted to quantify the incidence of drug–drug interactions in the community. A US community pharmacy study revealed a 4.1% incidence of interactions, whereas in a Swedish study the incidence was 1.9% (see Linnarsson, 1993). Although the overall incidence of adverse drug interactions is probably quite low (<1%), it is still a considerable problem in terms of the global number of patients at risk and the potential for morbidity and mortality.

Certain patients are at increased risk of interactions. Polypharmacy is common, and the more drugs a patient takes the greater is the likelihood of an ADR. A recent study found a positive correlation between the use of $\geqslant 9$ different scheduled medications and ADRs among geriatric nursing home residents. The reported exponential rise is partly due to drug interactions. Drug interactions are more likely to have serious consequences when they affect elderly or seriously ill patients. Patients at particular risk include those with hepatic or renal disease, those on long-term therapy for chronic disease (e.g. AIDS, epilepsy, diabetes), patients in intensive care, transplant recipients, patients undergoing complicated surgical procedures and those with more than one prescribing doctor. Critically ill and elderly patients are at increased risk not only because they take more medicines, but also because of impaired homoeostatic mechanisms that might otherwise counteract some of the unwanted effects. Interactions may occur in some individuals but not in others. The effects of interactions involving drug metabolism may vary greatly in different patients because of individual differences in the initial rates of drug metabolism and in susceptibility to microsomal enzyme induction. Certain drugs are frequently implicated in drug interactions and require careful attention (Table 1); these include agents with narrow therapeutic indices, steep dose-response curves and those with self-inducible or saturable metabolism.

III. MECHANISMS

The mechanisms commonly involved in drug interactions can be divided into those which have a pharmacokinetic basis and those which have a pharmacodynamic basis. Drug interactions often involve more than one mechanism.

III.a. Pharmacokinetic Interactions

Pharmacokinetic interactions may occur during one or more of the pharmacokinetic processes whereby the drug reaches its site of action and is then eliminated (i.e. absorption, distribution, metabolism and excretion). Such interactions may result in a change in the drug concentration at the site of action with subsequent toxicity or decreased efficacy.

Table 1. Some drugs associated with high risk of interaction

Concentration dependent toxicity
Aminoglycosides
Cytotoxic agents
Ciclosporin
Digoxin
Lithium
Tacrolimus
Theophylline
Warfarin
Steep dose-response curve
Levodopa
Sulphonylureas
Verapamil
Patient dependent on therapeutic effect
Antiarrhythmics
Antiepileptics
Glucocorticoids
Hormonal contraceptives
Immunosuppressives e.g. cyclosporin, tacrolimus
Saturable hepatic metabolism
Phenytoin
Theophylline

III.a.1. Absorption

Most drugs are given orally for absorption through the mucous membranes of the gastrointestinal tract. Absorption is dependent on a number of factors including the pKa and lipid solubility of the drug, aspects of the formulation, the pH, bacterial flora and blood flow in the gut. Most of the interactions which occur within the gut result in reduced rather than increased absorption (Table 2). It is important to distinguish between changes in the rate and extent of drug absorption i.e. a change in the rate of absorption alone will change the shape of the concentration-time curve after oral administration but will not alter the average or steady state drug concentration. Such changes may be important, however, in the case of drugs given in single doses where a threshold concentration for drug effect exists (e.g. analgesics). A delay in absorption in these circumstances, especially if the rate of elimination of the drug is high, may result in failure of therapeutic efficacy.

III.a.1.1. Changes in gastrointestinal pH. The absorption of a drug across mucous membranes depends on the extent to which it exists in the non-ionised, lipid soluble form. The ionisation state depends on the pH of its milieu, the pKa of the drug and formulation factors. Weakly acidic drugs, such as the salicylates, are better absorbed at low pH because the un-ionised form predominates. An alteration in gastric pH due to antacids, histamine H2-receptor antagonists or proton pump inhibitors therefore has the potential to affect the absorption of other drugs. The clinical significance of antacid-induced changes in gastric pH is not certain, particularly since relatively little drug absorption occurs in the stomach. However, it may be of importance with enteric-coated or delayed-release preparations; an antacid has been shown to increase the maximum level of delayed-release tolterodine by 50%. Changes in gastric pH tend to affect the rate of absorption rather than the total bioavailability, provided that the drug is acid labile. Theoretically antacids could be expected to influence the absorption of other drugs markedly via this mechanism, but in practice there are very few clinically significant examples. Antacids, histamine H2-receptor antagonists and omeprazole can significantly decrease the bioavailability of ketaconazole and itraconazole, as both require gastric acidity for optimal absorption. The absorption of fluconazole, however, is not significantly altered by changes in gastric pH. The alkalinizing effects of antacids on the gastrointestinal tract are transient and the potential for interaction may be minimised by leaving an interval of 2–3 hours between the antacid and the potentially interacting drug.

III.a.1.2. Complex formation in the gastrointestinal tract. Certain drugs are liable to react with other drugs in the gastrointestinal tract to form chelates and complexes that are not absorbed. For example, the serum levels of quinolones can be dramatically reduced by the concurrent administration of antacids containing aluminium or magnesium. In one study, significant reductions in ciprofloxacin bioavailability were seen when an aluminium hydroxide–magnesium hydroxide antacid was given 2 hours or 4 hours before ciprofloxacin. No effect was seen if the antacid was given 2 hours after or 6 hours before ciprofloxacin. The mechanism for the interaction is believed to involve chelation between the 3-carboxyl and 4-oxo functional groups of the quinolone molecule and the medications. The interaction can be prevented if the antibacterial is not given until at least 6 hours after the antacid. The absorption of levodopa, levodopa/carbidopa combinations and methyldopa is diminished by the concurrent use of iron supplements, with resultant loss of efficacy.

The absorption of tetracyclines is markedly reduced by aluminium and magnesium containing antacids. Tetracyclines may chelate other ions, in particular iron salts, with resultant poor absorption of both drugs. This interaction can be avoided by giving iron salts either 3 hours before or 2 hours after the tetracycline.

Bisphosphonates such as etidronate are often coprescribed with calcium supplements in the treatment of osteoporosis. If these are ingested concomitantly, the bioavailability of both is significantly reduced with the possibility of therapeutic failure. This may be avoided by allowing a sufficiently long dosage interval; a possible approach is to give etidronate for 2 weeks and calcium supplements for 10 weeks in a 12-week period.

The absorption of some drugs may also be reduced if they are given with adsorbents such as charcoal or kaolin, or anionic exchange resins such as colestyramine or colestipol. The absorption of propranolol, digoxin, warfarin, tricyclic antidepressants, ciclosporin and levothyroxine is reduced by colestyramine.

Most chelation and adsorption interactions can be circumvented by separating doses of the interacting drugs by a period of several hours, although note that this may not be wholly effective with drugs that undergo enterohepatic recirculation.

III.a.1.3. Gastrointestinal motility. Drugs that influence gastric emptying or gastrointestinal motility can affect the absorption of other drugs that are given concurrently. Drugs are absorbed much more rapidly from the small intestine than from the stomach. Agents that alter the rate of gastric emptying can change the rate of absorption of other drugs given concurrently. Levodopa, for example, is metabolised by the gastric mucosa, and if gastric emptying is delayed, less unchanged drug is available for absorption. Some drugs, such as penicillins, may be degraded by prolonged exposure to gastric acid.

Paracetamol is used as a model for drug absorption studies because it is a weak acid (pKa 9.5) that is largely non-ionised in both gastric and intestinal fluids and its rate of absorption in humans is directly related to the gastric emptying rate. Propantheline delays gastric emptying and reduces the rate, but not the extent, of paracetamol absorption. Other drugs similarly affected include diazepam, propranolol, phenylbutazone and lithium.

Anticholinergic drugs delay gastric emptying. These drugs are commonly used in the control of movement disorders but they have been shown to reduce the bioavailability of levodopa by as much as 50% and to reduce plasma chlorpromazine concentrations significantly. Other drugs with anticholinergic effects that might influence gastrointestinal motility include tricyclic antidepressants, phenothiazines, and some antihistamines.

Opioids such as diamorphine, pethidine, and pentazocine strongly inhibit gastric emptying and greatly reduce the absorption rate of paracetamol. Codeine, however, has no significant effect on paracetamol absorption. Morphine and diamorphine have been shown to reduce the absorption of antiarrhythmics such as mexiletine in patients with myocardial infarction.

The gastrointestinal prokinetic agent, metoclopramide increases gastric emptying and increases the absorption rate of paracetamol, an effect which is used to therapeutic advantage in the treatment of migraine. Other drugs whose absorption can be accelerated by metoclopramide are propranolol, mefloquine, lithium, and ciclosporin. In general, it can be said that this type of interaction is rarely clinically significant.

III.a.1.4. Toxic effects on the gastrointestinal tract. The absorption of some drugs may be reduced due to damage of the small intestine. This is most likely after cytotoxic therapy. The absorption of phenytoin and verapamil can be reduced by 20–35% in patients taking cytotoxic drugs such as methotrexate, carmustine, or vinblastine for the treatment of malignant disease. The reduced absorption was accompanied by evidence of loss of therapeutic effect.

III.a.1.5. Changes in gut flora. Bacterial flora predominate in the large bowel and are present in much smaller numbers in the stomach and small bowel. Thus, drugs which are well absorbed from the small bowel are less likely to be affected by changes in gut bacterial flora. Drugs that are metabolised to some extent by the gut flora include sulfasalazine and levodopa. (There is some evidence to suggest that ampicillin may reduce the effects of sulphasalazine by reducing the gut bacteria that act on sulphasalazine to release sulphapyridine and 5-aminosalicylic acid.)

Antibacterials may also prevent the intestinal bacterial hydrolysis of drug conjugates secreted into bile and thus reduce reabsorption of the active parent drug. In this way, antibacterials may reduce the

enterohepatic circulation of ethinylestradiol in oral contraceptives, leading to reduced circulating oestrogen levels with the potential for therapeutic failure. This is likely to be an extremely rare interaction; the enterohepatic circulation of ethinylestradiol is probably of very minor importance in most people, as judged from data from women with ileostomies.

III.a.2. Distribution

Once absorbed a drug is distributed to its site of action and during this process it may interact with another drug. In practice the main mechanism behind such interactions is displacement from protein binding sites. A drug displacement interaction is defined as a reduction in extent of plasma protein binding of one drug caused by the presence of another which competes for the same binding sites, resulting in an increased free or unbound concentration of the displaced drug. Many drugs and their metabolites are highly bound to plasma proteins. Generally, acidic drugs bind predominantly to albumin, though not necessarily to the same site. Basic drugs, such as tricyclic antidepressants, lidocaine, disopyramide and propranolol bind to the acute phase reactant protein alpha-1-acid glycoprotein as well as albumin. This displacement is readily demonstrated *in vitro* for many drugs and in the past it was thought to be an important mechanism underlying many clinically significant interactions. However more recently these protein binding displacement interactions have come under closer scrutiny with the conclusion that most are of doubtful clinical significance. Since displacement makes more unbound (free) drug available for metabolism of glomerular filtration and the displaced drug can normally distribute out of the plasma compartment, increased unbound drug concentrations are usually only transient, and, therefore, do not commonly give rise to altered pharmacological effects in the patient.

Phenylbutazone was recognised to potentiate the anticoagulant effect of warfarin as long ago as 1959. As subsequent *in vitro* studies confirmed that phenylbutazone displaced warfarin from its protein binding site, it was assumed that any non-steroidal antiinflammatory drug (NSAID) would enhance warfarin's anticoagulant effect in this way. However it is now known that the interaction is due instead to a stereoselective inhibition of the metabolism of warfarin. Warfarin is available as a racemic mixture of two enantiomers (*R* and *S*), and of these the *S* enantiomer is five times more potent as an anticoagulant. Phenylbutazone inhibits the metabolism of the more potent *S* warfarin and induces that of the less potent *R* warfarin, resulting in a greater proportion of the *S* warfarin in plasma, and increased anticoagulant effects. It is now clear that the majority of NSAIDs do not interact with warfarin or other anticoagulants by this mechanism. Current evidence suggests that, for most drugs, if a displacement interaction occurs, then the free concentration of drug will rise temporarily, but metabolism and distribution will return the free concentration to its previous level. The time this takes will depend on the half-life of the displaced drug. The biological signif-

Table 2. Some drug absorption interactions

Changes in gastrointestinal pH
Antacids, histamine H2-receptor antagonists and proton pump inhibitors reduce the absorption of
• atazanavir
• itraconazole
• ketoconazole
Complex formation
Antacids reduce the absorption of
• antibacterials – azithromycin, quinolones, rifampicin, tetracyclines
• bisphosphonates – alendronate, clodronate, etidronate
Colestyramine reduces the absorption of
• digoxin
• levothyroxine
• warfarin
Sucralfate reduces the absorption of
• levothyroxine
• phenytoin
• quinolones
Effects on gastrointestinal motility
Metoclopramide enhances the absorption of
• ciclosporin
• diazepam
• lithium
• paracetamol
Opioid analgesics reduce the rate of absorption of
• paracetamol
Anticholinergics reduce the rate of absorption of
• diazepam
• levodopa
• paracetamol
Toxic effects on the gastrointestinal tract
Cytotoxic chemotherapy such as cisplatin reduces the absorption of
• phenytoin

icance of the short term rise of free concentration is probably of minor importance. However, the effects of such interactions may need to be taken into account in therapeutic drug monitoring. For example, if a patient taking phenytoin is given a drug which displaces some phenytoin from its binding sites the total (i.e. free plus bound) plasma phenytoin concentration will fall even though the free (active) concentration remains the same.

III.a.3. Metabolism

Most clinically important interactions involve alterations in the rate of metabolism of the affected drug. Most drugs in use are lipid soluble and require conversion to more water soluble products that can be excreted in the urine or bile. The liver is the principal site of drug metabolism although other organs such as the kidneys, lung, gut, skin and placenta are involved. The two main metabolic processes are phase I and phase II reactions. Phase I reactions feature oxidation, hydrolysis or reduction. Phase II reactions involve conjugation of the drug (or the product of phase I metabolism) with substances such as glucuronic acid, sulphate, or glycine. Phase I metabolism generally involves the hepatic mixed function oxidase system, of which cytochrome P450 is the most important. P450 is a large superfamily of proteins, the synthesis of which is controlled by a superfamily of genes. As there are many different isoforms of these enzymes a classification for nomenclature has been developed. Four main sub-families of P450 isoenzymes are thought to be responsible for most (about 90%) of the metabolism of commonly used drugs CYP1, CYP2, and CYP3 in humans (Table 3). Within these families, six isoforms (CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4) are involved in the metabolism of a large proportion of drugs. The activity of these enzymes is modulated by genetic and other factors (e.g. age, ethnic origin, gender, diet, consumption of alcohol/tobacco) as well as pathological conditions. Genetic factors are undergoing increasing scrutiny. Genetic polymorphisms, which simply mean that some of the population have a variant of the isoenzyme with different (usually poor) activity, have been identified for CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP1E2; and, although polymorphism has not been identified for CYP3A4 its expression varies widely in the population. This explains why the occurrence of interactions involving metabolism shows considerable inter-individual variation.

The importance of these enzymes for drug interactions is that enzyme inducers and inhibitors may preferentially affect certain isoforms and consequently may only affect the metabolism of selected drugs. For example, ketoconazole has the potential to inhibit the metabolism of drugs metabolised to a great extent by the sub-family 3A (e.g. midazolam) but not of those metabolised by sub-family 1A (e.g. theophylline), 2C (e.g. diazepam), or 2D (e.g. metaprolol). In contrast, although fluconazole is a weaker inhibitor of the sub-family 3A than ketoconazole, it also inhibits the sub-family 2C, and so the interactions of fluconazole differ from those of ketoconazole.

III.a.3.1. Enzyme induction. Enzyme induction usually develops over a period of several days or weeks, depending on the dose and pharmacokinetic characteristics of the inducing drug and the kinetics of the enzyme affected. The effect generally persists for a similar period following withdrawal of the enzyme-inducing agent. The most powerful enzyme inducers in clinical use are carbamazepine, phenobarbitoal, phenytoin, and rifampicin (Table 4). Enzyme inducing drugs with short half-lives (e.g. rifampicin) will induce metabolism more quickly than

Table 3. Some drug substrates, inducers and inhibitors of the major cytochrome P450 isoforms

P-450 isoform	Substrate	Inducer	Inhibitor
CYP1A2	Theophylline, imipramine	Omeprazole, tobacco smoke	Fluvoxamine, furafylline
CYP2A6	Halothane	Phenytoin	Tranylcypromine
CYP2C9	Diazepam, diclofenac	Barbiturates	Suphaphenazole
CYP2C19	Citalopram, omeprazole	Rifampicin	Tranylcypromine
CYP2D6	Amitriptyline, codeine	Quinidine	
CYP2E1	Enflurane, halothane	Alcohol (chronic), isoniazid	Disulfiram
CYP3A4	Amiodarone, terfenadine	Carbamazepine, phenytoin	Erythromycin, grapefruit juice,
CYP4A1	Testosterone	Clofibrate	Itraconazole, ritonavir

Table 4. Some enzyme inducers

Barbiturates
Carbamazepine
Ethanol (chronic)
Griseofulvin
Phenytoin
Rifabutin
Rifampicin
Tobacco smoke

drugs with longer half-lives (e.g. phenytoin) because they reach steady-state concentrations more rapidly. Enzyme induction usually results in a reduced pharmacological effect of the induced drug but where active metabolites are responsible for a drug's effect the reverse may occur.

The metabolism of warfarin is increased by barbiturates, phenytoin, carbamazepine and rifampicin. The mechanism involves induction of the P450 isoform CYP2C9. If phenytoin is administered to a patient stabilised on warfarin the anticoagulant effect is reduced over a period of several weeks and the dose of warfarin may need to be increased to maintain the same effect on clotting parameters. When the enzyme inducing drug is withdrawn enzyme activity returns to normal, with a risk of haemorrhage unless the warfarin dose is correspondingly reduced.

Rifabutin is a rifamycin used for prophylaxis against *Mycobacterium avium* complex infections in patients with low CD4 count. As with rifampicin it induces hepatic enzymes, although to a lesser extent than rifampicin, and the effectiveness of some drugs including oral contraceptives may be reduced.

A reduced response to simvastatin was noted after phenytoin was added for epilepsy; the cholesterol level increased from 9.4 mmol/l to 15.99 mmol/l. The level decreased again when phenytoin was discontinued. Phenytoin induces the CYP3A4 isoform which is involved in simvastatin metabolism. Some other examples of this type of interaction are shown in Table 5.

III.a.3.2. Enzyme inhibition. A number of drugs have the potential to inhibit microsomal enzymes (Table 6). Inhibition of drug metabolism may therefore result in exaggerated and prolonged responses, with an increased risk of toxicity. The onset of enzyme inhibition is usually more rapid than induction, occurring as soon as sufficient concentrations of the inhibitor appear in the liver. Thus for drugs with a short half-life, the effects may be seen within 24 hours of administration of the inhibiting agent. The effects are not seen until later for drugs with a long half-life. The clinical significance of this type of interaction depends on various factors, including dosage (of both drugs), alterations in pharmacokinetic properties of the affected drug, such as half-life, and patient characteristics such as disease state. Interactions of this type are again more likely to affect drugs with a narrow therapeutic range, such as theophylline, ciclosporin, coumarin anticoagulants and phenytoin. Inhibition of metabolism may result in exaggerated and prolonged responses with an increased risk of toxicity. Another possible consequence is a reduction in levels of a drug's active metabolites.

Most of these interactions involve inhibition of cytochrome P450 drug metabolising enzymes. A number of drugs has the capacity to bind the enzyme tightly forming an inactive complex which prevents the access of other agents. In addition, more than one enzyme may be inhibited. Erythromycin, for example, inhibits both CYP1A2, which metabolises theophylline and warfarin, and CYP3A4, which metabolises many drugs, including astemizole, cisapride, terfenadine and triazolam. (Note: astemizole, cisapride and terfenadine have been withdrawn from most Western markets as they produced excessive QT prolongation.) The clinical significance of this type of interaction depends on the theraeputic ratio of the drug affected and on its initial plasma concentrations before the inhibiting drug is given.

Cimetidine inhibits oxidative drug metabolism and prolongs the half-life of many drugs including phenytoin, nitrazepam, diazepam, warfarin, and theophylline. Cimetidine reduces theophylline clearance by 30–40% and consequently serum levels rise by about one third. However, the increases have been much greater in some patients. The interaction can lead to serious adverse effects including convulsions and cardiac arrhythmias. If a patient taking theophylline requires an histamine H2-receptor antagonist, ranitidine or another member of the class is to be preferred. If cimetidine is used, the dose of theophylline may need to be reduced by 30–50% and the patient closely monitored.

Cimetidine's inhibitory effect on metabolising enzymes is more marked in smokers than non-smokers and in patients with impaired liver function. The onset and offset of enzyme inhibition is rapid

Table 5. Some examples of interactions due to enzyme induction

Drug affected	Inducing agent	Clinical outcome
Carbamazepine	Lamotrigine	Increased concentrations of epoxide metabolite leading to toxicity
Hormonal contraceptives	Rifampicin	Therapeutic failure of contraceptive
	Rifabutin	Additional contraceptive precautions required
	Carbamazepine	
Ciclosporin	Phenytoin	Decreased ciclosporin levels with possibility of transplant rejection
	Carbamazepine	
Paracetamol	Alcohol (chronic)	In overdose, hepatotoxicity may occur at lower doses
Corticosteroids	Phenytoin	Increased metabolism with possibility of therapeutic failure
	Rifampicin	

Table 6. Some enzyme inhibitors frequently implicated in interactions

Antibacterials
Ciprofloxacin
Erythromycin
Isoniazid
Antidepressants
Fluoxetine
Fluvoxamine
Paroxetine
Antifungal drugs
Fluconazole
Itraconazole
Ketoconazole
Miconazole
Antiviral drugs
Indinavir
Ritonavir
Saquinavir
Cardiovascular drugs
Amiodarone
Diltiazem
Quinidine
Verapamil
Gastrointestinal drugs
Cimetidine
Rheumatological drugs
Allopurinol
Azapropazone
Phenylbutazone
Other
Disulfiram
Dextropropoxyphene

and dose-related. The cimetidine molecule contains an imidazole ring which is believed to be a critical structural component in determining its enzyme inhibitory capacity. Other enzyme inhibitors such as metronidazole and azole antifungals also contain an imidazole ring.

The macrolide antibacterials (including erythromycin, clarithromycin and telithromycin) are often implicated in interactions, most frequently as a result of inhibition of the CYP3A4 enzyme system in the liver and enterocytes. Erythromycin inhibits the metabolism of carbamazepine, ciclosporin and theophylline; significant increases in serum levels and features of toxicity have been documented. Careful clinical and pharmacokinetic monitoring are required in a patient taking any of these drugs who requires concomitant erythromycin.

Some enzyme inhibitors, including macrolides, can cause the accumulation of drugs that have the potential to prolong the QT interval (a measure of the ventricular action potential and ventricular repolarization) on the electrocardiogram (ECG). Prolongation of the QT interval can cause arrhythmias, the most characteristic of which is torsades de pointes ("twisting of the points"). This is usually a self-limiting arrhythmia which causes dizziness or syncope, however, it can lead to ventricular fibrillation and sudden death. The main groups of drugs that can prolong the QT interval are shown in Table 7. The underlying mechanism is thought to involve drug-induced blockade of the repolarizing potassium channels, particularly the inward rectifier, causing prolongation of the action potential and duration and early after-depolarization.

In 1990 torsades de pointes was reported in a patient who had received both terfenadine and ketoconazole. Terfenadine is almost completely converted to an active metabolite in the liver. In patients with severe liver disease or those taking drugs that

Table 7. Some drugs which may cause QT interval prolongation

Antiarrhythmic drugs	Amiodarone, sotalol, quinidine, disopyramide
Antihistamines	Terfenadine, astemizole
Antiinfectives	Erythromycin (especially intravenous use), halofantrine, some quinolones
Psychiatric drugs	Amisulpride, haloperidol, sertindole, thioridazine, pimozide
Others	Cisapride

inhibit its metabolism, plasma levels of the parent drug can increase sufficiently to disturb ventricular repolarisation. Reduced metabolised in the liver and concurrent ingestion of the enzyme inhibitors erythromycin or ketoconazole can cause accumulation of unmetabolised terfenadine. Drug interaction studies with fexofenadine, which is the active metabolite of terfenadine, have shown no increased incidence of adverse effects or QTc prolongation when combined with ketoconazole or erythromycin. Astemizole and cisapride have been shown to cause arrhythmias by the same mechanism. Astemizole and cisapride were withdrawn from the US market in respectively 1999 and 2000 because of the risk of heart rhythm abnormalities. Enzyme inhibiting drugs (mainly inhibitors of CYP3A4) are contra-indicated in patients taking terfenadine, astemizole or cisapride. These interactions led to the restriction or withdrawal of these drugs in many countries.

The metabolism of ciclosporin is inhibited by diltiazem, verapamil, azole antifungal agents, erythromycin and clarithromycin with resultant potential for renal, hepatic and CNS toxicity. These interactions have been investigated as a cost saving device in organ transplant recipients, with the aim of using a lower dose of ciclosporin to achieve immunosuppression.

Mibefradil is a calcium antagonist which was withdrawn worldwide within a year of its introduction because of reports of serious interactions with other drugs. Mibefradil inhibits the action of CYP3A4; given concurrently with drugs metabolised by this enzyme, concentrations of these drugs would be expected to increase. Although the effects of drug interactions may be minimised by appropriate labelling and clear prescribing information, the company which marketed mibefradil believed that the complexity of such information would have been too difficult to implement.

Protease inhibitors, a class of antiretroviral drugs used in the management of HIV infection, are associated with a high risk of drug interactions largely because they are potent inhibitors of CYP450-mediated oxidative metabolism and also because optimal management of HIV infection requires the use of combination antiviral therapy to delay the emergence of resistance. Many patients will also require other medications for disease sequelae. There are numerous potential interactions and it can be difficult to ascertain which are of most concern. Ritonavir, indinavir, nelfinavir and saquinavir all inhibit the CYP3A4 isoenzyme. Ritonavir is a particularly potent inhibitor of isoenzyme CYP3A4 and it also inhibits CYP2D6 and CYP2C9/10; it is associated with a high risk of serious interactions. Saquinavir is a substantially less potent inhibitor of CYP3A4 than either ritonavir or indinavir. Many of the protease inhibitors are also metabolized by CYP3A4 and are given with low-dose ritonavir in order to increase their levels.

Many of the drugs likely to be taken by patients with HIV have a strong potential to interact with the protease inhibitors. In particular, the non-nucleoside reverse transcriptase inhibitors are also metabolised by CYP450 and have been shown to interact with protease inhibitors. Delavirdine is an inhibitor of CYP3A4 but nevirapine and efavirenz are inducers of CYP3A4. The protease inhibitors also interact with each other, and these interactions are being explored for their potential therapeutic benefits.

Many serious adverse interactions have been described with protease inhibitors. In a patient taking saquinavir, the use of midazolam lead to prolonged sedation requiring reversal with flumazenil. A case of severe ergotism resulting in amputation of the toes has been described in a woman receiving combination antiretroviral therapy comprising ritonavir who also took a remedy for gastric discomfort containing ergotamine. The total dose of ergotamine ingested was considerably lower than the maximum recommended daily dose. Ritonavir probably inhibited ergotamine's metabolism. Ergot alkaloids should not be given to patients taking ritonavir or other protease inhibitors.

A fatal interaction between ritonavir and MDMA (methylenedioxymethamphetamine, ecstasy) has been reported in an HIV-positive man (see Henry et al., 1998). The patient had allegedly taken MDMA on several occasions without untoward effects. However, several weeks after ritonavir was added to his regular medication with zidovudine and lamivudine, he took some MDMA for recreational purposes and died of a cardiorespiratory arrest within hours. Toxicology showed that the plasma MDMA concentration was about ten times that expected from the ingested dose. Inhibition of CYP2D6, the principal pathway for MDMA metabolism, by ritonavir was thought to be the most likely cause.

Protease inhibitors have the potential to interact with sildenafil, the orally active treatment for erectile dysfunction. Sildenafil is metabolised by the cytochrome P450 isoforms CYP3A4 and CYP2C9 and is also a weak inhibitor of CYP2D6. An interaction may occur, increasing the likelihood of sildenafil's adverse effects including headache, flushing, and hypotension. A myocardial infarction has been reported in a 47-year-old man treated for HIV-infection with ritonavir and saquinavir who took sildenafil for erectile dysfunction. The patient, who was a heavy smoker, subsequently died. Sildenafil should be used with caution in patients taking protease inhibitors, and dose restrictions apply.

As well as inhibiting certain CYP450 isoenzymes, ritonavir induces CYP1A2 and hepatic glucuronidation. Ritonavir significantly decreased the area under the concentration–time curve (-41%) and C_{max} (-32%) of oestrogen in healthy females taking an oral contraceptive. The mechanism is not yet clear but is thought to involve induction of CYP hydroxylation and/or hepatic glucuronidation. A similar reduction in oestrogen concentration has occurred when nelfinavir was given in combination with ethinyloestradiol. Alternative methods of contraception will be necessary for women taking ritonavir or nelfinavir.

Indinavir is associated with a dose-related risk of nephrolithiasis; the risk is thereby increased by drug interactions that result in increased plasma concentrations.

In patients taking rifabutin, protease inhibitors can significantly increase the area under the concentration–time curve. High concentrations of rifabutin can provoke uveitis. If the combination of rifabutin and a protease inhibitor is essential, dose adjustments are recommended.

Experience with protease inhibitors to date confirms that great vigilance for drug interactions is required, both those that are already documented and those that are predictable from pharmacokinetic profiles. Although many potential drug interactions are recognised, few studies have evaluated their magnitude and discussed their management. Retrospective medication reviews of US patients taking protease inhibitors have revealed a high incidence of potential drug interactions, many of which were classed as serious or life-threatening. Physicians and pharmacists should carefully review all concomitant medication in patients taking these drugs and must encourage patients to disclose details of all medications (including herbal and over the counter preparations) and illicit substances they may be taking.

III.a.4. Elimination

Most interactions involving elimination or excretion occur in the kidneys. Blood entering the kidneys is delivered to the glomeruli of the tubules where molecules small enough to pass across the pores of the glomerular membrane are filtered through into the lumen of the tubules. Larger molecules are retained. The blood then flows to other parts of the kidney tubules where drugs and their metabolites are removed, secreted, or reabsorbed into the tubular filtrate by active and passive transport systems. Interactions can occur when drugs interfere with kidney tubule fluid pH, active transport systems, or blood flow to the kidney thereby altering the excretion of other drugs.

III.a.4.1. Changes in urinary pH. As with drug absorption in the gut, passive reabsorption of drugs depends on the extent to which the drug exists in the non-ionised lipid-soluble form. Only the unionised form is lipid soluble and able to diffuse back through the tubule cell membrane. Thus, at alkaline pH weakly acidic drugs (pKa 3.0–7.5) largely exist as un-ionised lipid insoluble molecules which are unable to diffuse into the tubule cells and will therefore be lost in the urine. The renal clearance of these drugs is increased if the urine is made more alkaline. Conversely, the clearance of weak bases (pKa 7.5–10) is higher in acid urine. Strong acids and bases are virtually completely ionised over the physiological range of urine pH and their clearance is unaffected by pH changes.

This mechanism of interaction is of very minor clinical significance because most weak acids and

bases are inactivated by hepatic metabolism rather than renal excretion. Furthermore, drugs that produce large changes in urine pH are rarely used clinically. Urine alkalinisation may be used as a means of increasing drug elimination in salicylate poisoning. Intravenous sodium bicarbonate is given to ensure that urinary pH is between 7.5 and 8.5; the procedure is not without risk and frequent biochemical monitoring is required. Acidification of the urine has been used to enhance amphetamine elimination although other measures are probably more effective.

III.a.4.2. Changes in active renal tubule excretion. Drugs which use the same active transport system in the kidney tubules can compete with one another for excretion. One drug may, therefore, interfere with the renal excretion of another and cause accumulation and toxicity. The onset and offset of this inhibitory effect is often rapid and concentration-dependent, due to its competitive nature. Such competition between drugs can be used to therapeutic advantage. For example, probenecid may be given to increase the serum concentration of penicillins by delaying their renal excretion. Increased methotrexate toxicity, sometimes life-threatening, has been seen in some patients concurrently treated with salicylates and some other NSAIDs. The development of toxicity is more likely in patients treated with high dose methotrexate and those with impaired renal function. The mechanism of this interaction may be multifactorial, but competitive inhibition of methotrexate's renal tubular secretion is likely to be involved. If salicylates or NSAIDs are essential in patients treated with methotrexate for malignancy, the dose of methotrexate should be reduced. Patients taking low doses for rheumatoid arthritis may take concurrent NSAIDs, but close monitoring for bone marrow toxicity is vital.

III.a.4.3. Changes in renal blood flow. Blood flow through the kidney is partially controlled by the production of renal vasodilatory prostaglandins. If the synthesis of these prostaglandins is inhibited (e.g. by indomethacin), the renal excretion of lithium is reduced with a subsequent rise in serum levels. The mechanism underlying this interaction is not entirely clear, as serum lithium levels are unaffected by some potent prostaglandin synthetase inhibitors (e.g. aspirin). If an NSAID is prescribed for a patient taking lithium the serum levels should be closely monitored.

III.b. Drug-Transporter Proteins

Drugs and endogenous substances are known to cross biological membranes, not just by passive diffusion, but carried by transporter proteins. Significant advances in the identification of various transporters have been made, although the contribution of many of these to drug interactions in particular, is still unclear. The most well known is P-glycoprotein, an efflux pump found in the membranes of certain cells. By transporting metabolites and drugs out of the cells P-glycoprotein can affect the extent of drug absorption (via the intestine), distribution (e.g. to the brain) and elimination (in the urine and bile).

The pumping actions of P-glycoprotein can be induced or inhibited by some drugs. So for example, the induction of the activity of intestinal P-glycoprotein by rifampicin causes digoxin to be ejected into the gut more vigorously, resulting in reduced digoxin levels. In contrast, verapamil appears to inhibit the activity of P-glycoprotein, and is well known to increase digoxin levels. Ketoconazole also has P-glycoprotein inhibitory effects, and has been shown to increase CSF levels of ritonavir, possibly by preventing the efflux of ritonavir from the CNS. Note that there is evidence that P-glycoprotein inhibition may have a greater impact on drug distribution than on drug absorption.

III.c. Pharmacodynamic Interactions

Pharmacodynamic interactions generally involve additive, synergistic or antagonistic effects of drugs acting on the same receptors or physiological systems. These interactions are more difficult to classify than those with a pharmacokinetic basis. They are fairly common but may not always be recognised.

III.c.1. Antagonistic or Opposing Interactions

It is to be expected that a drug with an agonist action at a particular receptor type will interact with antagonists at that receptor. For example, the bronchodilator action of a selective beta-2-adrenoceptor agonist such as salbutamol will be antagonised by non-selective beta-adrenoceptor antagonsists.

There are numerous examples of interactions occurring at receptor sites, many of which are used to therapeutic advantage. Specific antagonists may be used to reverse the effect of another drug at receptor sites; examples include the opioid antagonist naloxone and the benzodiazepine antagonist flumazenil. Alpha-adrenergic agonists such as metaraminol and

methoxamine may be used in the management of priapism arising due to excessive alpha-adrenergic antagonism by phentolamine and related compounds.

III.c.2. Additive Effect/Potentiation/Synergy

If two drugs with similar pharmacological effects are given together, the effects can be additive. Although not strictly drug interactions, the mechanism frequently contributes to adverse drug reactions. For example, the concurrent use of drugs with CNS depressant effects such as antidepressants, hypnotics, antiepileptics and antihistamines may lead to excessive drowsiness, yet such combinations are frequently encountered. Combinations of drugs with arrhythmogenic potential such as antiarrhythmics, neuroleptics, tricyclic antidepressants, and those producing electrolyte imbalance (e.g. diuretics) may lead to ventricular arrhythmias and should be avoided. Other examples of additive interactions are shown in Table 8.

III.c.3. Interactions Due to Changes in Drug Transport Mechanisms

One drug may interfere with the uptake and transport of another to intracellular sites of action. The antihypertensive effects of adrenergic neurone blocking drugs such as guanethidine and debrisoquine are prevented or reversed by tricyclic antidepressants, though these antihypertensives are now seldom used. The pharmacological action of the adrenergic neurone blockers appears to depend on a similar mechanism of neuronal uptake as noradrenaline and other sympathomimetic amines, known as uptake 1. Therapeutic doses of amphetamines, pseudoephedrine, phenothiazines and tricyclic antidepressants can inhibit the hypotensive effects of adrenergic neurone blockers by competitive prevention of their access to the noradrenaline storage sites.

III.c.4. Interactions Due to Disturbances in Fluid and Electrolyte Balance

Changes in electrolyte balance may alter the effects of drugs, particularly those acting on the myocardium, neuromuscular transmission and the kidney. An important interaction is the potentiation of the effects of cardiac glycosides such as digoxin by diuretics and other drugs which decrease plasma potassium concentrations. Similarly, diuretic induced hypokalaemia increases the risks of ventricular arrhythmias associated with antiarrhythmic drugs such as sotalol, procainamide, quinidine and amiodarone. Angiotensin-converting enzyme inhibitors have a potassium-sparing effect, such that the concurrent use of potassium supplements or potassium sparing diuretics may lead to dangerous hyperkalaemia. Co-administration of tacrolimus with potassium-sparing diuretics and potassium supplements can also lead to life-threatening hyperkalaemia, especially in patients with renal failure.

Lithium intoxication can be precipitated by the use of diuretics, particularly thiazides and metolazone, and ACE inhibitors. NSAIDs can also precipitate lithium toxicity, mainly due to NSAID inhibition of prostaglandin-dependent renal excretion mechanisms. NSAIDs also impair renal function and cause sodium and water retention, effects which can predispose to interactions. Many case reports describe the antagonistic effects of NSAIDs on diuretics and antihypertensive drugs. The combination of triamterene and indomethacin appears particularly hazardous as it may result in acute renal failure. NSAIDs may also interfere with the beneficial effects of diuretics and ACE inhibitors in heart failure. It is not unusual to see patients whose heart failure has deteriorated in spite of increased doses of frusemide who are also concurrently taking an NSAID.

Table 8. Some additive or synergistic interactions

Interacting drugs	Pharmacological effect
NSAID and warfarin	Increased risk of bleeding
ACE inhibitors and K-sparing diuretic	Increased risk of hyperkalaemia
Verapamil and beta-adrenergic antagonists	Bradycardia and asystole
Neuromuscular (NM) blockers and aminoglycosides	Increased NM blockade
Alcohol and benzodiazpines	Increased sedation
Thioridazine and halofantrine	Increased risk of QT interval prolongation
Clozapine and co-trimoxazole	Increased risk of bone marrow suppression

III.c.5. Indirect Pharmacodynamic Interactions

There are many indirect pharmacodynamic interactions which are of potential clinical significance. In insulin-dependent diabetics the normal recovery from an episode of hypoglycaemia may be impaired to some extent by propranolol. In addition, the blood-glucose lowering effects of the sulphonylureas may occasionally be reduced by beta-adrenoceptor antagonists. Non-selective beta-blockers block the mobilisation of glucose from the liver so that recovery from hypoglycaemia is delayed. They can also block beta-2 receptors in the pancreas that mediate insulin release, preventing the effects of the sulphonylureas. These interactions have been well studied and marked effects on blood glucose control appear to be unusual. Patients whose diabetes is controlled by insulin or oral antidiabetics can be treated with selective beta-blockers, but they should be aware that the familiar warning signs of hypoglyacaemia may be masked and blood glucose should be carefully monitored.

Monoamine oxidase inhibitors (MAOIs) are effective antidepressants which inhibit the intraneuronal enzyme monoamine oxidase (MAO) thereby reducing the breakdown of noradrenaline in the adrenergic nerve ending. This leads to the nerve ending having large stores of noradrenaline which can be released into the synaptic cleft in response to either a neuronal discharge or an indirectly acting amine. The action of directly acting amines (adrenaline, isoprenaline, noradrenaline) appears to be unchanged or only moderately increased in patients taking MAOIs, although in patients with underlying cardiovascular disease there may be some adverse consequences. In contrast, the concurrent use of MAOIs and indirectly acting sympathomimetic amines (e.g. amphetamines, tyramine, MDMA, phenylpropanolamine, pseudoephedrine) can result in a potentially fatal hypertensive crisis. Some of these compounds are contained in proprietary cough and cold remedies. Tyramine is normally present in foodstuffs (e.g. cheese and red wine) and is metabolised in the gut wall by MAO to inactive metabolites. In patients taking an MAOI, however, tyramine will be absorbed intact. If patients taking MAOIs also take these amines there may be a massive release of noradrenaline from adrenergic nerve endings with a resulting syndrome of sympathetic overactivity characterised by hypertension, headache, excitement, hyperpyrexia, and cardiac arrhythmias. Fatal intracranial haemorrhage and cardiac arrest may result. The risk of interactions continues for several weeks after the MAOI is stopped as new MAO enzyme must be synthesised. Patients taking irreversible MAOIs should not take any indirectly acting sympathomimetic amine. All patients must be strongly warned about the risks of cough and cold remedies, illicit drug use, and the necessary dietary restrictions imposed.

MAOIs are associated with other potentially dangerous interactions. Their combination with drugs that block serotonin reuptake is potentially lethal. The basis of the interaction is thought to be an increase in serotonin levels within the CNS, and may be described as serotonin syndrome. This is a rare syndrome which is becoming increasingly well recognised in patients receiving combinations of serotonergic drugs. It can occur when two or more drugs affecting serotonin are given at the same time, or after one serotonergic drug is stopped and another started. Serotonin syndrome is characterised by a variety of symptoms including confusion, disorientation, abnormal movements, exaggerated reflexes, fever, sweating, diarrhoea and hypo- or hypertension. Diagnosis is made when three or more of these symptoms are present and no other cause can be found. Symptoms usually develop within hours of starting the second drug but occasionally they can occur later, and may only occur after a dose increase of one of the offending drugs.

Drug-induced serotonin syndrome is generally mild and resolves when the offending drugs are stopped. However, it can be severe and deaths have occurred. A large number of drugs have been implicated including tricyclic antidepressants, monoamine oxidase inhibitors (MAOIs), selective serotonin re-uptake inhibitors (SSRIs), pethidine, lithium, and dextromethorphan. The most severe type of reaction has occurred with the combination of selective serotonin re-uptake inhibitors and monoamine oxidase inhibitors. Both non-selective MAOIs such as phenelzine and selective MAOIs such as moclobemide and selegiline have been implicated.

Serotonin syndrome is best prevented by not using serotonergic drugs in combination. Special care is needed when changing from an SSRI to an MAOI and vice versa. The SSRIs, particularly fluoxetine, have long half-lives and serotonin syndrome may occur if a sufficient wash-out period is not allowed before switching from one to the other. When changing

from an MAOI to an SSRI, a two week gap should be allowed before starting the SSRI. When changing from an SSRI to an MAOI, the guidance in manufacturers' summaries of product characteristics should be followed.

Clinicians must be aware of this rare but potentially serious problem. It may be difficult to distinguish serotonin syndrome from the clinical features of depression, adverse effects, and withdrawal effects.

IV. DRUG–HERB INTERACTIONS

The use of herbal medicines in the Western world has markedly increased in recent years, and, not surprisingly, reports of interactions with 'conventional' drugs have arisen. The most well-known and documented example is the interaction of St John's wort (*Hypericum perforatum*) with a variety of drugs (Table 9). Evidence has shown that the herb can induce CYP3A4, and can also induce P-glycoprotein. There have also been isolated reports of other herbal drug interactions, attributable to various mechanisms, including additive pharmacological effects. Based on these reports, there is a growing number of reviews of herbal medicine interactions, which seek to predict likely interactions, based on the often hypothesised actions of various herbs. Many of these predictions seem tenuous at best. A good example of why these predictions may not be wholly clinically relevant is that of the potential interaction between herbal medicines and warfarin. It has been suggested that if a plant contains natural coumarins it will have anticoagulant properties. More than 3,400 coumarins occur naturally throughout at least 160 plant families. Of these, just 13 have been tested for antithrombotic or anticoagulant activity, and only about half (7) were found to be active. There are no established interactions between warfarin and herbal medicines that have been attributed to the coumarin content of the herb. This suggests that the occurrence of coumarins in dietary supplements or herbal medicines should not trigger immediate concern.

An additional problem in interpreting the interactions of herbal medicines, is that the interacting constituent of the herb is usually not known and is therefore not standardised. It could vary widely between different products, and batches of the same product. Although there are, increasingly, some well-conducted studies investigating the effects of herbal medicines on 'conventional drugs', at present information regarding the clinical effects of drug–herb combinations remains sparse.

V. CONCLUSION

Clinically significant drug interactions are an uncommon, but nonetheless important, cause of morbidity and occasionally mortality. It is impossible to remember all known important interactions, but keeping certain basic principles in mind can help pharmacists and clinicians minimise their occurrence. Many serious interactions occur as a result of decreased drug activity with diminished efficacy or increased drug activity with exaggerated or unusual effects. Drugs with a narrow therapeutic window (e.g. anticoagulants, digoxin, lithium, immunosuppressives) are often implicated. The most important

Table 9. The effect of St John's wort (*Hypericum perforatum*) on some 'conventional drugs'

Drug	Effect
Buspirone	Additive CNS effects
Carbamazepine	Reduced levels of single-dose carbamazepine, no significant effect on multiple doses of carbamazepine
Digoxin	Reduced digoxin levels; digoxin toxicity seen in one patient when St John's wort stopped
Hormonal contraceptives	Breakthrough bleeding and contraceptive failures reported
Indinavir	Marked reduction in indinavir levels
Irinotecan	Decreased levels of the active metabolite of irinotecan
SSRIs	Cases of the serotonin syndrome reported
Verapamil	Reduced verapamil bioavailability
Voriconazole	Reduced voriconazole levels
Warfarin	Moderate reduction in the effects of warfarin reported

pharmacokinetic interactions involved drugs which can induce or inhibit hepatic cytochrome P450 enzymes; vigilance is required when these are prescribed. The effects of pharmacodynamic interactions can often be predicted when the pharmacology of co-administered drugs is known. Remember the patients groups who are most susceptible to interactions, particularly the elderly, the critically ill, and those with impaired organ function. In many cases, drugs with the potential to interact may be given concurrently provided any necessary monitoring is carried out and changes to dose or therapy carried out promptly, if required. However, where the risks associated with a potential drug interaction are high, concurrent use of the drugs involved should always be avoided unless there is no safer alternative.

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[1] Editor's note: In the field of drug interactions there is a mass of unsupported and unsupportable "information", particularly in the area of herbals. We therefore want to refer the reader first of all to Stockley's Drug Interactions (see Baxter K, 2007). By listing the latter in the bibliography the reader is provided with somewhere to go where the original documentation can be found.

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Chapter 16

Drug Misuse – Harmful Use, Abuse and Dependence*

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I. BACKGROUND AND DEFINITIONS

There is a good deal of confusion over several of the terms used concerning the negative health effects of psycho-active medicinal products. Such confusion is difficult to avoid since the word "drug" to some means "a substance which is used, often illegally, to produce a psychological effect". To others it is synonymous with a medicinal product used on prescription or under the advice of a health professional.

Although it may seem a boring way to commence a chapter, confusion over the terms used in this area leads to mis-communication which can have serious social, health and legal consequences both for health professionals and for patients.

It is essential always to ensure that there is clear understanding of how terms are being used, and there is considerable confusion between authorities using the same terms. In this chapter the following definitions will be used. They adhere as far as possible at least to the concepts, if not the actual text, used in the World Health Organisation's International Classification of Diseases 10th ed. (ICD 10):

- Drug – any medicinal product
- Misuse – use of a drug or substance, without or against health professional guidance, for its pharmacological effects
- Abuse – persistent or unjustified use of a drug or substance in a prolonged, unnecessary way or at excessive dosage
- Harmful use – pattern of psycho-active drug or substance use that is causing damage to health (mental or physical)

Note: Misuse, abuse and harmful use are often used interchangeably, but it is often useful to distinguish between the occasional "misuse" of a drug, from the more persistent and damaging "abuse" of a drug which the ICD10 now uses in a differential way to distinguish non-dependence producing drugs from "harmful use" which is only applied to psycho-active (dependence-producing) drugs. Almost all drugs which are psycho-active have a misuse or abuse potential.

"Dependence" is psychic craving for a substance (incl. drugs). Note: The dependence syndrome includes:

1. A strong desire or compulsion to take the substance.

* This chapter is heavily based upon the excellent reports from the World Health Organisation, and on clinical experience.

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2. Difficulties in controlling substance-taking behaviour in terms of onset, termination, or levels of use.
3. A physiological withdrawal state.
4. Tolerance.
5. Progressive neglect of alternative pleasures and interests.
6. Persistence with substance use despite clear evidence of overtly harmful consequences.

A definite diagnosis of dependence should usually be made only if three or more of the above features occur during the previous year. Dependency may result after the prolonged use of any drug which acts upon known cerebral receptors. Re-regulation of those receptors provides a pharmacological explanation, but it should be remembered that a clinical dependence may exist without the pharmacological basis being recognized.

"Withdrawal state (or syndrome)" – symptoms of variable clustering and severity occurring on discontinuation of the drug or substance, or on dose reduction. Note that withdrawal states usually occur after prolonged and/or high doses. The time relationships of onset and course of the withdrawal state are related to the type of substance and the dose used immediately before the withdrawal state. Withdrawal syndrome is a particularly difficult term because it is not only used only for syndromes relating to dependence. The term is also used related to the consequences of down-regulation of pharmacological receptors in a more general sense. Moreover, rebound of previously suppressed psychological symptoms can be confused with a withdrawal state. For the strict diagnosis of dependence to be warranted the withdrawal symptoms must be more severe than any pre-existing symptoms and, in this context, does not necessarily refer to a pharmacological state of receptors, but to a serious clinical situation. For example convulsions are a frequent component of withdrawal states. The careful use of "dependence" is essential. In therapeutic situations, for example with the SSRI drugs it is not uncommon to find that patients have a withdrawal syndrome, but otherwise to not fufill the strict criteria mentioned above. On the other hand, patients who experience withdrawal symptoms from SSRIs present real and serious clinical issues (see below).

"Tolerance" – increased doses of psycho-active substances (incl. drugs) are required to achieve effects originally produced by lower doses. Note that this term is again used in receptor pharmacology for down regulation of receptors, which, although it may be the reason for the clinical state, needs to be distinguished from the clinical observations.

"Drug addiction" is synonymous with "Drug dependence".

II. GENERAL CLINICAL GUIDELINES ON DRUG DEPENDENCE

There is much written about the pre-disposing factors of drug dependence. In this chapter only a few basic practical points will be discussed rather than trying to elucidate psycho-pathological mechanisms.

Many victims of dependence have apparently normal backgrounds. Some simply make the mistake of trying a substance in some social situation which supports the pleasurable affects, and the substance's pharmacology merely takes over, after a variable period of misuse and abuse. Other victims may have personalities which lead them to escape life's normal pressures, therefore their need for mood enhancement or alteration of consciousness can be an additional pressure on the need to continue the substance. This may be particularly true as tolerance develops and dose increase is necessary to attain the initial effect.

Sometimes the reason for a drug use may be understandable. To attempt to elevate the blackness of a bereavement seems to be a perfectly humanitarian aim, but it is starting a pattern of use-to-misuse-to-abuse-to-dependence for some people. Also it seems generally wrong to assume that all life's down times should be "treated". Learned behaviour seems likely to play some part in dependence. The children of parents who use drugs frequently are more likely to be high users and even abusers themselves.

Whatever the background psychology of a substance dependent person, their behaviour must be considered clinically as a mix between their basic psychology, the effects of the drug (e.g. confusion; aggression) and, at various times, the particular drug withdrawal state. How the victim feels and behaves will depend upon the particular timetable of drug use. Chronic drug abusers and dependent people are very aware of this changing state; their lives revolve around it and talking about it to the exclusion of almost all else in some.

By illustration, one patient, one week after being released from a 2 year jail sentence for the possession of drugs, came to try to get a prescription

for barbiturates. On failing to get what he wanted he asked for a city street map and, in the clinic, plotted the doctors who might be an "easy touch" on a bus route. Some weeks later he again came to medical attention in a different way. He had been giving himself injections in the arm veins; they became thrombosed and infected; he used his femoral veins after consulting an anatomy text in the library, accidentally hit the artery which produced a large haematoma. He had noticed he had a large dorsal penile vein; he used that until it thrombosed. He then used a vein in his forehead using a mirror, but finally injected powdered drug into the temporal artery. This caused necrosis over a large area of scalp due to micro-embolisation (good collateral supply does not prevent such a catastrophe!) which needed grafting. Such are the lengths some patients are prepared to go!

Heavily drug dependent people sometimes steal or prostitute themselves to get money. The costs of escalating drug use are high and there is little time left for them to work when they are relatively normal and not looking for the next "fix". It is not surprising that such behaviour is regarded as unacceptable but it must be seen against the uncontrollable desire to get their "fix". This is why there is a debate still about whether it is reasonable to give way to dependant patient's demands for their substances to be available in a similar way to insulin for a diabetic. This approach reduces the risk of dirty injections (therefore avoiding hepatitis B and HIV infection), allows some level of control and knowledge about the sociology of substance abuse, and allows for psychosocial support. The disadvantages are those of a society becoming the main supplier of drugs and even the definite risk of starting or much prolonging a dependant state. The danger of a patient using some of their supply to gain money from other people, is a risk requiring utmost vigilance. The policy of supplying less harmful and dependence producing drug substitutes seems to be a socially acceptable compromise (e.g. using methadone to substitute for heroin). It is an approach used in many countries but is variably successful depending on the degree of motivation of the patient to stop substance abuse, the degree of control and follow up possible, the availability of the preferred substance and most importantly the degree to which the patient finds the substitute an acceptable replacement.

Seriously dependant patients may abuse anything. Multiple substance abuse is common, with the patient trying almost anything offered, even though they may have a preference. Some young people may also try all kinds of available substances under peer pressure, as experiments, with little understanding of risks. In a school where solvent abuse was currently common, a chemistry class was badly supervised at a time when the class was involved in smelling chlorine gas. Several pupils, disregarding warnings from the teacher, inhaled large amounts of gas. Three were admitted to intensive care but survived. The abuse of a wide range of volatile substances varies with time and location, and is best dealt with by educational programmes and product warnings.

Violent acts are a part of the drug abuse scene. Such acts may result from psychosis and excitable states produced by substances such as amphetamines and similar, from frustrated attempts to obtain substances, by merciless substance vendors – the "pushers" (who may themselves be abusers), and from the criminal sub-culture which can attract and prey on those who hopelessly substance dependant. One should take care in managing all situations with substance abusers to avoid personal risk, which must also include the risk of infection with HIV and hepatitis.

The interaction of health professionals to substance abusers can be in four areas.

- Health professionals may carry drugs desirable for drug dependant people and they may therefore be targets for theft, with or without personal violence: they must guard against this risk.
- Health professionals may need to treat dependant individuals for intercurrent disease. Then they should be aware of the risks of HIV and hepatitis to themselves. They need to consider the possibility of interactions with drugs they may prescribe with other substances their patient may be using. The management of pain for example can be considerably complicated by concomitant heroin use. Tolerance to opiates will be present, and some drugs, such as buprenorphine might provoke partial withdrawal states because it competes strongly for opioid receptors, without having the same agonist effect as heroin.
- Some health professionals will find themselves in the situation of treating or managing addiction. For the most part this is an area for experts. It involves social and medical care, psychotherapy and the use of maintenance therapy either with the patients preferred substance or a substitute drug,

for example methadone or buprenorphine for opiate addiction. Many difficult practical and ethical issues can be involved. One common example is the assessment of a patients drug needs. Patients given too much maintenance methadone may sell the drug which is in excess of their needs to other addicts or others. Thus the dose must be very carefully considered and the drug ingestion supervised. In some countries the provision of clean syringes and needles to addicts has raised the ethical issue of whether this encourages the continuation and propagation of intravenous drug use. Since drug use is illegal in many countries, and "pushing" drugs may have severe penalties, even the death sentence in some legislatures, the conflict between providing care for patients and reporting/not reporting patients to the authorities for criminal activity may be very difficult. The crime may not even be directly related to drugs. As mentioned above theft and prostitution are fairly common ways for addicts to find money. It is important not to miss an opportunity, when the patient is well motivated to provide maximal all round help. It is very difficult or impossible to make a poorly motivated give up a serious substance abusing habit. Keeping useful supportive contact with the patient and not being pulled into providing them with drugs is difficult. Patience in monitoring substance abusers is very important to find the time when they may be motivated to change their lifestyle, which often involves much more than giving up abuse. Further discussion of the expert management of addiction is beyond the scope of this book. Suffice it to say this is a therapeutic area for experts.

- More health professionals will be involved in the acute management of addicts in situations where they have taken an inadvertent overdose or have withdrawal. Overdose management is no different from the usual management, with the exception that it may be very difficult to ascertain which substances are involved. Both the patient and relatives or friends may be reluctant to admit to illegal substance abuse. Withdrawal is a different problem. Many addicts will seek supplies of drugs with genuine or acted out withdrawal syndromes and may thus obtain satisfactory supplies of drugs from a series of gullible prescribers. This situation requires care. Consultation with local drug rehabilitation centres and hospitals or colleagues may provide information on the patient if they have given the correct name. On the other hand it is clear that this is time consuming and may be unhelpful. If the genuine patient's demands are ignored some withdrawal syndromes can be severe and even fatal: barbiturate withdrawal can lead to fatal convulsions.
- Health professionals may find that drugs they use during their treatment of pain, anxiety, depression and the use of other psychoactive products may find that they have, or may be in danger of producing therapeutic dependence. Some therapeutic situations lead to a withdrawal syndrome which does not fulfill the criteria of dependence, but can nevertheless lead to difficulties in discontinuing a drug. This may happen with SSRIs, for example, and it is essential to consider whether the problem is related to a need for continuing general support from the health professional which is not drug related, whether the treatment has been discontinued to early with a simple recurrence of the original symptoms or whether there are new symptoms, or worsened symptoms, indicating a true drug withdrawal syndrome.

The best practical advice is as follows. Make as sure as possible that the patients requirement is reasonable and any symptoms genuine. If possible give a single supervised dose, but beware that this could be an excessive dose if the patient thought he was likely to get away without the dosing being supervised. The amount given should be related to the time it should take for the patient to get expert help. You must recommend expert help: if this is immediately available, ideally arrange for secure transport to get the patient there. Do not leave the patient unsupervised in your health care facility. Be sure that you are acting within the law.

III. COMMENTS ON SOME ABUSED SUBSTANCES

Most of the research and results have been focused on the effects of drug therapy on the disorders induced by alcohol, and by opiates abuse. For all drugs, the first objective is to wean the patients from the drug, treating or preventing the effects of withdrawal for those drugs which cause physical dependence (alcohol, nicotine, opiates, caffeine, certain psychotropic agents such as benzodiazepines, possibly antidepressants). The second phase is the prevention of recurrence or relapse, which relies on a com-

bination of social support, psychotherapy, and behavioural approaches, and pharmacotherapy where available.

Note: It is a good general practice to avoid treating the symptoms of use, withdrawal and overdose with other drugs. General support and control are often adequate. On the other hand the use of anticonvulsants should be prompt and the use of other drug supports considered carefully, in relationship to the clinical, psychological and social situation.

III.a. Opiates

On the whole dependence is quite quickly induced, when these drugs are used socially. Experience in terminal care has shown that careful long term control of pain does not usually need escalation of dose.

The withdrawal syndrome starts with flu-like symptoms, yawning and sweating. Next, weakness, chills and "gooseflesh" are added ("cold turkey") and then vomiting, hyperthermia, involuntary movements, hypertension, myalgia. The whole syndrome usually takes about a week to resolution but hypotension, bradycardia and mydriasis may be present for months. Note that miosis is the normal drug effect. Withdrawal is very unpleasant but not usually dangerous.

Treatment of opioid abuse and dependence, beyond the social prevention of complications, especially infectious linked to intravenous use (HIV and hepatitis B), relies on the use of substitutive drugs that can be either pure agonists, or partial agonist-antagonists (methadone, buprenorphine, or more recently naltrexone), with the objective of limiting receptor desensitization and the development of tolerance. The success of the treatment of opiate dependence maybe as much in the re-establishment of healthcare contact and social rehabilitation as in the decrease of the abuse behaviour itself. A systematic review to be found in the Cochrane Library of eight studies involving 423 people concluded that "Although a treatment, like detoxification, that exclusively attenuates the severity of opiate withdrawal symptoms can be at best partially effective for a chronic relapsing disorder like opiate dependence, this type of treatment is an essential step prior to longer-term drug-free treatment and it is desirable to develop adjunct psychosocial approaches that might make detoxification more effective". (See Amato et al., 2004.)

In overdose, managing respiration is essential. Opiate antagonists may be used, but can provoke withdrawal. Dextropropoxephene is dangerous in overdose. Patients on opiates tend to be sleepy and passive.

III.b. Barbiturates

Doctors are prescribing barbiturates less, and the illegal use of barbiturates has also substantially declined, although barbiturate abuse among teenagers may be on the rise compared with the early 1990s. Addiction to barbiturates, however, is uncommon today. Powerful dependence can be produced quickly. The withdrawal syndrome is associated with convulsive behaviour, which must be anticipated and controlled, preceded by a period (about 12 plus hours) of confusion, vomiting and twitching. Barbiturates can be prescribed, but fits may need to be controlled with additional anticonvulsant drugs. Again management of respiration is essential in overdose. A person taking barbiturates is often confused and aggressive.

III.c. Hallucinogens

There are a wide variety of these, including plant products and some solvents. In addition to phencyclidine (PCP or Angeldust), other commonly abused hallucinogens include LSD (lysergic acid diethylamide), psilocybin (mushrooms, "shrooms"), and peyote (a cactus plant containing the active ingredient mescaline). LSD is one of the strongest mood-changing drugs. Under the influence of hallucinogens, people see images, hear sounds, and feel sensations that seem real but do not exist. Some hallucinogens also produce rapid, intense emotional swings. Hallucinogens are used for "tripping" with unpredictable results, giving some "bad trips" with frightening hallucinations and delusions. Many PCP users are brought to emergency rooms because of overdose or because of the drug's unpleasant psychological effects. In a hospital or detention setting, people high on PCP often become violent or suicidal. Sudden death can occur from the use of these substances due to their cardiovascular and nervous stimulation. Keeping the patient from injury whilst the psychic effects are present is a key to management, though restraint may be difficult. Talking to the patient to keep them calm may be very time consuming.

Some patients have attacks of confusion even without taking the substances for variable periods after excessive, so called "flash-backs". The use of tranquillizers and antipsychotics may be needed.

Inhaled substances may be associated with practices and equipment that may lead to suffocation. Commonly abused inhalants include model glue, spray paints, cleaning fluids, gasoline, liquid typewriter correction fluid, and aerosol propellants for deodorants or hair sprays. Most inhalants produce a rapid high that resembles alcohol intoxication. If sufficient amounts are inhaled, nearly all solvents and gases produce a loss of sensation, and even unconsciousness. Adverse effects may include severe organ damage.

III.d. Stimulants

These (including the widely-used Ecstasy) produce excitment, loss of appetite, possibly sexual stimulation, increased motor activity, mania and psychosis often with formication. Sudden death with fits and respiratory depression may occur with high doses, for instance with cocaine. It has been suggested that use at discos, when the subject may dehydrate because of excessive physical activity dancing, is especially dangerous. Rehydration, and general supportive and symptomatic treatment is used as necessary. Ecstasy (3,4-methylenedioxymethamphetamine, MDMA) is a psychoactive drug chemically similar to the stimulant methamphetamine and the hallucinogen mescaline and it therefore has stimulant as well as psychodelic properties.

III.e. Marihuana

This is the most commonly used illegal drug in the US with as its main active chemical is THC (delta-9-tetrahydrocannabinol). On the whole this is not a dangerous substance apart from the long term possibility of carcinogenesis, bronchitis etc. related to smoking it, and chromosome damage. The effect it has is to produce tranquillity and depersonalisation after a period of euphoria and laughter. The conjunctiva is reddened and the blood pressure lowered. Short-term effects include memory and learning problems, distorted perception, and difficulty thinking and solving problems. There have been cases reported of frank psychosis and dementia but these are rare.

III.f. Alcohol

Ethanol has a special place in substance abuse. Its use is almost universally condoned, and many people have benefit from its use unrestricted by legislation. It is a "social enhancer", loosening people's inhibitions, though an excess will lead to irresponsible and aggressive behaviour and is a major cause of morbidity and mortality. Overuse also results in the "hangover" with headache, nausea, weakness and trembling as components, lasting for up to a day following an excess use. Such symptoms are said to be due to cerebral dehydration (from the diuretic affect of alcohol by ADH suppression), from the metabolite acetaldehyde and from the aromatic congeners that are present in some drinks. The extent to which these different mechanisms operate can vary and such variation is illustrated by the wide variety of "hangover cures" and types of drink which should be avoided! Early oral rehydration is a safe preventative and the use of paracetamol in normal doses is useful for headache (alcohol may add to the gut irritation from aspirin, but it may also damage the liver in high doses, adding to the risk of liver damage from paracetamol in excessive doses). An acute toxic state from alcohol is best treated with making sure that the patient cannot harm themselves or others, maintaining the airway (particularly clear from vomitus) and correcting any metabolic upset.

Harmful use of alcohol is common and unfortunately often condoned. Such use includes frequent drunkenness, and the use of alcohol when its effects may be dangerous, for example when driving and operating other machinery. Less obvious, but sometimes disastrous, harmful effects may result from errors of judgement in inter-personal relationships and in decision making in general.

Gastro intestinal bleeding, acute pancreatitis, a toxic confusional state, and acute hepatistis/hepatic failure are each possible results of a very heavy drinking "binge". Heredity appears to play a major role in the contraction of alcoholism, with recent discoveries of genes that influence vulnerability to this disorder.

There are major consequences of alcoholism, from child abuse to domestic or public violence to traffic accidents and from cirrhosis to hypertension. Mean life expectancy of alcohol abusers is around 55 years. Alcohol seems involved in several hundred thousand deaths each year in Europe, with considerable added social and health care costs. This is in clear contrast with the little attention paid to the treatment of alcohol dependence and abuse. *It is important to note that there is an increasing knowledge of similar effects on driving etc. from other psychoactive substances, particularly from the sedative/tranquillizer drugs and antihistamines*.

Frequent and excessive use of alcohol may not in itself indicate dependence, but it is very important to try to ascertain whether the alcohol use is increasing and whether the patient may manage without alcohol, without withdrawal symptoms. Excessive long term use of alcohol, with or without dependency, may result in chronic liver damage and cirrhosis and central nervous system damage with dementia (Wernicke–Korsakoff syndrome). The substitution of alcohol for food leads to malnutrition and thiamine and other vitamin deficiency which exacerbates the CNS damage and is associated with neuropathy, cerebellar dysfunction and memory impairment. Thiamine 50 mg intravenously and then orally daily until a normal diet is taken is useful therapy. Alcohol should be avoided in pregnancy, particularly heavy consumption in the first trimester. The fetal damage which may result is a mental retardation and many other physical abnormalities which are recognisable as a "fetal-alcohol syndrome". Chronic heavy alcohol ingestion has also been linked with an increased risk of cancer of the liver and GI tract, heart disease and with gynaecomastia, testicular atrophy, hypoglycaemia and hyperaldosteronism.

The development of alcoholism is often insidious, proceeding from frequent drunkenness to dependence over years. Since this is so, and since alcohol may interact with other treatment (other psychoactive substances and via its effects on the liver), a careful check of a patient's intake is an important part of the medical history. It is vital to know about alcohol abuse before anaesthesia, since it may make the anaesthetic difficult and alcohol withdrawal may complicate the recovery period.

The withdrawal syndrome from ethanol includes anxiety, insomnia, possibly convulsions and visual hallucinations (delirium tremens – the Dts). It is treated or better still prevented by a calm environment, adequate (but not excessive) hydration, and careful monitoring, with the added use of anticonvulsive/sedative agents, mainly benzodiazepines to prevent or treat convulsions. The preventive effects of benzodiazepines on withdrawal morbidity has been clearly demonstrated. There do not seem to be major differences between benzodiazepines, such as chlordiazepoxide or diazepam or others. Because of the abuse potential in these highly susceptible patients, these should be rapidly weaned, and proper prevention of relapse instituted. Other drugs such as meprobamate and clomethiazole (Hemineurin) are commonly used in some countries. The effectiveness of clomethiazole has not been clearly demonstrated, and it is quite toxic in overdose.

Prevention of relapse: The aims of treatment may be to maintain total abstinence, avoid the cognitive and social consequences of alcoholism, or possibly allow a return to the "normal" social use of alcohol. The latter is rarely obtained, probably because of long-term neuroadaptation to dependence, which make alcoholism a life-long disease, at least in the present state of knowledge and treatment. Disulfiram and other acetaldehyde dehydrogenase inhibitors cause reactions (Antabuse) when alcohol is ingested, forming the basis of aversive therapy associated with behavioural intervention, which with support groups and psychosocial intervention has long been the mainstay of therapy. Prevention of alcoholic relapse through two very different mechanisms not involving aversion, has been demonstrated with two drugs, acamprosate and naltrexone, which act. Naltrexone is essentially an opioid antagonist, whereas acamprosate probably acts through N-methyl-D-aspartic acid (NMDA) receptors. Both have been approved for this indication in several countries. They have been shown to decrease relapse rates, improve short and medium term prognosis, improve compliance to medication and treatment, and possibly, perhaps in some ill defined patient subtypes actually decrease or modify the craving for alcohol. Though at least six months of treatment seems necessary, the effects of long-term treatment, and the optimal duration of treatment are not known: should one treat continuously, treat until patient stability, then stop until eventual relapse. Much work remains to be done in this field, and the emergence of pharmacological tools may provide for a better understanding of possible subtypes, either neurochemical or treatment-related. It can be hoped that the commercial success of a drug in this field will lead to further development of what to most respects is still an orphan field.

III.g. Methanol

Methanol or methyl alcohol can become an alcoholic's main source of alcohol because it is cheaper. Methanol is frequently used as an additive for industrial ethanol to circumvent taxes. Methanol may be purposely adulterated to make it less palatable, but it is used nevertheless! Methanol ingestion can be fatal due to its CNS depressant effects. In addition it is toxic because it is a substrate for alcohol dehydrogenase forming formic acid and formaldehyde which

cause permanent blindness. Early blurring of vision without much confusion should alert to the possibility of methanol use. The smell of formaldehyde is also an indication of methanol ingestion. Ethanol may be used as a treatment for acute methanol intoxication because of its greater affinity for alcohol dehydrogenase, so that less of the formates are produced.

The use of methanol is a dangerous sign in the alcoholic usually indicating that all finances have been used, that the dependancy is high, and that diet is likely to be very poor.

III.h. Nicotine

Cigarette smoking represents a dangerous way of using nicotine. Nicotine itself may have cardiovascular effects which are harmful but not as harmful as the tars and other combustion products including carbon monoxide in cigarette and to a little less extent in pipe and cigar smoke. Consequently there is a current view that to provide nicotine in a safer form is a good step forward even if the nicotine addiction continues. It has been shown that approximately 3–5% of quit attempts succeed using willpower alone and that Nicotine Replacement Therapy (NRT) can double this rate to approximately 6–10% (see Silagy et al., 2004). Nicotine is available as chewing gum and transdermal delivery patches. The chewing gum may have the advantage of controllable delivery depending on how much the subject chews. Chewing gum may also provide the "oral satisfaction" which some smokers feel is part of their habit.

Varenicline is the first approved nicotinic receptor partial agonist. In this respect, it differs from other smoking cessation aids, such as the nicotinic antagonist, bupropion and nicotine replacement therapies. In May 2006, it was approved for sale in the United States. Varenicline increased the odds of successful long-term smoking cessation approximately threefold compared with pharmacologically unassisted quit attempts. In trials reported so far, more participants quit successfully with varenicline than with bupropion (see Cahill et al., 2007).

Better long term results are possibly obtained by combinations with psychological and social programs, together with firm action in public health programs in insisting on smoke free environments. The danger with stigmatizing smokers is that they can become antagonistic and smoke in defiance of what they see as an interfering bureaucracy. On the other hand, there is a health risk for other people from "passive smoking", so that needs to be strongly considered in the public health interest.

The negative impact on public health expenditure and on life expectancy is vast, and health professionals have a duty to educate and warn about the risks of cigarette smoking whenever they reasonably can. Many cigarette smokers stop after they have been ill in other ways and are advised by their doctor concerning the risks to health of smoking: many re-start, but the opportunities that health consultations provide should not be ignored as times when a non-smoking programme can be commenced.

IV. TREATMENT OF CRAVING

Most of the psychoactive substance use problems are characterized by dependence and tolerance. Though the factors involved in the craving (as opposed to the purely physical need to avoid or treat withdrawal symptoms) are largely unknown, there are indications that there is a common pathway involving dopamine. There have been some trials of various drugs applied to alcohol, opiate or other abuses (such as cocaine) other than using the substance itself or congeners (e.g. nicotine gums or patches, or methadone substitution) to treat craving, with unclear success. Drugs that have shown some activity are clonidine, lithium carbonate, and bromocriptine, though much remains to be done in this field.

V. CLINICAL GUIDELINES ON THE DIAGNOSIS OF DRUG DEPENDENCE ARISING IN THERAPEUTIC SITUATIONS

For the purposes of these guidelines only drugs which have psychological effects are considered whether or not such effects are the primary intention of the drug treatment.

V.a. Clinical Features

Unlike drug dependence arising during drug abuse, florid psychiatric symptoms during drug use and the rapid escalation of drug dose are much less frequent. The patient experiences pleasure with the drug, most frequently expressed as an early, excessive or in appropriate expression of its efficacy. This efficacy may not measure up to an objective improvement in the patients presenting complaint. Occasionally the patient may indicate that a pleasurable side effect

such as euphoria or excitability has occurred. The physician must be alert to this situation, since it is easy to be complacent when dealing with a patient who expresses such satisfaction with treatment.

It is at this point that the physician will reconsider the patient's clinical history. Often alcohol or previous drug abuse is hidden by the patient, but direct questioning may elicit such a history indicating a higher risk for dependence. Similarly, psychosocial risk factors for dependence such as chronic anxiety, living alone and having substance dependent or abusing close relatives or friends may be disclosed. These indicators for dependence should in theory have been considered before treatment commenced, however, this guideline is not concerned with prevention and, on many occasions, this information is only obtained by close examination often considered unnecessary by busy clinicians. It is, however, clear that to know ones patient before prescribing potentially dependence producing drugs is a very important step in prevention.

Continuing drug use should lead to tolerance as the dependence develops, though this is not always clinically apparent. In a minority of patients, perhaps about one in ten, this will lead to requests for increasing doses. However, many patients do not make such requests and more commonly tolerance is indicated by the patient expressing lack of effectiveness of treatment. If this situation is not recognised abrupt changes in therapy may lead to some withdrawal effects of the original drug or the patient may seek help from another source leading to "doctor-hopping", or even to help from non-professional sources. At the least this is a situation where the doctor–patient relationship can become difficult with the original clinical problem still requiring management as well as handling withdrawal.

Requests for confirmation of treatment despite apparent lack of effectiveness may be expression of the fact that the patient has already tried to stop the drug but became subjectively worse due to withdrawal rather than the re-emergence of the original symptoms. On the other hand requests for repeat prescription may also indicate a dependence in a therapeutic relationship, the patient needing support and contact. The prescription of a drug is then merely a vehicle which the patient finds acceptable as a reason for approaching the doctor. This may be particularly true for elderly, lonely patients.

The occurrence of withdrawal phenomena are possibly the clearest indication of dependence in the therapeutic situation. On the other hand the diagnosis of a withdrawal syndrome is not easy, and in any case its occurrence is in some way a result of failure to recognise earlier signals and to take appropriate management action including slow drug dose reduction. A withdrawal syndrome may be characterized by the reappearance of the original clinical symptoms prior to drug use in a more severe form as well as the presence of new neuro-psychiatric symptoms such as convulsions. It is possible that a withdrawal syndrome will occur in the neonatal offspring of a dependent mother. Any of these situations should be regarded as strong suspicions of dependence.

The development of a withdrawal syndrome should bear a reasonable relationship with the clearance of the drug, and this may help in distinguishing withdrawal from simple recurrence of symptoms. Similarly withdrawal symptoms will diminish with time whereas, for instance, a chronic anxiety state may persist unchanged. These chronological factors, however, are not always helpful and withdrawal symptoms may persist for many months after drug discontinuation. It is not obvious how to relate these persistent symptoms to the known pharmacology of the drugs and it is possible that they represent a modified constellation of symptoms due to persistence of the underlying psychopathology.

If drug dependence is recognized during treatment, gradual withdrawal of the drug should be used to avoid precipitating clinical symptoms. This reduction may need to be continued over many months, and short half-life drugs substituted for those that have longer half-lives to make the process easier.

VI. REPORTING OF DEPENDENCE

The cardinal features to note which indicate clinical dependence are:

1. Unexpected neuropsychiatric symptoms, which are regarded as pleasurable by the patient, and particularly if they use associated with objective changes in mood or behaviour.
2. The development of tolerance indicated either by reducing drug efficacy or tendency to increase dose.
3. Withdrawal symptoms, even those that may appear only to be related to the presenting illness, particularly when apparently satisfactory clinical management has been utilized.

Strong suspicions of dependence should be reported always. Without such signals improvements in drug use will not be initiated: there is no such thing as a false signal! Work to establish the nature of the causality and other clinical and epidemiological features of drug adverse reaction relationship will always be necessary.

Reporting of suspicions of dependence should be to the national adverse drug reaction centre, but other reporting requirements under national laws must be followed.

VII. PREVENTION

Health professionals must play a part in the prevention of substance abuse and dependence. Legislation and punishment of substance abusers varies considerably in severity in different countries. Punishment may have some deterrent effect, but the heavily dependent person is often so strongly driven by the craving for the substance, they may not have the awareness or appreciation of the risks they are undertaking. For the purveyor of drugs punishment seems to be a useful deterrent; the only difficulty being that many drug users also "push" drugs to get money to feed their habit and to survive.

It is clear that legislation alone will not prevent substance abuse. Education is an essential complement and all health care workers should play their rôle in individual or group education. They should also be good rôle models. Health professionals have easy access to drugs and they must be very careful that they do not fall temptation to the misuse of psychoactive products to alleviate their mood, prevent tiredness, and to combat other stress related symptoms. They should manage their patients along the same lines.

The extensive use of *any* psychoactive substance carries some risk of misuse. This very general assertion is often challenged, but in the author's experience is true to a greater or lesser extent. No patient should be given uncontrolled repeat prescriptions of such substances.

VIII. CONCLUSION

The clinical diagnosis of drug dependence arising during therapy with drugs acting directly or indirectly on control nervous system receptors is always difficult. These type of drugs should always be used with a high index of suspicion, with careful monitoring of the patient for the development of dependence. The diagnosis of dependence and awareness of its possibility in managing patients is extremely important.

Should there be any suspicion of development of dependence, the drug should be discontinued slowly and with adequate support for the patient. Dependence, however, is an adverse reaction which has been reported for a wide range of drugs, controlled and non-controlled. In some situations, treatment needs to be continued despite the manifestation of side-effects, even dependence. For example, in cancer patients suffering from severe pain in terminal illness, opioid medication should be continued whether or not dependence is developing. The concept of risk-benefit balance must always be used in any clinical setting. The suspicion of dependence should be reported at least to the national authorities.

The long term management of dependence is a matter for experts, but other health professionals need to be able to manage acute situations in dependant people, such as inter-current disease, overdose and acute withdrawal. Beware of HIV and hepatitis B, as concurrent problems in intravenous abusers.

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Chapter 17

Clinical Pharmacology of Poisoning

Kenneth Hartigan-Go

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I. INTRODUCTION

I.a. Significance of Poison in Different Societies and Civilization

It was Paracelsus, who in the 16th century stated "all substances are poisons, there is none which is not a poison. The right dose differentiates a poison and a remedy".

Ancient civilizations have come in contact with poisons in nature. Tribes in Africa and in Asia possess a wide range of knowledge of natural poisons which is applied in their daily lives, in hunting, rituals and medicinal cures. The first documentation of the use of natural poisons for their medicinal properties was found in Egyptian papyrus scrolls dated 1550 BC. This was followed later by the Greeks and the Romans who used poisons in political activities and in executions. From the Middle Ages to the Renaissance period, political assassinations using poisons were also common practice. In the 19th century, the Spanish chemist and physician Bonaventura Orfila published his work "Traite des Poisons", which described his scientific procedures for testing animals and developing methods for chemical analysis of identifying poisons in body fluids and tissues, correlating biological and chemical information, hence paving the way for modern toxicology and the application of analytical procedures in forensic science.

Poisoning, which can occur with chemicals and pharmaceuticals, is a global problem. The unfortunate fact about poisoning is that, in many instances, it is entirely preventable. Inadvertent therapeutic overdose due to medical negligence, therapeutic errors and iatrogenic causes, misinterpretation of prescription, accidental ingestion by children because of easy access to medicines, intentional overdose in suicides, intentional doping with drugs for criminal purposes, intoxication following recreational drug abuse are but a few instances when pharmaceutical agents, an indispensable part of our daily lives, can be harmful. The study of toxicology is in fact not emphasized in many parts of the world and, in some cases, is only covered by a few hours of instruction in the undergraduate medical curriculum in developing countries. It is therefore necessary to emphasize to various academic health institutions, as well as clinical centres, that poisoning is a reality that we must deal with. The recognition and the management of pharmaceutical poisoning should be taught to our medical students and doctors if we want to make drugs and drug use safer in our society. This applies also to medicines and their adverse effects, which are often indistinguishable from clear-cut cases of poisoning, because there are features that overlap. Knowledge of adverse drug reactions can be valuable in the management of drug induced poisoning cases.

I.b. Different Branches of the Study of Poisoning

Toxicology, the study of poisoning and the harmful effects of chemicals on living organisms, can be divided into different branches or fields. Descriptive toxicology or experimental toxicology refers to the study of animal toxicity testing, intended to provide

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information that can be later utilised to evaluate the risk posed to humans and the environment. Mechanistic toxicology refers to that branch which studies the mechanisms by which these chemicals produce their toxic effects on living organisms (toxicodynamics). Regulatory toxicology is that branch of toxicology which is concerned with regulating chemicals or drugs that pose a risk to consumers when marketed. This area also establishes the permissible standards of chemicals in air, water, food and medicines. Forensic toxicology or analytical toxicology emphasizes the use of analytical chemistry and fundamental principles of laboratory procedures and may, on many occasions, assist in medicolegal investigations. Environmental toxicology is the study of pollutants on wildlife and its harmful consequences on our ecosystem. Occupational toxicology refers to the specialized study of chemicals and how it affects workers in the industrial or other workplace setting. Clinical toxicology is concerned with disease caused by toxic chemicals and the physician's clinical management of such patients. Clinical trials in medical toxicology, involving human subjects, are neither easy to do nor always possible because of ethical considerations.

I.c. Various Toxicants

There are many different kinds of toxicants. Chemicals that are used for industrial and household purposes can be poison when misused or when there is an accident. Agricultural pesticides in the field can also cause poisoning. Chemicals might come in the form of conventional drugs which we use in a legitimate way, or in the form of designer drugs used illicitly for recreational substance abuse. Natural toxins found in the environment, such as mushrooms, plant toxins, snake/insect toxins and marine toxins, can also inadvertently harm a patient.

I.d. Methods of Poisoning

Exposure to toxicants can vary, producing what is known as acute or chronic poisoning. Poisoning can also be classified according to the intent of use. Poisoning can either be suicidal (non-accidental) or accidental in nature. Recreational poisoning, such as substance abuse, can be a source of harmful intoxication and, in some cases, can lead to addiction and withdrawal symptoms. Intentional harm is observed when there is criminal doping with sedative-hypnotic medicines, often associated with robberies. In some cases, clinical toxicology also has to address issues of occupational (agricultural workers and pesticides, industrial workers and solvents), environmental toxicology and mass poisoning due to chemical disasters. Drug–drug interactions can also be reasons for poisoning. In developing countries, poisonings do occur as a result of misuse of abortifacient drugs.

I.e. Drug Kinetic During Normal Therapy Is Different from Toxicokinetics

Drugs enter our bodies in various ways. Examples of the modes of entry include dermal, oral ingestion, parenteral such as intravenous and intramuscular route, and inhalational routes.

What the body does to the drugs which enter the system may be referred to as pharmacokinetics. During a drug overdose and subsequent intoxication, the various parameters for pharmacokinetics are altered, and these will include changes in elimination half-lives, protein binding, saturation kinetics and excretion. These deviations from the normal pharmacokinetics may be referred to as toxicokinetics.

It is important to know the differences between pharmacokinetics and toxicokinetics as the understanding of these differences will guide the physician in managing the poisoned patient.

II. PREVENTION OF POISONING

II.a. Significance of Prevention

The mainstay of the management of poisoning is really prevention. The information needed to improve prevention can come both in the form of better collection and interpretation of case data on poisoning and/or better communication of risk and harm to those who have to deal with medicines and chemicals. In the clinical sense, physicians will have to inform their patients about the risk or harm from a drug. In the regulatory sense, safety labels and packaging, as well as product information, can be improved to accommodate new warnings. While those who have intention for self-harm cannot be entirely prevented from doing so, there may be ways to minimize these events. It is said that many depressed patients who commit or attempt suicides may have been seen by their doctors at some stage prior to the attempt. It is important for the physician to evaluate their patient thoroughly to prevent another attempt.

Much can be done in the occupational setting starting with education about chemical hazards and risk situations with chemicals as a part of school lessons. Education and informational materials relating to chemical and other hazards should always be provided in the work place. Furthermore, such materials must always be presented in an understandable way.

II.b. Global Efforts on Poisoning Prevention

In 1980, the International Programme on Chemical Safety (IPCS) was established by the World Health Organization, International Labour Organization and the United Nations Environmental Programme following the decision of the World Health Assembly to control and limit the impact of chemicals at the international level. One of the main roles of IPCS is to strengthen national capabilities through technical cooperation in order to respond to the harmful effects of chemical exposure, including drugs. They have been particularly effective in assisting developing countries and supporting national programmes for the prevention and the treatment of poisonings through the setting up of poisons control centres.

One of the activities in poisoning prevention is the INTOX project, a Poison Information Package consisting of a database (peer reviewed poisons information monographs) and an information management system for the standardized method for the collection and analysis of case data on poisoning. Another project of interest is the Antidotes project where IPCS evaluates antidotes used in poisoning management and provides some scientific evaluation of their use. Through toxicovigilance, risk communication, public awareness programmes on risks, education on safe use, and the prevention of exposure to toxic chemicals is being achieved through member countries of the World Health Organization.

II.c. Local Efforts on Poisoning Prevention – Role of Poison Control and Information Services/Centres

In many countries around the world, poison information centres are established to address the concerns of the general public as well as the needs of health professionals in managing a poisoned patient. Historically, the poison centres arose from the need to provide information on the diagnosis and treatment of poisoning cases. In the United States, for example, centres like these were developed by pediatricians in response to numerous accidental childhood poisonings. Soon, other medical specialties and emergency medical services and centres also developed their expertise in toxicology. The information they provide should be timely and accurate and adapted to the situation of the poisoning case. Oftentimes, they participate in the decision making of the clinician in identifying the possible complications that may arise from the incident and finding ways to manage them. This may also include where to source antidotes and how to use them properly. These centres usually have a collection of product registry containing the data on the contents of the products, a treatment protocol on how to handle intoxication, and a telephone hotline to handle emergencies and referrals. In these centres, case data of poisoning are collected and analyzed with the view to promoting educational campaigns to recognize hazards from drug or chemical use and how to prevent them.

There may be merit to consider the cooperation of centres dealing with drugs. Ideally, poison centres, drug information centres, and pharmacovigilance centres for adverse drug reaction monitoring can work collaboratively. ADR cases have been known to be referred to the poison centres while overdose cases may be referred to pharmacovigilance centres. The provision of drug information overlaps with poisons information at times. An educational benefit, apart from not losing valuable case data, might be sharing of library resources, staff expertise, and identification of common problem areas in drug safety and possibly considerable cost savings to the operation of these centres.

III. TREATMENT OF POISONING

III.a. Principles in the Management of Poisoning

The general approach to the management of poisoning can be summarised according to a few principles. These principles of clinical toxicology are easy to remember and follow. One of these is to treat the patient and not the poison. The basic application of sound medical care is more important than to concentrate on the toxic agent used. Because of the medico-legal nature of poisoning cases, it will be in the best interest of the clinician if he could verify, validate or confirm events surrounding the poisoning. Obtaining as good a clinical history as possible

is very important (see below), and it may be necessary to get information also from emergency services personnel, relatives and others, if the patient cannot or will not help. Try to confirm as much information as possible from a third source. Little is known about the effects of drug overdose on pregnancy and their outcome, and it will be necessary for the physician to document whether the poisoned patient might be pregnant.

In a patient who is suspected to have been poisoned, emergency stabilization comes first, followed by clinical evaluation, elimination of the poison or decontamination, promotion of excretion of absorbed poison, administration of antidotes, supportive treatment and observation, and finally disposition.

In emergency stabilization, life-saving measures should always take priority over all other decontamination techniques. We have advocated the following approach: ABCDE.

A stands for provision of airway
B stands for breathing and ventilation
C stands for circulation support
D stands for drug-induced depression (central nervous and respiratory system) and
E for electrolyte and metabolic abnormalities and their correction.

III.b. Managing Medical Complications Associated with Poisoning

III.b.1. Common Emergency Care

Care of the patient's airway, respiratory support, and treatment of cardiovascular abnormalities are all part of the early support that may be required. The needs for these situations are common to all medical emergencies, though in the poisoned patient, potential interactions between therapy and suspected poison(s) must be considered.

One of the common manifestations of unknown poisoning is convulsion. This may be due to the convulsant effect of the poison, the cerebral hypoxia from cardiopulmonary depression or secretions obstructing the ventilation, hypoglycemia, severe muscle spasm, substance abuse withdrawal reactions, or lowering of seizure threshold in an epileptic patient. Treatment of convulsions should be directed towards the etiology. Diazepam or phenytoin may help but this is only palliative, though control of fits may be life saving. Also remember that the effects of any drug which you have to give will be superimposed on the effects of the poison; these may include pharmacodynamic and pharmacokinetic effects.

Another common manifestation is coma. In such cases information on the cause may not be available or may be circumstantial. All patients in coma of unknown etiology should be given the following diagnostic test which may be therapeutic in some cases when patients respond: naloxone (at least 1.2 mg) intravenously administered initially, followed by 0.4 mg every 3–5 minutes for a total of 2 mg dose or 0.03 mg/kg/dose IV in children. If patient recovers consciousness, then consider the possibility of opiate intoxication and treat accordingly. Thiamine (100 mg) followed by 50–100 ml of D_{50-50} are given next if the patient does not respond to naloxone. If the patient responds to thiamine, consider alcohol intoxication and if the patient recovers after dextrose, then consider hypoglycemia. Pyridoxine (5 grams) may be of value specially in cases of isoniazid overdose and if the coma is due to postictal depression following isoniazid convulsions.

III.b.2. Diagnosis

Clinical evaluation means taking a good history and conducting a thorough physical examination. Note the following: time of exposure, mode of exposure, intake of other substances, the circumstances prior to poisoning, current medications, past medical history, any first aid or home remedies that may have been given. Is the poisoning event intentional/self-inflicted or inflicted by others? Is this accidental, acute or chronic? Remember also that there are poisons with delayed signs of toxicity. Some examples are ethylene glycol (after 6 hours or more), salicylates (12 hours), barbiturates (24 hours), paracetamol (36 hours), methanol (48 hours), thyroxine (4 weeks). Physical examination should center on the general status: examine the skin, smell the patient's breath, listen to the lungs and heart, examine the abdomen. Careful neurological examination is essential also. In the presence of an alcoholic breath, do not be too ready to attribute the manifested neurological deficits to ethanol intoxication if head trauma may conceivably be associated.

Toxidrome is a term which is used to describe a constellation of signs and symptoms, which when taken collectively, may characterize the poison in question. This is particularly important if patient has altered sensorium, and there is no reliable informant for a medical history. It may be important to review physical features and the differential diagnosis of the

Table 1. Example of toxidromes

Consciousness	Respiration	Pupils	Other features	Possible agent
Coma	Increase/decrease	Pinpoint		Mushroom
Coma	Increase/decrease	Pinpoint	Hypersalivation, bradycardia, muscle fasciculation and tremors, hyperactive bowel sounds, diarrhea and urinary incontinence; sometimes with smell of petroleum distillates (solvent)	Organophosphate pesticides
Coma	Decrease	Pinpoint	Hypoactive to absent bowel sounds	Opiates
Coma	Decrease or apneustic	Pinpoint	Movement disorder, rigidity, extrapyramidal signs, high grade fever, cardiac arrhythmia	Phenothiazine and haloperidol
Coma	Decrease	Dilated	Arrhythmia, convulsions	Tricyclic antidepressants
Coma	Decrease	Dilated	Hypothermia	Barbiturates or other sedatives
Coma	Increase		Diaphoresis, tinnitus, fever	Salicylates
Coma	Increase/decrease		Seizures, metabolic acidosis	Isoniazid
Agitated	Increase	Dilated	Psychosis, tachycardia, hypertension, insomnia	Methampethamine
Agitated	Increase	Pinpoint	Psychosis, hallucinations	Phencyclidine
Awake or coma		Dilated	Tachycardia, arrhythmia, seizures	Theophylline
Agitated	Increased	Dilated	Hallucinations, hypertension and tachycardia, dry skin, mucous membranes, flushed skin with fever	Anticholinergic drugs

poisoned patient in order to manage cases appropriately (see Table 1).

A point of concern with toxidromes: these are not hard and fast rules and what is classically expected may not be present. Sound clinical judgment is necessary. Do not readily assume that an agitated person coming into the emergency room suffering from hallucination, fever, and body rigidity is a case of abuse of methamphetamine or cocaine or other 'uppers'; it might in fact be bacterial meningitis. If your only tool is a hammer, you might treat each case as a nail!

Laboratory tests are of value but must be interpreted with care because of possible false results. Our experience notes that these tests are only helpful when certain precautions are taken into consideration, and the results correctly interpreted. For example, taking blood specimens too early or too late, or not containing them in proper temperatures (as in the case of erythrocyte cholinesterase determination), can give very misleading results. The timing of samples relative to ingestion must always be recorded and considered in interpretation.

III.b.3. Specific Management Issues

Decontamination may either be external or internal. External decontamination with soap and water are particularly necessary following dermal exposure to toxic agents. There has been some debate about the value of internal gut decontamination. Induction of emesis is not highly recommended currently because the resulting benefits do not necessarily outweigh the risks involved. Gastric lavage may be of benefit only if this is performed early. Activated charcoal appears to be of value for many agents. Cathartics have not been conclusively proven to be of value for most pharmaceutical overdoses, have few benefits and many potential complications. Whole bowel irrigation is an alternative to consider, particularly when dealing with body packers (who transport prohibited

substances by swallowing plastic wrapped material, hoping to recover it intact through defaecation!).

Elimination of absorbed substances may be accomplished by administering multiple dose activated charcoal for poisons with entero-hepatic recirculation or by altering urine pH to promote excretion. Forced diuresis, if warranted, should only be done after carefully exercising precautions such as the provision of adequate hydration and maintaining electrolyte balance.

Antidotal therapy is valuable, but only if the above maneuvers are performed. There are many specific antidotes to poisons but they are seldom necessary or are only useful if appropriate supportive management is provided.

Because many of these cases are suicides, it may be necessary to exercise precautions to prevent future attempts while at home or in the hospital. Supportive management entails carefully noting the clinical and laboratory parameters of improvement while looking actively for any complications of the poisons as well as from the therapy instituted to save the patient's life. Psychiatric evaluation is often necessary in these cases.

Clinicians must learn to appreciate the value of toxicovigilance. This means that preventive activities for poisoning, such as education of the patient and family or peers, could be done. Informing responsible authorities of an index poisoning case could lead to better and concerted epidemiological investigations and perhaps lead to better health warnings and policy modifications.

III.c. Prevention of Further Absorption of Poison: Decontamination

The basic principle in the management of oral overdoses with medicines is to limit further absorption, decrease further exposure and prevent damage. Considering that ingestion is one of the most common methods of poisoning, early decontamination is important. One of the controversial areas of medical toxicology is gastrointestinal decontamination. There are many ways to accomplished this: by induction of emesis pharmacologically, by gastric lavage, by chemical adsorption with activated charcoal, and in the case of alkali and weak acids the use of dilution and neutralization, and cathartics. The controversy appears to follow critical appraisal of gastrointestinal decontamination studies in literature because of inconsistency in protocols and techniques. There is no consensus among emergency room doctors and toxicologists on the methods used in decontamination for mild to moderate poisoning. This section will describe the various methods used in decontamination.

It is safe to say that washing with tepid water and soap, for external poisons (just cold water for the eye) and activated charcoal are the two simple and effective remedies which have the most universal benefit, according to current knowledge.

III.c.1. Emesis

Ipecac or syrup of ipecac is made from the dried rhizome and roots of Cephaelis acuminata or C. Ipecacuanha plant. It contains the alkaloids emetine and cephaeline. Both have emetic properties and can induce nausea and vomiting. When applied, the emetic effect may last for 2 hours with a range of 1–8 episodes of vomiting. This is not a popular method for gastric decontamination because it prolongs the time patients stay at the emergency room and delays activated charcoal administration. Lastly, this is not an efficient method for recovering ingested substances, usually retrieving only around 50% of the substance. There is likewise a fear that there may be propulsion of the gastric contents into the duodenum. While the early and prompt evacuation of ingested substances appears logical, the clinical usefulness of induced emesis remains to be proven. The contraindications to emesis induction include: altered consciousness such as stupor and coma when the presence of impaired gag reflex may lead to aspiration, ingestion of corrosive substances where greater damage to the esophagus and stomach is likely, ingestion of volatile petroleum liquid where the hydrocarbon may be aspirated into the lungs, and likelihood of convulsions.

No studies so far have shown that the use of ipecac in the management of acute oral poisoning modifies patient's clinical outcome and because they can lead to complications and prolonged hospital course, the ipecac carries no role in the routine toxicology management. There may be some acceptable benefit-to-risk in using ipecac but only in rare situations, as found in consensus guideline prepared by the American Association of Poison Control Centers.

III.c.2. Gastric Lavage

This used to be one of the most popular methods for gastric decontamination but should not be considered a routine procedure for all poisoned patients.

It is useless for a non-toxic agent. There are few adequate studies on the matter with the limitation of using undifferentiated poisoned subjects and hence the value for lavage and its outcome are controversial. There is some evidence to suggest that it is effective and better than ipecac-induced emesis.

It has been shown that lavage, together with activated charcoal, may be of benefit if performed within one hour after an oral overdose. This is a technique best undertaken in a hospital setting where the staff is trained. The technique involves a cooperative patient in a left lateral decubitus position, with the head lower than the body to prevent aspiration should the patient vomit unexpectedly. Using a wide bore gauge orogastric tube or a large bore nasogastric tube, ascertain that the tube is in the stomach position by ascultating epigastrum while injecting air into the tube, deliver 200–300 ml of water as aliquots, then allowing it to drain into a collection container. Procedure should continue until the lavage fluid is clear. Warm water appears to confer some benefit in terms of faster removal time and reducing peristalsis which prevents propulsion of the ingested substance into the pylorus. Contraindications to gastric lavage include: ingestion of strong corrosives, hydrocarbons and foaming agents, where the patient has unprotected airways, and when the patient has undergone recent surgery, or is in unstable clinical condition. The complications of gastric lavage include laryngeal spasm, regurgitation of gastric contents, esophago-gastric lesions or perforations, pneumothorax among others.

Current evidence demonstrated no benefit for the use of gastric lavage in the management of acute poisoning patients and may increase the risk for iatrogenic complications.

III.c.3. Chemical Adsorption with Activated Charcoal

Activated charcoal is the product of pyrolysis and destructive distillation of different organic materials such as wood pulp, coconut shell, further treated with high temperature and then with oxidizing gas such as steam, carbon dioxide or strong acids to increase the adsorptive capacity. What results is a fine black powder that has increased surface area (>100 m^2/g) for increase binding activity with drugs, forming a drug-activated charcoal complex.

Activated charcoal efficacy is time-dependent, best when performed early or within 60 minutes of ingestion, or in the setting of sustained release pills or drugs with anticholinergic effects. It is reported to be better than syrup of ipecac and gastric lavage in both efficacy and safety parameters. Charcoal should not be used when the poisoned patient has intestinal obstruction which, aside from vomiting and aspiration, is a reported complication arising from charcoal use. In addition, there are limits to the toxic substances which can be removed by charcoal; these include corrosive agents, cyanide, ethanol, ethylene glycol, iron, lithium, methanol, petroleum distillates.

There appears to be some recent evidence that charcoal has limited clinical efficacy and found not to offer benefit over just supportive care and can prolong hospital course, though some of the results of clinical studies have limitations because of unsatisfactory design. Activated charcoal has not been demonstrated to cause a better clinical outcome for oral poisoning patients and hence is recommended not to be routinely used. While volunteer studies show that charcoal reduced drug absorption, these are of questionable clinical significance when used beyond one hour of toxic ingestions. The potential for its use in clinical setting beyond one hour cannot be excluded.

III.c.4. Chemical Inactivation

This is known also as dilution and neutralization. Ideally, this is never done for the ingestion of non-caustic substances (most medicines) because this is not beneficial and may cause more harm. Dilution as a method for gastrointestinal decontamination has been demonstrated to be harmful because it increased the rate of absorption and hence led to toxicity. Dilution for orally ingested alkaline or weak caustic acids with water may be beneficial if done early (immediately) after exposure. The purpose of this is to decrease the contact time with the oropharyngeal, esophageal and gastric mucosa as well as lessen the heat produced by these chemicals. As a first aid measure, cool water or milk appear to have some value in achieving neutralization. Both dilution and neutralization should never be performed for those patients who have ingested concentrated acids until much of that acid is removed by nasogastric tube (preferably with endoscopy because of the risk of perforation of an already damaged esophagus). Otherwise, the addition of water might produce exothermic heat reaction and liberation of gas. There are many reported cases of caustic ingestions in literature; however, the efficacy of fluid administration for dilution and neutralization has not been thoroughly evaluated.

Potential complications to the use of dilution and neutralization include distention of the stomach, vomiting, aspiration, worsening of the mucosal injuries, and perforation. This procedure should never be done on patients with altered consciousness, as well as on those who are unable to swallow, are in respiratory distress, or in severe abdominal pain.

III.c.5. Cathartics

Cathartics were traditionally used in the management of poisoning as intestinal cleansing agents. The basic theory underlying their use was to decrease gastrointestinal transit time by promoting intestinal evacuation. It has been suggested that salt cathartics also induce secretion of cholecystokinin-pancreozymin which inhibits intestinal water and electrolyte absorption, accelerates gastro-intestinal motility and promotes water secretion. Although local practices and traditions often determine its use in the clinical management of poisoning, the intention was to reduce the bioavailability of slow-release drug preparations, to expel drug–charcoal complex or to prevent potential constipation. However, the present evidence for the use of cathartics in the management of oral drug overdoses is not strong and the experimental data is conflicting when cathartics are used in combination with activated charcoal.

Two general types of cathartics are: (a) the sugar osmotics, like lactulose, mannitol, sorbitol; and (b) poorly absorbed salt cathartics like sodium containing cathartics and magnesium containing cathartics. Cathartics are useless for drugs/chemicals that are either readily absorbable like cyanide or non-toxic agents. Cathartics would be dangerous when given to patients who have ingested caustic agents. In general, cathartics are best avoided in patients with absent bowel sounds that suggest ingestion of poisons which induce paralytic ileus (such as opiates and anticholinergic agents), and following recent bowel surgery. Cathartics should not be used in patients with severe fluid and electrolyte disturbances or used in the extremes of age (i.e. old and young patients).

The evaluation of the contribution on relative efficacy by cathartic agents to the overall management of oral drug overdoses is often difficult because of limitations of human volunteer studies that do not simulate clinical conditions, because of multiple therapies employed, because the dosage for cathartics used were not comparable, and because the expected theoretical effects were not observed. No clinical studies are at hand to study the effect of cathartic, with or without activated charcoal, in reducing the bioavailability of drugs of to improve the outcome of poisoned patients; hence the routine use of cathartic with activated charcoal is not recommended in the clinical management of oral poisoning following drug overdoses.

III.c.6. Whole Bowel Irrigation (WBI)

WBI can be viewed as an extension of cathartics by decreasing systemic availability of oral toxicants. This method rapidly evacuates the gut within 4–6 hours. This method utilizes a high molecular weight polyethylene glycol (PEG-3350) and isomolar electrolyte solution (PEG-ELS). The requirements for this procedure include a small bore (12 Fr) nasogastric tube, a feeding bag and intravenous (IV) pole, a commode, and PEG lavage solution (PEG 3350, sodium chloride, potassium chloride, sodium bicarbonate, sodium sulfate and water).

It eliminates the whole bowel contents by preventing the active transport of sodium and the shift of fluid across the intestinal wall and because PEG is poorly absorbed from the gastrointestinal tract. This technique is considered safe because there are no significant alterations in terms of serum electrolytes and osmolality as might be observed with cathartics, but aspiration, bloating, cramping, and vomiting have been reported. While volunteer studies have reported decreases in drug bioavailability, clinical efficacy and improvement of patient outcome following WBI is still wanting. Current recommendations state that it may be useful as gut decontaminant for very toxic drugs, large overdoses of sustained release drug preparations (prolonged absorption potential), possible iron or lithium poisoning, ingestion of drug packets by body packers or stuffers, ingestion of substances that are not effectively adsorbed by activated charcoal, and radiographic evidence of unabsorbed drug in the GI tract. It should not be used routinely in the management of oral intoxications. Concurrent use of WBI and activated charcoal may limit the charcoal efficacy. Contraindications to WBI use are the same as for cathartics.

III.c.7. Inhalation and Dermal Exposure to Poisons

With exposure to poisons by inhalation, the basic principle is to remove the patient to a well ventilated area. With dermal exposure, and skin contamination,

the rule is to perform immediate flushing with copious amount of tepid water. Water hot enough to cause skin vasodilatation should be avoided on the theoretical grounds of increasing absorption from the surface. All contaminated clothing should be removed, taking care to clean the hair, nails and skin folds.

III.d. Enhanced Elimination of the Poison

III.d.1. Biotransformation

Living organisms are capable of modifying the activity of xenobiotics or toxicants by enzymatic conversion, or biotransformation in the liver. This process will necessarily involve the deactivation of the toxicants (changing them from highly lipophilic, lipophilic to polar compound and then to hydrophilic compounds) through a series of oxidation, reduction, hydrolysis. Further conversion by conjugation reactions occurs, leading eventually to excretion of the toxicants through bile and urine. Saturation of conjugation reactions and glutathione substrate at times of paracetamol overdose can lead to hepatic cell death.

III.d.2. Biliary Excretion

This refers to the use of multiple dose activated charcoal as a means for blocking drugs with enterohepatic recirculation and hence enhancing the biliary excretion of the toxicant. There are several mechanisms by which multidose charcoal works, by the adsorption of unabsorbed drug present in the intestinal tract (usually those that are slowly absorbed such as slow release preparations or in cases of delayed gastric emptying due to tricyclic antidepressants overdose). The adsorption of drugs secreted in the bile stops enterohepatic recirculation. Examples of drugs with enterohepatic circulation are barbiturates, digitalis, tricyclic antidepressants. Adsorption of drugs that penetrate the gut through active secretory mechanism may benefit from multiple dose charcoal, leading to increased elimination.

III.d.3. Urinary Excretion

Forced diuresis should be considered carefully in patients with an impaired ability to handle fluid loads and with electrolyte imbalances, particularly those with renal and heart failure and at the extremes of age.

Drugs and poisons can in principle be removed from the systemic circulation by forced osmotic diuresis. These are theoretical concepts used in the past for the clinical management of poisoned cases; however, they have not been subjected to the benefit of controlled studies. At times, if there is no monitoring of fluid and electrolyte balance and adequate evaluation of the patient's clinical features, there may be more harm than benefit to be derived from using these techniques. Forced osmotic diuresis is accomplished by increasing urine flow through volume loading (isotonic saline solution 500 ml–1 l/hour) and administration of diuretics (i.e. mannitol or furosemide) in order to reduce tubular absorption of urine and enhancing the elimination of toxicants.

Both acid and alkaline manipulation of urine applies the principle of ion-trapping in the renal tubules. However, acid diuresis is not advocated because of the risk of developing myoglobinuria and acute renal failure. The intent of modifying the urine pH toward an acidic side is to promote the excretion of drugs with an alkaline pKa such as phencyclidine or amphetamine.

Urine alkalinization is a treatment modality that increases elimination of poisons by the intravenous administration of sodium bicarbonate to produce urine with a pH of more than or equal to 7.5 and must be supported by high urine flow. This technique might be useful for the elimination of drugs with an acid pKa such as salicylates (but not recommended for phenobarbital intoxication for which multiple-dose activated charcoal is better), chlorpropamide, 2,4-dichlorophenoyacetic acid, diflunisal, fluoride, mecoprop, methotrexate. Complications include severe alkalemia, hypokalemia, hypocalcemia and coronary vasoconstriction.

III.d.4. Dialysis

These are invasive techniques where the blood circulates extra-corporeally through a semipermeable membrane, allowing molecules to diffuse toxic substances passively and remove them from the blood and the body (hemodialysis). The use of hemodialysis for the management of poisoning is of value only if the percentage of free drug in the blood is high and the volume of distribution (V_d) is low; or when the molecules of the toxicant is small (<500 daltons), water-soluble, and with low protein-binding. Examples of drugs which might benefit from hemodialysis are ethanol, methanol, ethylene glycol, lithium and acetylsalicylic acid.

Hemoperfusion is like hemodialysis except that blood is circulated extracorporeally through a column with adsorbent material like resin or charcoal, which binds molecules electrostatically. The molecules likely to be removed are characterized as poorly dialyzable, lipid-soluble, protein bound. Among the indications for hemoperfusion in the management of poisoning include: the presence of a poison in a patient with impairment of excretory system (i.e. damaged kidneys), intoxication of a drug known to produce delayed toxicity or metabolized to a more toxic metabolite (i.e. paraquat or methotrexate), deterioration of the clinical state of the poisoned patient despite conservative therapy (i.e. convulsions or cardiac arrhythmias following theophylline intoxication), or development of coma as a complication.

Hemofiltration is similar to hemoperfusion but where the blood enters a filter pumped by anteriovenous pressure difference. There is a lack of controlled clinical investigations to study the efficacy of all these techniques and there are inherent risks to these procedures, including hypotension, bleeding, air embolism and metabolic imbalance.

III.d.5. Antidote: Antagonism or Chemical Inactivation of an Absorbed Poison

Antidotes can be referred to as therapeutic substances utilized to counteract the toxic actions of a particular xenobiotic. When used in a timely manner, they can improve the outcome of the poisoned patient. There are various mechanisms describing how antidotes work. Antidotes can bind to the poison and thereby neutralize it (i.e. digoxin poisoning treated with fab fragments of digoxin-specific antibodies; heavy metal poisoning and some chelating agents). The metabolism of the toxicant is modified in such a manner that the toxicity is minimized or eliminated (i.e. paracetamol and the use of acetylcysteine). The toxic action of the poison is antagonized at the receptor sites (i.e. benzodiazepines and the use of flumazenil; narcotic overdose and the use of naloxone). The last mechanism of an antidote is to heal or counteract the toxic injury (i.e. warfarin and the use of phytomenadione or vitamin K1). Other examples include pralidoxime/obidoxime and atropine for organophosphate toxicity; ethanol and fomepizole for ethylene glycol and methanol poisoning; glucagon for beta-blocker or calcium blocker overdose; hydroxocobalamin for cyanide toxicity. Some antidotes are rarely used but do provide life-saving potential in managing poisoning. Often the problem is in stocking or having rapid access to these orphan drugs.

IV. CONTINUING CRITICAL CARE

Following active treatment of the poisoned patient, it will be necessary to continue intensive monitoring of the patient. Constant examination of the neurological status is important because metabolic complications such as hypoglycemia may develop. The administration of decontamination and elimination techniques may lead to fluid and electrolyte abnormalities which should be corrected. While treating the patient with antidotes, there might be drug induced adverse events; for instance, administering atropine to an organophosphate intoxicated patient may lead to heightened anticholinergic response.

V. CONCLUSION

Toxicology is an interesting medical discipline. The principles of management are prevention, toxicovigilance and careful assessment of the clinical features of the poisoned patient, and providing timely and appropriate therapy. In most cases, these are symptomatic and supportive measures, on top of decontamination, elimination of the poison, and provision of specific antidotes.

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Section II

Pharmacotherapeutic Products

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Chapter 18

Neurohumoral Transmission

Martin Pfaffendorf

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I. THE AUTONOMIC AND SOMATIC MOTOR NERVOUS SYSTEM

In general there are two possibilities for the transmission of a signal via nerves: an electrical and a chemical transmission. The electrical transmission is effectuated by a continuous or a saltatoric propagation of a fast membrane depolarization, an action potential. This type of transmission is mainly restricted to individual nerve cells where the membrane depolarization starts for example at a site close to the soma and runs down the axon in the direction of the nerve ending which in many cases is part of a synapse with another nerve or a cell from a target organ like a smooth muscle or a glandular cell on the other side of the cleft. The depolarization *per se* is not able to cross the synaptic cleft. At this site the second form of signal transmission is important: the neurohumoral transmission with a presynaptic release and postsynaptic recognition of neurohumoral transmitters.

I.a. Anatomy and General Function

The autonomic or vegetative nervous system is present throughout the periphery in the form of nerves, ganglia and plexuses. It regulates organ functions which adapt the body to the actual requirements and which are not under conscious control. It innervates for example, the cardiovascular system, the gastrointestinal, respiratory and genitourinary tract. Its direct targets are cardiac myocytes, smooth muscle and glandular cells.

Autonomic nerves are formed by two neurons which communicate the efferent signals by neurohumoral transmission in ganglia. The two parts of the nerves are named according to their anatomical location relative to this sites of nerve to nerve signal transmission: preganglionic and postganglionic. The postganglionic neuron hits directly the target organ where it modulates the otherwise independent basal activity.

It is a main anatomical characteristic of this part of the nervous system that the ganglia are situated in the periphery, that is outside the cerebrospinal axis. This forms one of the major differences to the somatic nerves which innervate exclusively skeletal muscles and do not have ganglia outside the central nervous system.

Beside the efferent innervation by the autonomic nervous system there are peripheral afferent sensory fibers which form the autonomic reflex arcs. They play a major role in the transmission of visceral sensations and are responsible for visceral reflexes, for example in the autonomic regulation of the blood pressure.

On the level of the central nervous system the integration of the autonomic system is mainly located in the hypothalamus although there are many loci known where the autonomic and somatic nervous system are integrated as well. On the efferent side the autonomic nervous system can be divided into the sympathetic and the parasympathetic branch. Most of the visceral target organs of the autonomic nervous system are innervated by both, sympathetic and parasympathetic fibers, which commonly mediate opposing effects in the particular structure. In general, the sympathetic influence can be considered as ergotrophic, that is effectuating an energy expenditure, whereas the activity of parasympathetic nerves modulate the system in the direction

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Table 1. Examples of the opposing effects of sympathetic and parasympathetic stimuli on various target organs of the autonomic nervous system

Organ or tissue function	Adrenergic receptor	Adrenergic response	Cholinergic response
Eye			
Radial muscle of the iris	α_1	Contraction (mydriasis)	–
Sphincter of the iris	–	–	Contraction (miosis)
Ciliary muscle	β_2	Relaxation for far vision	Contract for near vision
Heart			
Rate (SA node)	β_1	Increase	Decrease
Contractile force (atrium)	β_1	Increase	Decrease
Contractile force (ventricles)	β_1	Increase	None
Lungs			
Bronchial smooth muscle	β_2	Relaxation	Constriction
Bronchial glands	α_1, β_2	Decreased secretion, increased secretion	Increased secretion
Blood vessels			
Arterioles (viscera, skin, brain)	α_1	Constriction	Dilatation (via EDRF)
Coronary vessels	β_2, (α_1, α_2)	Dilatation (constriction)	Constriction
Skeletal muscle	β_2, (M?)	Dilatation	Dilatation
Veins	α_1	Constriction	–
GI tract			
Walls (tone and motility)	α_2, β_2	Relaxation	Contraction
Sphincters	α_1	Contraction	Relaxation
Urinary bladder			
Detrusor muscle	β_2	Relaxation	Constriction
Trigone sphincter	α_1	Contraction	Relaxation
Uterus	α_1	Contraction	Variable
	β_1	Relaxation (non-pregnant > pregnant)	
Penis, seminal vesicles	α_1	Ejaculation	Erection
Salivary glands	α_1	Increased secretion of K^+ and H_2O	Increased secretion of K^+ and H_2O
	β	Increased secretion of amylase	
Sweat glands	α_1	Increased secretion	Increased secretion (sympathetic)
Liver	β_2	Glycogenolysis	Glycogen synthesis
Fat cells	β (β_3)	Lipolysis	None
Renin secretion	β_1	Increase	None
Insulin secretion	α_2	Decrease	Increase

of a trophotropic state, that is, leading to growth and recuperation. This historic view still holds true, even if it does not provide a mechanistic insight. Beside these functional differences there are anatomical differences. In Table 1 examples of both are given.

The autonomic nervous systems modulates the visceral functions of the organism. A pharmacological interference with the autonomic nervous system offers the possibility to influence this modulation in case of dysfunction. The autonomic nervous system can be divided in a central and a peripheral part. The central part is located in the spinal cord and in the brain stem. The possibilities for a specific pharmacological intervention at this level are therefore quite limited. Especially the efferent part of the peripheral autonomic nervous system forms the target for the pharmacotherapy.

In a anatomical, physiological but also pharmacological sense the autonomic nervous system can be divided in two parts: the parasympathetic and the

sympathetic branch. The sympathetic preganglionic fibers leave the central nervous system exclusively from the spinal cord segments Th1 to L3. In contrast are the preganglionic parasympathetic fibers which join the *nervus oculomotorius*, the *nervus facialis*, the *nervus glossopharyngicus* and, mainly, the *nervus vagus*. Only the fibers innervating the organs in the small pelvis leave the spinal cord at the sacral level (pelvic nerve). The effects of the parasympathetic and sympathetic part of the autonomic nervous system are enumerated in Table 1, in which the different synapses with their respective transmitters are shown. It is obvious that a pharmacological interference with the autonomous nervous system is not restricted to nerves but includes the target organs as well. At this level, which might be a cardiac myocyte, a smooth muscle cell or a glandular cell, the actions of the respective transmitters, released from the postganglionic nerve, can be inhibited or imitated by drugs. According to the transmitters released from the nerve ending peripheral neurons can be subdivided in two groups. First the cholinergic fibers, which synthesize and release acetylcholine as neurotransmitter. To this group belong nearly all efferent fibers leaving the central nervous system so as all preganglionic nerves of the autonomic nervous system, the somatic (non-autonomic) motor fibers innervating the skeletal muscle, the postganglionic parasympathetic fibers and a small number of postganglionic sympathetic neurons. The second type are the adrenergic fiber which synthesize and release noradrenaline as neurotransmitter and which mainly consists of the postganglionic sympathetic neurons. Similar to the nomenclature for nerve fibers drugs are classified as *cholinergic* or *adrenergic*.

A cholinergic drug provokes the same actions at the target organ as the neuronal release of acetylcholine, an adrenergic drug the same as an adrenaline- or noradrenaline-release. Cholinergic receptors are not a homogeneous population but can be subdivided by pharmacological means, that is by different affinities to specific agonists and antagonists. At the level of the sympathetic and parasympathetic ganglia an acetylcholine receptor can be found which is part of a sodium channel in the cell membrane and which has a high affinity to the alkaloid nicotine. A quite similar type of receptor is located on the membrane of skeletal muscle cells on the postsynaptic side neuromotoric junction. The neuronal type of this *nicotinic* acetylcholine receptor can be blocked for example by trimetaphane whereas D-tubocurarine is a blocker of the muscular type of this receptor.

A second type of acetylcholine receptor can be found on the cell surface of parasympathetically innervated visceral organs and in the central nervous system. This receptor is sensitive to the alkaloid muscarine and coupled to guanylnucleotide binding proteins (G-proteins), which are responsible for the intracellular transduction of the signal following the receptor activation. A further pharmacological subclassification of muscarinic acetylcholine receptors into five subpopulations (M_1–M_5) has been made by various antagonists, but has resulted only in one more or less selective drug in therapeutic use (pirenzepine, M_1) so far.

In the sympathetic part of the peripheral autonomic nervous system the situation is less complicated since only the sympathetically innervated visceral organs have receptors sensitive to the transmitter of the postganglionic sympathetic neuron noradrenaline. However, the noradrenaline sensitive receptors, which all belong to the G-protein coupled receptor superfamily, can be subdivided in at least three subtypes: α_1-, α_2- and β_1-adrenoceptors. These receptors are to a similar extent sensitive to adrenaline, a humoral transmitter which is released under sympathetic control from the adrenal medulla. Adrenaline, in contrast to noradrenaline has affinity to a forth type, the β_2-adrenoceptor. In general drug interacting with the autonomous nervous system can be subdivided according to their mechanism of action.

I.a.1. Drugs which Have Affinity to Autonomic Receptors

In the parasympathetic branch this is nicotine at the ganglia and muscarine at the postganglionic level. In the sympathetic nervous system it is nicotine at the ganglion and noradrenaline and adrenaline at the postganglionic level.

The binding of a compound at the receptors at the cell surface of the target organs can result in three different consequences. A drug can mimic the transmitter and thereby activating the receptor. In this case it is an agonist which is called a sympathomimetic or parasympathomimetic drug. Other compounds just bind but do not activate the receptor, thereby preventing the natural agonist to interact with this structure. Such compounds are called antagonists or sympatholytics or parasympatholytics.

There is recent evidence that a third form of interaction is possible. If a receptor system has a basal activity without a receptor–agonist interaction then there exist the possibility of an so-called inverse agonism, that is a drug that actually inhibits the basal activity as a result of its binding to the receptor. This phenomenon has been shown for various sympatholytic drugs.

I.a.2. Drugs which Interact on the Level of the Transmitter Metabolism (Synthesis, Tissue Storage, Release from the Nerve Ending, Elimination)

Since those drugs do not interact directly with the receptors at the target organs but with the neuronal signal transmission they are called indirect acting compounds. The indirect acting parasympathomimetic drugs which are inhibitors of the eliminating enzyme acetylcholine esterase, play a certain role in the therapy of an atonic gut and bladder, the myasthenia gravis and glaucoma. The equivalent in the sympathetic nervous system are the indirect sympathomimetic drugs, which increase the transmitter concentration in the synaptic cleft by releasing noradrenaline and/or inhibiting its re-uptake into the nerve ending. The vasoconstrictive and centrally stimulating amines belong to this group. Furthermore, there are the inhibitors of the enzyme monoaminooxidase (MAO) which reduce the intracellular break down of noradrenaline.

In the sympathetic nervous system there is the possibility to reduce the release of noradrenaline. The alkaloid reserpine is known to interfere with the ability of the postganglionic sympathetic nerves to store noradrenaline. This results in a reduction of the sympathetic tone which is a useful measure in the treatment of essential hypertension. These type of drugs are classified as antisympathotonics.

The release of transmitters from the nerve endings is controlled centrally but also locally. There are receptors on the cell surface of the nerve terminals which are sensitive to the released transmitter. The interaction of these receptors with the transmitter modulates the release in the sense of a feedback. Beside this short term regulation there is a long term adaptation of the target organ to the tone of the autonomous nervous system. Constantly elevated levels of the transmitter in the synaptic cleft lead to a desensitization of the target organ towards the transmitter either by a reduced efficacy of the receptor-G-protein coupling or by a down-regulation of the receptor density at the cell surface. The therapeutic use of an antagonist can restore the sensitivity as has been shown in the case of β-adrenoceptor blocker in heart failure.

In most cases the target organs are innervated by fibers of both branches of the autonomous nervous system, which, under physiological conditions, results in a balanced situation since the transmitters cause functionally opposing effects. In Table 1 examples for this functional antagonism are given together with the receptor subtypes through which these effects are mediated. It should be noted however that there are always limitations to the selectivity of the various agonist for these receptors.

By regulating the tone of one or the other branch the target organ can be influenced in a certain direction and thereby adapt to the actual needs of the organism. An example for the complicated interplay between the both branches of the autonomous nervous system is the nervous control of the urinary bladder. The emptying of the bladder is provoked by a high parasympathetic activity and inhibited by an elevated sympathetic tone. Drugs inhibiting or enhancing the respective branch will either promote or obstruct miction, the latter being a common side effect of parasympatholytics and sympathomimetics.

The adaptation of the function of the visceral organs to the actual requirements of the body is regulated by reflex. Examples for that are the blood pressure regulation, the light-dependent opening of the pupillae and the saliva production. The interplay between both branches of the autonomic nervous system has a strong connection to the mental state. Up to now only postganglionic transmitters of the sympathetic and parasympathetic fibers and their role in regulating the function of the visceral organs have been mentioned. As to be mentioned elsewhere there are other transmitters and hormones which exert a regulatory effect of these structures like histamine, dopamine, serotonin (5-HT), adenosinetriphosphate (ATP), prostanoids, angiotensin II, substance P, enkephalines, etc.

All of those substances have specific binding sites at the respective organs. The occupation of these receptors result in a transmitter-characteristic pattern of effects. These transmitters gain increasing interest as therapeutic targets as well as mechanisms for unwanted biological effects.

II. THE PARASYMPATHETIC SYSTEM

The main precursor of acetylcholine is choline, originating from the aminoacid serin, which is acetylated by the cholineactyltransferase using acetyl coenzyme A as a substrate. In the nerve terminals acetylcholine is stored in vesicles. On an appropriate stimulus, like a fast membrane depolarisation, the vesicles can fuse with the outer cell membrane and liberate their contents into the synapthic cleft (see Fig. 1). This process is dependent on an increase of the intracellular concentration of free calcium ions. After release acetylcholine diffuses through the synaptic cleft, binds and activates the specific receptors at the postsynapthic membrane. Acetylcholine is degraded very rapidly to choline and acetic acid by the enzyme acetylcholine esterase, which is located at the pre- and postsynapthic membrane. Choline is actively taken up by the neuron to serve as substrate for the *de novo* synthesis of acetylcholine. Beside these specific acetylcholine esterases in and around the synaptic cleft there are unspecific esterases (pseudocholine esterase, butyrylcholine esterase) in the plasma which can degrade acetylcholine but other choline esters as well, for example the drug suxamethoniumchloride.

The main effects of acetylcholine are: a reduction in the heart rate and heart contractility; a reduction of the peripheral resistance in the circulation; the stimulation of almost all excretory glands; a contraction of the ciliar muscle in the eye; a stimulation of smooth muscle tone in the gastrointestinal, the genitourinary and the respiratory tract; and a narrowing of the pupillae. It should be realized that the sweat glands are innervated by sympathetic fibers but the transmitter of these postganglionic nerves is acetylcholine. For this reason all measures interfering with the parasympatholytic transmitter acetylcholine do also interfere with the sympathetically controlled function of thermoregulatory sweating. The molecular basis of the acetylcholine effect is the change of membrane permeability for sodium, potassium and calcium ions. At smooth muscle cells, ganglia cells and at skeletal muscle cells acetylcholine increases

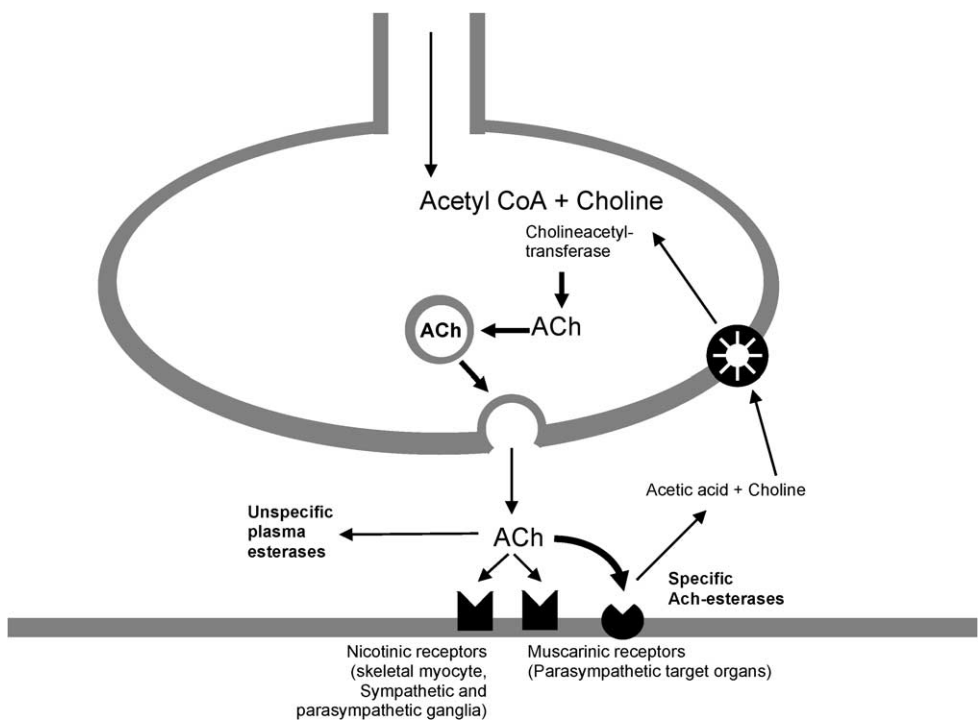


Fig. 1. Schematic drawing of the cholinergic neurotransmission. In case of ganglionic and neuro-muscular synapses, the receptor is of the nicotinic, sodium channel-coupled type, in case of synapses at the parasympathetic target organs, the receptor is of the muscarinic, G-protein-coupled type. The predominant elimination pathway of the transmitter acetylcholine (ACh) is the enzymatic hydrolysis to acetic acid and choline.

the sodium permeability thereby inducing a depolarization of the cell membrane. At pace maker cells in the heart acetylcholine increases the potassium permeability and thereby inducing a hyperpolarization with the result of a decrease in heart rate. At various glandular cells acetylcholine increases mainly the permeability for calcium ions resulting in an enhanced secretory function.

II.a. Parasympathomimetics

II.a.1. Direct Parasympathomimetics

Since the genuine transmitter acting on the muscarinic acetylcholine receptor, acetylcholine, is rapidly degraded by various enzymes it can not be used for systemic therapy. However, acetylcholine can be used locally in the therapy of glaucoma. Accordingly, the main difference of direct parasymapthomimetics and acetylcholine is their resistance to esteratric degradation.

Carbachol, being a carbamic ester and not an alcohol is a far less suitable substrate for the esterases. The indications for carbachol are glaucoma, postoperative atonic states of the urinary bladder and the gut as well as supraventricular paroxysmal tachycardia.

Like carbachol bethanechol is an esterase resistant quaternary ammonium compound which can be used for the same indications.

Pilocarpine is an naturally occurring alkaloid that is only used in the therapy of glaucoma. It induces, like the other parasympathomimetics, a continuous contraction of the *musculus ciliaris*. This results in a narrowing of the pupillae and a concomitant drain of the intra-occular fluid. The effect persists for about 6–12 hours. During this time the patient is shortsighted (myoptic). Since there is a considerable diffusion barrier in the eye all these compounds, when given as eye drops, must be applied in a rather high concentration. In principle all these drugs show the typical signs of an elevated parasympathetic tonus with bardycardia, sweating, pronounced salivary secretion, nausea, emesis and diarrhea. In patients with heart failure, coronary heart disease, bronchial asthma or hyperthyroidism the use of parasympathomimetics should be avoided. All these side effects can be treated effectively by atropine.

II.a.2. Indirect Parasympathomimetics

The inhibitors of the acetylcholine esterase reduce the rate of hydrolysis of acetylcholine since they concentration-dependently reduce the number of active enzymes. The parasympathetic tonus, under physiological conditions, is an equilibrium situation between the release of acetylcholine from the postganglionic nerves and the enzymatic break down of the transmitter. By reducing the elimination at a given release of acetylcholine, the concentration in the synaptic cleft will increase and thereby induce an enhanced parasympathetic tone. This mechanism is not restricted to the parasympathetic target organs but holds true in all other cholinergic synapses like the neuro-muscular junction. The esterase inhibitors can be subdivided in two groups, the carbamate inhibitors and the organophosphorsus inhibitors.

The alkaloid physostigmine and the synthetic compounds edrophonium, neostigmine and pyridostigmine act as reversible inhibitors of the acetylcholine esterase. They are carbamyl esters which are in principle a substrate for the acetylcholine esterase but the hydrolysis is much slower than that of acetylcholine. In contrast to the permanently positively charged compounds neostigmine and pyridostigmine, physostigmine can enter the central nervous system which disqualifies the drug for therapeutic use in peripheral disorders. It is used as an antidot for parasympatholytic drug intoxications.

The ester of the phosphorous acid or organophosphorsus inhibitors of the acetylcholine esterase phosphorylate serine in the active center of the enzyme. The phosphorylated enzyme is extremely stable, resulting in an irreversible inhibition. The duration of action of this compounds is determined by the rate of enzyme synthesis *de novo*.

Organophosphorsus inhibitors have been developed as insecticides (paraoxon, parathion) and for chemical warfare (soman, tabun, sarin). They are extremely toxic and lethal either by cardiac arrest of general paralysis and subsequent suffocation.

The indications of indirect parasympathomimetics are in principle the same as for the directly acting drugs with some exceptions like the treatment of the myasthenia gravis. This weakness of skeletal muscle is most probably due to a reduction of nicotinic acetylcholine receptors on the postsynaptic membrane of the neuromuscular junction on the basis of an autoimmune process against this structure. Since the acetylcholine esterase is present in all cholinergic synapses, these drugs, namely neostigmine and pyridostigmine, can be used to increase the transmitter concentration and thereby improve the

neurotransmission to the skeletal muscle. Parasympatholytic drugs are given to avoid effects at visceral organs due to muscarinic receptor stimulation.

Neostigmine and pyridostigmine are used to reverse the effect of neuromuscular blocking agents like D-tubocurarine, which is used as adjunct medication in general surgery. Various esterase inhibitors have been used with some success in the therapy of degenerative forms of dementia (Alzheimer's disease). The principle is the same as in the treatment of myasthenia gravis: the improvement of an impaired neurotransmission. An essential prerequisite is the ability of those drugs to enter the central nervous system. In this indication the acetylcholine inhibitors tacrine, donepezil, galantamine and rivastigmine are used. Ecothiophat and isoflurophate are used as glaucoma therapeutics.

II.b. Parasympatholytics

Parasympatholytics are specific antagonists at the muscarinic acetylcholine receptor. They inhibit the parasympathetic branch of the autonomous nervous system at the level of the neurotransmission from the postaganlionic neuron to the target organ. With the exception of pirenzepine, which exerts a certain selectivity for the M_1-subtype and the antimuscarinic agents with selectivity for the M_3-subtype and which are used for overactive bladder symptoms, almost all parasympatholytics in therapeutic use are more or less unselective muscarinic antagonists and thereby induce a general inhibition of all respective target organs. Furthermore all drugs in this group are competitive antagonists, that is the inhibitory effect can be overcome by an increase in agonist concentration, which is important in the therapy of intoxications with parasympatholytics.

Atropine, an alkaloid from *Atropa belladonna*, is the classical parasympatholytic compound. It competes with acetylcholine for the binding at the muscarinic receptor. Its affinity towards nicotinic receptors is very low, so that it does not interfere with the ganglionic transmission or the neuromotor transmission, at least in therapeutic dosages. However, in the central nervous system muscarinic receptor do play an important role and while atropine can penetrate the blood–brain barrier it exerts pronounced central effects. Atropine, like all other antagonists of the muscarinic acetylcholine receptor inhibit the stimulatory influence of the parasympathetic branch of the autonomous nervous system. All excretory glands (tear, sweat, salivary, gasto-intestinal, bronchi) are inhibited, resulting in a dry skin, eyes and mouth as a prominent symptom. In the eye the *musculus ciliaris* is paralyzed which results in a widening of the pupillae and the disability of the eyes to accommodate. An impaired visus, photophobia and an increase of the intra-occular pressure are the consequences.

In the cardiovascular system the effect on the heart rate is prominent. The depressive influence of the *nervus vagus* on the pacemaking activity in the heart is concentration dependently reduced and thereby the heart rate increases. This can be therapeutically useful in various forms of bardycardia, especially if they are caused by a vagus overstimulation, for example in the carotis-sinus syndrom. There is hardly any effect on the vasculature except a vasodilatation in the thoracic region after very high doses of atropine.

All smooth muscle activity which is physiologically under a strong parasympathetic influence is effectively inhibited by atropine, for example in the gastrointestinal, genitourinary and respiratory tract. Parasympatholytics are very useful drugs in the treatment of spastic conditions (colic) in these regions.

Parasympatholytics are used to induce a mydriasis in the ophthalmology for the examination of the retina. They are applied locally as drops or ointment. The drug-induced inability of the eyes to accommodate results in a serious, although transient, impairment of the visus. Therefore the long-acting atropine (7–10 days) is replaced by short-acting compounds like homatropine (1–3 days), cyclopentolate (1 day) or tropicamide (6 hours).

In the gastrointestinal tract parasympatholytics are used for the treatment of diarrhea and states of hypermotility as well as for spasms of the bile duct. The gastric secretion can be inhibited by these drugs for the treatment of gastric ulcer. In this indication pirenzepine, a muscarinic antagonist with a certain selectivity for the M_1-subtype, which plays a dominant role in the regulation of gastric secretion, is commonly used. The main advantage is the avoidance of cardiac side effects. Like in most other indications which concern visceral organs compounds with a quaternary amine structure like methylscopolamine, hexocyclium, isopropamide, glycopyrrolate or oxyphenonium should be given, since these compounds are unable to penetrate the central nervous system and are devoid of central side effects.

This holds true for the use of parasympatholytic drugs in the therapy of bardycardia due to vagal overstimulation. Individuals with an overactive

carotis-sinus reflex experience faintness and even syncope as a result of vagal discharge for example as a result of pressing the neck. These patients benefit from a parasympatholytic drug with a quaternary amine structure.

Atropine and other drugs from this group has been a standard preoperative adjuvant therapy in general anesthesia since they inhibit the reflex increase of bronchial secretion due to mechanical irritation (intubation) and volatile anaesthetics.

In asthma bronchiale anticholinergic drugs can be used to relieve bronchial obstruction either by bronchodilatation or by reducing an overproduction of saliva and mucus. Non-central acting drugs should be used in this indication as well (ipatropium, oxitropium). A new development is the long acting tiotropium which is claimed to exert a certain selectivity to the M_3-cholinoceptor, the prominent population of muscarinic receptor in the bronchial system. This effect is due to subtype selective dissociation rates of tiotropium from the receptor. The M_3-cholinoceptor subtype shows the slowest rate of dissociation and thereby its complexes with tiotropim are the most stable ones.

Anticholinergics are the most effective for alleviating symptoms of overactive bladder and reducing episodes of urge incontinence. These drugs include tolterodine, oxybutynin, an oxybutynin skin patch, trospium and solifenacin. Apart from tolterodine, which has affinity for the M_3-cholinoceptor as well as for the M_2-cholinoceptor, these agents have a certain selectivity for the M_3-cholinoceptor. The most common side effects of these drugs are those of all anticholinergics, i.e. dry mouth, decreased gastric motility, headache, constipation, dry eyes and sleepiness.

Parkinson's disease is an unbalance between dopaminergic and muscarineric neurotransmission in the extra pyramidal system due to degenerative processes in the *substantia nigra*. This movement disorder can be treated by an increase of the dopaminergic or a reduction of the muscarinic activity in the *corpus striatum*. Central acting parasympatholytic drugs like benztropine, biperiden, chlorphenoxamine or ethopropazine can be used for the treatment of this disease.

Furthermore, central-acting antimuscarinic drug are effective in the treatment of motion sickness. In this indication the alkaloid scopolamine has been shown to be effective. It can be applied orally, intra venously or via a transdermal therapeutic system.

Parasympatholytic drugs can be used as antidots in the poisoning with cholinomimetics like the afore mentioned organophosphorous compounds. These esterase inhibitors, as used as insecticides, induce a massive increase of the acetylcholine concentration, resulting in a central and peripheral overstimulation of muscarinic receptors. A central-acting antimuscarinic drug can prevent the life-threatening consequences. However, the therapy with a parasympatholytic does not prevent the overstimulation of the nicotinic acetylcholine receptors which can finally induce a general paralysis and suffocation.

Another possibility to treat a poisoning with esterase inhibitors of the organophosphorous type are the so called esterase reactivators: compounds with an oxime structure like obidoxime and pralidoxime. The oxime moiety has a very high affinity for the phosphorous atom and can thereby under certain circumstances hydrolyze the otherwise stable organophosphorous–enzyme complex.

Since muscarinic receptors are widely spread within the organism a selective therapeutic intervention with parasympatholytic drugs is hardly possible. Atropine is able to block all parasympathetic functions in a predictable manner. The severity of the adverse effects depend on the status of the individual patient. Underlying diseases like ischemic heart disease, prostate hyperplasia, glaucoma etc. must be considered as contraindications. In adults atropine is a relatively save drug, even when given in excess dosages. The main symptoms are a flushed dry skin, a non-steroidal anti-inflammatory (NSAID)-insensitive hyperthermia, tachycardia, dry mouth, agitation and delirium, the latter two less pronounced or absent in case of quaternary amines. Children are much more sensitive to the hyperthermic effect of atropine and fatal intoxications have been described even with doses lower than 3 mg.

Since the therapy with esterase inhibitors is not without risk a poisoning with atropine or other parasympatholytic drugs is treated only symptomatically.

II.c. Ganglion-Blocking Drugs

In the adrenal medulla and the ganglia of parasympathetic and sympathetic nerves, the neurotransmission is mediated by acetylcholine. On the postsynaptic membranes the transmitter activates the neuronal-type of the nicotinic acetylcholine receptor. This receptor type is in fact a sodium channel, its activation leads to a sodium influx and a membrane depolarization. A pharmacological interference at the

level of the autonomic ganglia inhibits both branches of the autonomous nervous system. This rather unspecific blockade of the autonomic outflow confers a broad range of effects. Ganglion blocking agents have been developed originally for the reduction of the sympathetic tone on the vascular system and thereby reducing the blood pressure. However, since the parasympathetic ganglia are blocked as well side effects in the organs predominantly innervated by this branch are the common side effects of this type of drugs: dyspepsia, constipation, urinary retention, cycloplegia in the eye with a loss of accommodation and sexual dysfunction. Due to this broad range of unwanted effects ganglia blockers are almost obsolete for clinical use.

Like in the neuromuscular junction the neurotransmission can be inhibited either by receptor blockade (non-depolarizing) or by overstimulation (depolarizing) of the receptors. The alkaloid nicotine, in low doses, stimulates ganglia and the adrenaline release from the adrenal medulla. High doses lead to a continuous depolarization of the postsynaptic membrane and thereby to an inactivation of the neurotransmission. All ganglion blockers in clinical use were synthetic amines of the non-depolarizing type: trimethaphan, hexamethonium and mecamylamide.

The site of inhibition is in case of hexamethonium in the sodium channel, whereas trimethaphan blocks the acetylcholine binding site of the receptor.

Constantly positively charged ganglion blockers like the quaternary amine hexamethonium or the sulfur containing trimethaphane are unable to cross the blood brain barrier and thereby are devoid of central side effects. Mecamylamide, on the other hand, readily enters the central nervous system and has been reported to induce sedation, tremor, and mental aberrations. For the same reason mecamylamide is only orally available.

Nowadays a broad spectrum of quite specific blood pressure lowering drugs is available which restricts the use of ganglion blockade. There are only a few situations in which the pharmacological blockade autonomous ganglia is clinically useful: hypertensive emergencies, controlled hypotension in neurosurgery and in the treatment of pulmonary edema.

II.d. Neuromuscular Blocking Drugs

Similar to the neurotransmission in the autonomous ganglia and the parasympathetic target organs, acetylcholine is the transmitter at the neuromuscular junction, the connection between motoneurons and skeletal muscle cells. The receptors are from the nicotinic type and are, like in the ganglia, sodium channels. The activation of the receptor results in an increase in sodium permeability and thereby leads to a depolarization of the postjunctional membrane. Although similar the receptor is not identical with the neuronal-type of nicotinic acetylcholine-receptor which is evident by a different pattern of sensitivity to various drugs acting on this level. This particular type of receptor is referred to as muscular-type of nicotinic acetylcholine receptor.

Beside this there are some major differences with the neurotransmission in the autonomous nervous system: The contractile activity of the skeletal muscle is almost completely dependent on the innervation. There is no basal tone and a loss of the innervation is identical to a total loss in function of the particular skeletal muscle. In contrast to the target organs of the parasympathetic nervous system the skeletal muscle cells only have acetylcholine receptors at the site of the so-called end-plate, the connection between neuron and muscle cell with the rest of the cell surface being insensitive to the transmitter. The release of acetylcholine results in a postjunctional depolarization which is either above the threshold to induce an action potential and a contraction or below the threshold with no contractile response at all. In contrast to the graduated reactions of the parasympathetic target organs, this is an “all or nothing” transmission.

Like in the parasympathetic and ganglionic neurotransmission, the eliminating enzyme acetylcholine esterase is present at the postsynaptical membrane where it very efficiently reduces the free concentration of the transmitter.

Neurotransmission can be blocked pharmacologically at the level of the neuromuscular junction either by an antagonist which competes with acetylcholine at the binding site without activating the receptor or by an agonist which induce an overstimulation of the receptor and thereby a blockade of the transmission.

Neuro-muscular blocking agents are useful to reduce the activity of skeletal muscle. The main indication is the surgery when the general anaesthetics used are not able to reduce the muscular tone sufficiently. Furthermore, these drugs are useful in the treatment of poisoning or diseases inducing a high motor activity like strychnine intoxication or infection with *Clostridium tetani.* Another indication

is the adjuvant therapy in patients receiving electro shock therapy in the psychiatry.

Two precautions should be kept in mind: Neuromuscular blocking drugs inhibit, concentration-dependently, all skeletal muscles including those necessary for respiration. If these muscles are paralyzed by these drugs artificial respiration must be applied since central or peripheral nerve stimulation, for example with analeptics are useless. Furthermore is it important to realize that the individual subjected to a efficient neuro-muscular blockade is fully conscious and aware of any pain although completely unable to express discomfort.

II.d.1. Non-depolarizing Neuro-Muscular Blocking Agents

The best known example for non-depolarizing type of neuro-muscular blocking agents is the alkaloid D-tubocurarine, which has been used as hunting poison by South American Indians. The sensitivity towards D-tubocurarine varies which makes an individual dosage necessary.

D-tubocurarine can induce a release of histamine which results in a massive drop of blood pressure, an increase of saliva and mucus secretion and laryngal and bronchospasms, which can interfere with the intubation. In patients with asthma bronchiale on an allergic basis the use of this drug should be avoided. Due to its ganglion blocking properties D-tubocurarine can induce a histamine-independent drop in blood pressure.

According its competitive mode of action the effect of non-depolarizing neuro muscular blocking drugs can be overcome by an increase of the acetylcholine concentration, for example, by using esterase inhibitors like neostigmine. This is done either to terminate the paralysis after surgery or in case of intoxications with this type of drugs.

Synthetic compounds are pancuronium, vecuronium, atracurium and gallamine. All drugs of this class currently in clinical use have at least one quatanary amine moiety and are constantly positively charged. This prevents these drugs from crossing the blood–brain barrier and from enteral resorption after oral administration.

II.d.2. Depolarizing Neuro-Muscular Blocking Agents

The second group of neuromuscular blocking drugs are those of the depolarizing type. These compounds resemble the structure of two molecules of acetylcholine. In contrast to D-tubocurarine they do not block but activate the receptor. Since their turnover at the receptor and in the synaptic cleft is much slower than that of acetylcholine, the receptors stay activated and the postjunctional membrane deploarized. Since the exitation–contraction coupling of skeletal muscle cells require repetitive stimulation and subsequent repolarization to maintain muscle tension, a flaccid paralysis results. In this state a further activation is not possible and thereby the system is blocked. The best know depolarizing neuromuscular blocker is succinylcholine. Since it is hydrolyzed by unspecific esterases it has a much shorter duration of action than D-tubocurarine. It is useful either for short lasting applications or for infusion which can be readily controlled.

The disadvantages are side effects caused by ganglionic stimulation: bradycardia with a subsequent tachycardia and a rise in blood pressure. The general depolarization of all skeletal muscles result in a transient increase in potassium in the serum with the possible hazard of cardiac arrest. Patients with nerve damage, neuro-muscular diseases, burns, recent trauma or renal failure have an increased risk of hyperkalemia. Succinylcholine can increase the intra-occular pressure, so that it should be applied with care during eye surgery. A number of patients suffer from muscle pain after succinylcholine, which might result from the generalized activation of all muscle cells. Low doses of D-tubocurarine have been shown to effectively prevent this postoperative pain, although the succinylcholine dosage has be to increased.

Some patients show a hypersensitivity to succinylcholine, which is related to an acquired or inherited dysfunction of unspecific esterases. The reduced rate of elimination results in a more effective and longer duration of action.

III. THE SYMPATHETIC SYSTEM

As mentioned above the efferent sympathetic fibers leave the spinal cord (Th1-L3) as so-called preganglionic neurons, since the signal has be transmitted to a second neuron before the target organ is reached. At this ganglionic transmission from the first to the second sympathetic neuron acetylcholine is always the transmitter. The location of this transmission is either prevertebrally in the cervical ganglia or paravertebrally in the sympathetic ganglion

chain. Numerous sympathetic nerves, like most of the parasympathetic nerves, however, have their ganglia close to or within the target organ. This is especially the case in the gut (Celiac ganglion, Superior mesenteric ganglion, Inferior mesenteric ganglion).

The distal end of the postganglionic sympathetic neurons splits into many small branches. These nerve endings look like a string of pearls with repeated swellings of the cell body, the so-called varicosities. In these structures the neurotransmitter is stored in vesicles. The stimulation of a particular postganglionic sympathetic neuron results in a release of the transmitter at numerous, distinct locations. An adrenergic synapse is shown schematically in Fig. 2. Nerve activity releases the endogenous neurotransmitter noradrenaline (NA) and also smaller amounts of adrenaline from the varicosities. Noradrenaline and adrenaline reach the postsynaptic receptors (adrenoceptors) on the cell membrane of the target organ by diffusion. In Fig. 3 adrenergic neurotransmission is shown. Depending on the particular target organ, the postsynaptic, G-protein coupled receptors are of α_1- (pharmacologically subdivided in α_{1A}, α_{1B}, and α_{1D}), α_2- (pharmacologically subdivided in α_{2A}, α_{2B}, and α_{2C}), β_1-, β_2- and β_3-adrenoceptor subtypes. The classification of α adrenoceptors does not include an α_{1C}-receptor, because the original α_{1C}-receptor was later determined not to be unique and it was reclassified as an α_{1A}-receptor. The precise roles for each of these adrenoceptor subtypes in the regulation of human physiology are not completely defined. The predominant elimination pathway of the transmitter noradrenaline is neuronal re-uptake. Stimulation of postsynaptic receptors occurs either by the endogenous neurotransmitter or by a synthetic agonist, so that an agonist-receptor complex is formed which, according to classic receptor theory, induces a 'stimulus', and consequentely brings about a physiological or pharmacological effect. The 'stimulus' is assumed to stimulate intracellular effector structures. Adrenoceptors on the presynaptic membrane, which are mainly of the α_2-subtype (see inset in Fig. 3), activated by endogenous noradrenaline and also by exogenous agonists, induce inhibition of noradrenaline release, while blockade of these adrenoceptors facilitates neurotransmitter release.

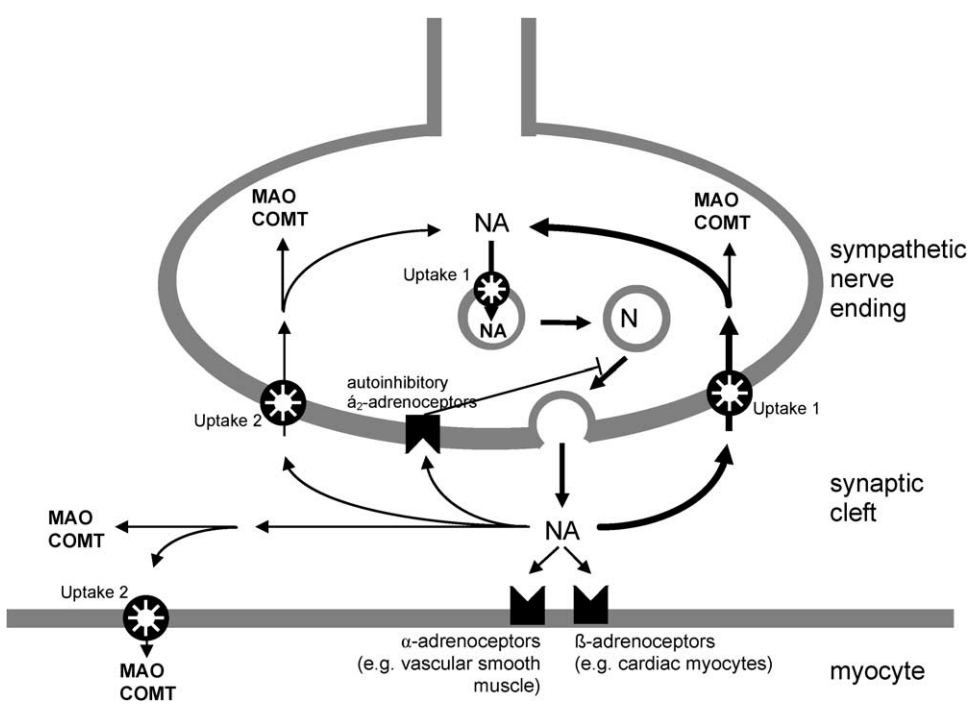


Fig. 2. Schematic drawing of the adrenergic neurotransmission. Dependent on the target organ, the postsynaptic, G-protein-coupled receptors are of the α_1-, α_2- or β_1-adrenoceptor subtype. A presynaptic α_2-adrenoceptor acts as an inhibitory autoreceptor. The predominant elimination pathway of the transmitter noradrenaline (NA) is the neuronal re-uptake (uptake 1, 90%) of noradrenaline.

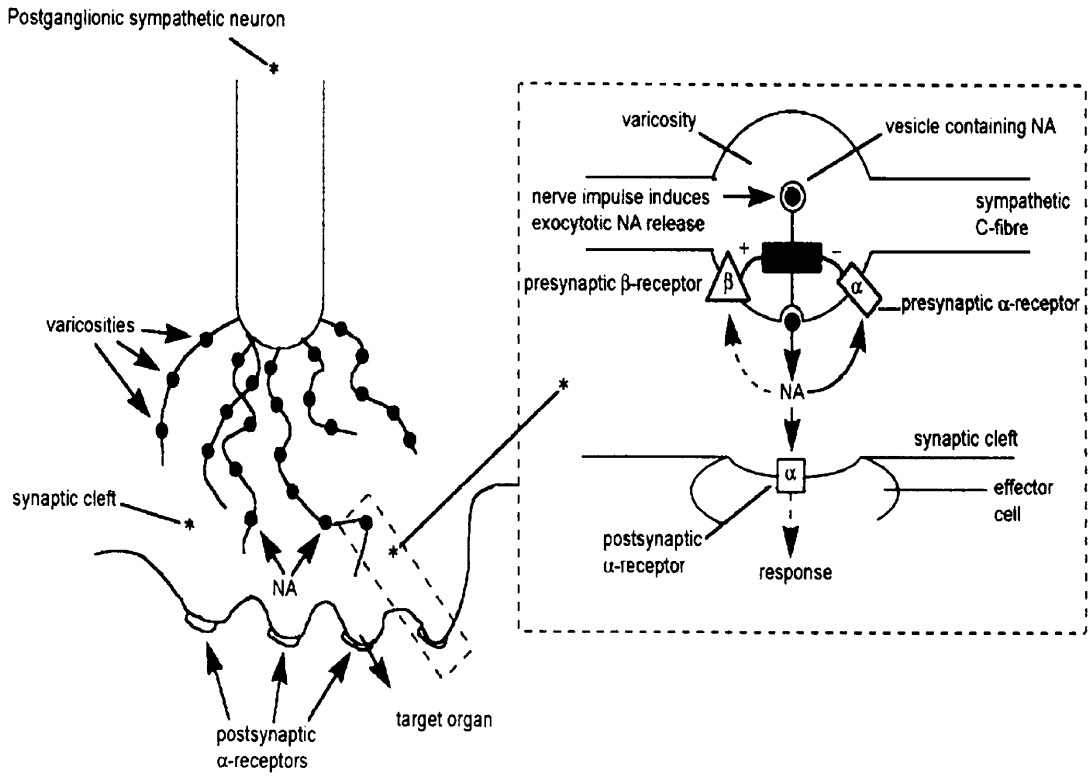


Fig. 3. Schematic drawing of an adrenergic synapse. Nerve activity releases the endogenous neurotransmitter noradrenaline (NA) and small amounts of adrenaline from the varicosities.

If compared to the neuro muscular junction at skeletal muscle the diffusion distance for the transmitter in the synaptic cleft is much longer. Furthermore, the membrane of the target cell is not specialized at the site of the junction but has receptors at the whole surface. In contrast to the all or nothing response of the skeletal muscle cell, the response of the sympathetic target cell to the transmitter is concentration-proportional, or graduated.

III.a. Catecholamines

The neurotransmitters of the sympathetic nervous system are the catecholamines noradrenaline (mainly in the nerve terminals of peripheral nerves and in the central nervous system), adrenaline (mainly in the adrenal medulla) which has to reach the target organs with the blood stream and dopamine.

III.a.1. Noradrenaline and Adrenaline

These transmitters are synthesized from the amino-acid L-tyrosine (see Fig. 4). In the axon and the glandular cells of the adrenal medulla L-tyrosine is hydroxylated enzymatically to L-dopa (dihydroxyphenylalanine) and decarboxylated to dopamine. Dopamine is then taken up by the vesicles. In some neurons, like particular fibres in the substantia nigra, there is no further processing and dopamine serves there as transmitter. In the postganglionic sympathetic neurons and in the adrenal medulla, a further hydroxyl group is introduced in the side chain, resulting in noradrenaline. The glandular cells of the adrenal medulla transform noradrenaline to adrenaline by N-methylation. The membrane of these 500–900 nm vesicles originates form the Golgi apparatus and has to be transported all the way down from the cell soma to the nerve endings. Adrenaline and noradrenaline are stored in high concentrations in these vesicles most probably bound to specific proteins (chromgranins) and ATP.

In the unstimulated state electrostatic forces prevent the melting of the vesicle membranes with the outer cell membrane. If the outer cell membrane is depolarized by either an action potential or acetylcholine (in the adrenal medulla) the electrostatic repulsion is neutralized by positively charged

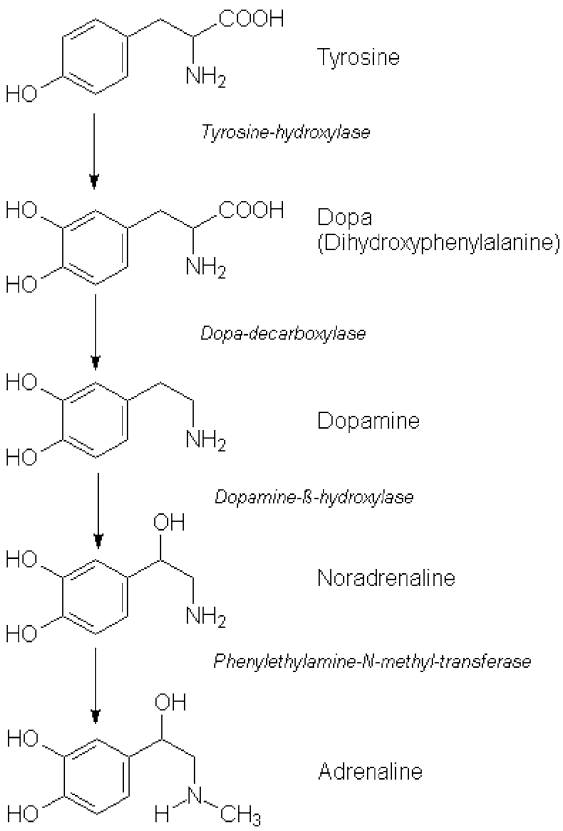


Fig. 4. Pathway of noradrenaline and adrenaline biosynthesis.

ions most probably calcium, and the vesicles fuse with the outer cell membrane and release their contents into the synaptic cleft. Various drugs can interact with this exocytotic emptying of the granules. The vesicular membrane is taken up to the cytosol and reused. This catecholamine release is regulated by presynaptic inhibitory autoreceptors of the α_2-subtype. This negative feedback protects the target organ against an excessive noradrenaline exposition and prevents large amounts of transmitter to escape from the site of release thereby inducing unwanted systemic effects. Other presynaptic inhibitory receptors on the sympathetic nerve endings are the muscarinic acetylcholine receptors.

As mentioned above, the receptors which are sensitive to catecholamines are the so-called adrenoceptors. At least five major subtypes are present and of physiological relevance: the α_1- (pharmacologically subdivided in α_{1A}, α_{1B}, and α_{1D}), α_2- (pharmacologically subdivided in α_{2A}, α_{2B}, and α_{2C}), β_1-, β_2- and β_3-adrenoceptor subtypes, which all belong to the G-protein coupled receptor superfamily.

Adrenoceptors of the α_1- and α_2-subtype are often co-localized on the postsynaptic membrane. β_1-Adrenoceptors are mostly in the close vicinity of the synaptic cleft whereas β_2-adrenoceptors appear to be localized in some distance to this structure. A great number of sympathomimetics and sympatholytics exist which display different affinities towards the different adrenoceptor subtypes. This is of considerable therapeutic relevance.

The occupation of adrenoceptors with the agonistic transmitters result in an interaction with G-proteins which can activate two different mechanisms: either an interaction with intracellular second messenger producing enzymes like the adenylate cyclase and the phospholipase C or a direct interaction with ion channels. Cyclic 3′-5′-adenosine monophosphate (cAMP) which is the product of the adenylate cyclase is a transmitter involved in many cellular processes. It activates proteinkinase A, which transfers phosphate groups to proteins. The phosphorylation of enzymes, for instance changes their metabolic activity. Cardiac calcium channels are also a substrate for the proteinkinase A; the phosphorylated channel has a higher open state probability, which contributes to the positive inotropic effect seen under catecholamines. The actual intracellular concentration of cAMP is the result of the production by the adenylate cyclase and its degradation by the enzyme phosphodiesterase, which by itself forms a target for pharmacological interventions like the inhibitors theophylline or amrinone.

The intracellular signaltransduction of α_1-adrenoceptors is effectuated by a G-protein-dependent activation of the phospholipase C. This enzyme cleaves phosphatidylinositol, a phospholipid present in cell membranes, into inositol-1,4-5-triphosphate (IP_3) and diacylglycerol (DAG). IP_3 is a strong inductor of intracellular calcium release which leads to an increase of smooth muscle tone or the liberation of hormones stored in vesicles. Noradrenaline which is released by exocytosis, spreads by diffusion only. Only a small fraction of the total amount of the transmitter released will actually reach the postsynaptic membrane and bind to its specific receptors. Another fraction escapes the synapic cleft by diffusion and is finally enzymatically degraded in the interstitial fluid. Another fraction is taken up postsynaptically and metabolized enzymatically by the target cells (uptake 2). By far most of the transmitter (90%) is actively taken up by the releasing neuron itself (uptake 1 or neuronal re-uptake). In the

axon noradrenaline is stored in the vesicles again for re-use. The actual tonus of the sympathetic system is a balance of these mechanisms. Any pharmacologically interference, for example by cocaine, indirect sypathomimetics or tricyclic antidepressants, result in a change in sympathetic activity.

In contrast to the highly specific structural requirement for ligands at the various adrenoceptor subtypes the re-uptake mechanism (into the axon and into the vesicle) are less discriminative. Compounds without hydroxyl moieties at the phenyl ring have no affinity towards the adrenoceptors but serve as a substrate for the re-uptake mechanisms, thereby competing with noradrenaline and as a consequence increasing its concentration in the synaptic cleft. Drugs enhancing the sympathetic tone by this mechanism are called indirect sympathomimetics, for example tyramine, ephedrine, amphetamine.

Adrenaline and noradrenaline are unstable in aqueous solution where they are subjected to spontaneous oxidation. In vivo this mechanism is only relevant under pathophysiological conditions of an catecholamine excess, since two enzymes, the catechol-O-methyltransferase (COMT) and the monoamineoxidase (MAO), inactivate physiological amounts of the transmitters. There are at least two subtypes of the enzyme MAO, A and B, which can be inhibited selectively for therapeutic purposes, for example by moclobemide and selegiline.

Noradrenaline is not only present in the sympathetic nerve endings but in the glandular cells of the adrenal medulla as well. The contents of noradrenaline in the medulla is dependent on the functional state of the gland and the species. Noradrenaline is always the precursor of adrenaline. In the central nervous system there are regions with a high noradrenaline content: the hypothalamus and vegetative centers.

Adrenaline is the main hormone released from the adrenal medulla. The glandular cells in this structure correspond to the second, postganglionic neuron of the sympathetic nervous system. Furthermore, adrenaline can be found in chromaffin cells in various tissues. For the better understanding of the function of noradrenaline it is important to realize that this substance, as a neuronal transmitter, affects only the innervated target structure, that is it acts mainly locally. Among these effects are the activation of the *musculus dilatator* to widen the pupillae in response to a reduced light intensity, an increase in heart rate as a response to a blood pressure drop due to a reduction of the peripheral resistance or constriction of small skin vessels to prevent the loss of heat at low ambient temperatures.

In contrast, adrenaline originating from the adrenal medulla always induces a generalized response since it is released into the blood stream. The over all pattern of reactions can be characterized by as an increased state of fitness: the blood pressure increases, the bronchi are dilated and substrates for muscle activity are mobilized from depots (glucose, free fatty acids), the mind and the senses are sharpened. Organ functions which are not particularly necessary are reduced, for instance the activity of the gastrointestinal tract. An increase of adrenaline secretion always takes place if there is a real or imaginative need for an enhanced performance. This is an essential mechanism if it supports physical activity but it might be harmful when activated by mental stress. The latter is an example for the fact that autonomic functions are influenced by the mental state. Another mechanism of an induced adrenaline release with severe pathological consequences is the chronic exposure to the ganglionic stimulator nicotine by the use of tobacco.

Noradrenaline and adrenaline increase blood pressure, although in various organs the perfusion can actually be reduced. Since adrenaline, in contrast to noradrenaline, stimulates α- and β_1-adrenoceptors and the β_2-subtype as well, its vascular effects are more complex than those of noradrenaline. In many vessel beds like the splanchnic area and the skin the α-adrenoceptor-mediated vasoconstriction is dominant. However, in others, like the active skeletal muscles, the β_2-adrenoceptor-mediated vasodilatation increases the blood flow. In the lower concentration range adrenaline induce an increase in blood pressure without elevated diastolic values. Catecholamines reduce the permeability of the vascular endothelium which might be of some importance for their antiallergic properties.

Qualitatively the effects of adrenaline and noradrenaline at the heart is similar, although noradrenaline is somewhat less effective. The β_1-adrenoceptor is the predominant subtype in the heart. The sinus rhythm and the rhythm of secondary pacemakers is increased (positive chronotropy), the excitability is increased (positive bathmotropy), and the velocity of signal propagation is increased (positive dromotropy). With high doses of adrenaline extrasystoles and irregularities develop until ventricular fibrillation occurs. At cardiac arrest adrenaline can induce pacemaker activity. The force of contraction of both, atria and ventricles is increased

(positive inotropy) although the duration of contraction is decreased. The oxygen consumption of the heart is increased over proportionally by catecholamines, that is the heart works more but less efficiently. In patients with a compromised coronary system the increased oxygen demand of the heart by even physiological concentrations of adrenaline can induce episodes of cardiac hypoxia (angina pectoris attacks).

At the bronchi, predominantly β_2-adrenoceptors are present on the smooth muscle cells. Therefor noradrenaline has hardly any influence on the muscular tonus whereas adrenaline induce a dilatation especially of precontracted bronchi, independent of the cause (histamine, acetylcholine, kinines, prostanoides). This effect can be used therapeutically in the therapy of bronchial asthma. In general the local application by aerosol is more useful than the systemic application, due to lesser side effects and the additional, beneficial effect of the reduction of mucosa swelling.

Mydriasis is induced by α_1-adrenoceptor-mediated contraction of the radial pupillary dilator muscle of the iris. Furthermore, activation of this receptor subtype induces an increased outflow of humor from the eye while β-adrenoceptor stimulation mediate an enhanced humor production which contributes to an increased intraocular pressure. β-Adrenoceptor antagonists (β-blocker) can be used in the treatment of glaucoma.

Adrenaline and noradrenaline reduce the peristaltic movements and the frequency of the intestinal smooth muscle both by α- and β-adrenoceptor stimulation. The stimulation of α_2-adrenoceptors at presynaptic neurons in the intestinal plexus reduces the release of activating transmitters, such as acetylcholine.

The effect of catecholamines on the human uterus, which can be mediated by α- and β-adrenoceptors, depends on its functional state. During pregnancy β_2-adrenoceptor stimulation decrease the uteral tonus, an effect that can be used therapeutically. β_2-Adrenoceptor agonists are in use as tocolytics. In the bladder base and the urethral sphincter α-adrenoceptors are present, mediating a contraction, whereas the β_2-adrenoceptors of the bladder wall induce a relaxation of the particular smooth muscles present at these structures. Ejaculation is regulated by α-adrenoceptors.

Catecholamines exert a pronounced effect on intermediary metabolism. An activation of β-adrenoceptors leads to lipolysis and glycogenolysis resulting in increased plasma glucose and free fatty acid levels in the blood. β-Adrenoceptors mediate a potassium uptake into cells and thereby a decrease of the plasma potassium concentration, which is probably important to avoid a rise in plasma potassium during exercise. The β_3-adrenoreceptor plays a major role in lipolysis. But β_3 adrenergic receptors are present not only in adipose tissue but also in human gall bladder, colon, prostate, and skeletal muscle. Their role in these tissues is not well studied. A number of hormone systems are under the control of sympathetic transmitters. Insulin secretion is enhanced by β- and inhibited by α_2-adrenoceptor activation. The same pattern holds true for the renin secretion which might have clinical implications for the therapeutic effect of β_1-blocker. Further target systems are the parathyroid hormone, calcitonine, thyroxine, and gastrin, although the physiological relevance of this control mechanisms are not fully established yet.

Due to the widespread physiological functions, catecholamines can be used clinically for numerous indications. However, specific effects are most commonly associated with unwanted effects. Catecholamines are very potent drugs – 1 mg is a toxic dose – although the interindividual sensitivity can vary considerably.

When applied locally the small arteries close to the surface constrict and thereby reduce the bleeding of open wounds and the swelling of the mucosa, for example in the mouth or nose. The same α-adrenoceptor mediated effect can be used systemically in patients with a circulatory shock which is caused by a vasodilatation.

In patients with cardiac arrest, for example as a result of an intoxication with local anaesthetics, quinine or other cardiodepressant drugs, the stimulatory action of adrenaline on the impulse formation and propagation in the heart can be life saving.

Adrenaline but not noradrenaline is useful in the therapy of bronchial asthma since the dilatory effects on the smooth muscle in this area are mediated via β_2-adrenoceptors. Furthermore, a swelling of the mucosa, which might considerably contribute to the airway resistance, is reduced by β_2-adrenoceptor activation. In this indication selective β_2-mimetics are useful due to less circulatory side effects.

There are various contra-indications for the clinical use of catecholamines. Hyperthyroidism goes together with an abnormal increase of sensitivity of the heart towards the sympathetic transmitters. An atherosclerotic compromised coronary circulation might not be able to sufficiently supply blood

for the unproportional increased oxygen demand induced by catecholamines. A sudden increase in blood pressure may lead to vascular rupture in patients with a generalized atherosclerosis.

Catecholamines, when given in combination with local anaesthetics, can induce gangrene in fingers, toes, penis, nose and ears. Local anaesthesia at these locations should be done without an vasoconstrictive additive.

III.a.2. Dopamine

Dopamine is an intermediate product in the biosynthesis of noradrenaline. Furthermore it is an active transmitter by itself: in basal ganglia (caudate nucleus), the nucleus accumbens, the olfactory tubercle, the central nucleus of the amygdala, the median eminence and some areas in the frontal cortex. It is functionally important, for example in the extra-pyramidal system and the central regulation of emesis. In the periphery specific dopamine receptors (D_1-receptors) can be found in the upper gastrointestinal tract, in which a reduction of motility is mediated, and on vascular smooth muscle cells of splanchnic and renal arteries. Beside its effect on specific D-receptors, dopamine activates, at higher concentrations, α- and β-adrenoceptors as well. Since its clinical profile is different from adrenaline and noradrenaline there are particular indications for dopamine, like situations of circulatory shock with a reduced kidney perfusion. Dopamine can dose-dependently induce nausea, vomiting, tachyarrhythmia and peripheral vasoconstriction. Dopamine can worsen cardiac ischaemia.

III.b. Sympathomimetics

Sympathomimetics are drugs which resemble the phenylalkylamine structure of the catecholamines and induce similar effects as adrenaline and noradrenaline. According to their molecular mechanism there are direct- and indirect-acting sympathomimetic drugs, the latter of which release noradrenaline from and/or inhibit its re-uptake into the presynaptic sympathetic axon.

III.b.1. α-Sympathomimetics

The hydroxyl groups of the phenyl ring are a prerequisite for the activation of all adrenoceptors, if both are absent the molecule has only an indirect sympathomimetic effect (see Fig. 5). Indirect sympathomimetics only have α_1-, α_2- and β_1-adrenoceptor activity since they act via an increase of the noradrenaline concentration in the synaptic cleft. If the methyl-group at the N-position of adrenaline is substituted by a longer or more bulky moiety the molecule gains affinity for the β- and loses affinity for α-adrenoceptors. An isopropyl moiety is already the optimum for the affinity towards β-adrenoceptors (isoprenaline), larger substituents enhance only the binding to the β_2-subtype (for example fenoterol).

The lack of hydroxyl moieties and the introduction of a methyl group to the side chain makes the molecule more lipophilic and thereby increases its ability to enter the system after oral application and cross the blood–brain barrier. This is the case with indirect sympathomimetic drugs of the amphetamine type. The methyl substituent in the side

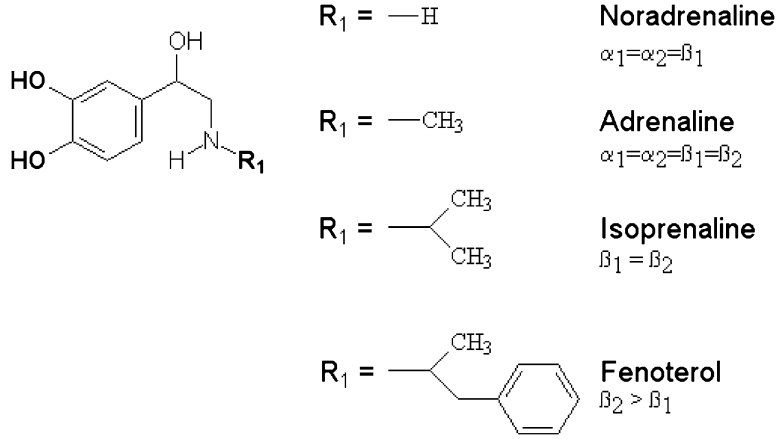


Fig. 5. Influence of substituents at the catecholamine molecule: the hydroxyl-groups at the phenyl-ring are mendantory for any affinity to all adrenoceptor subtypes. The substituent at the nitrogen in the side chain determines the degree of affinity to the particular adrenoceptor subtypes.

chain protects the molecule form degradation by MAO, lacking hydroxyl groups prevent a eliminating metabolism by the COMT.

Other indirect sympathetic mechanisms are the inhibition of the extra neuronal uptake of noradrenaline (uptake 2) by corticosteroids and metanephrine and the inhibition of MAO for example by moclobemide or tranylcypromine.

The indirect sympathomimetic drugs can be used clinically for systemic or local vasoconstriction. Since the mechanism is an increase in the noradrenaline concentration there are always β_1-adrenoceptor-mediated effects like tachycardia and extrasystoles. Since the re-uptake of noradrenaline is necessary to sufficiently refill the axonal vesicles, a frequent use of indirect sympathetic drugs results in a loss of efficacy by transmitter exhaustion. This phenomenon of use-dependent loss of effect is called tachyphylaxis.

Due to their mostly lipophilic character, indirect sympathomimetics are, in contrast to the catecholamines, able to enter the central nervous system. A central stimulation of adrenergic transmission, for example in the cortex and the reticular activating system, results in wakefulness, alertness, a decreased sense of fatigue, an elevation of mood and initiative, self-confidence, an increased ability to concentrate, elation and euphoria. The necessity for sleep is reduced as well as the sense of appetite. Physical performance is improved. The indirect sympathetic ephedrine, an alkaloid from *Ephedra vulgaris*, like cathinone and norpseudoephedrine from *Catha edulis* have been used as psychostimulans since ancient times. Norpseudoephedrine is still in use as anorexic drug. Amphetamine and its derivatives methamphetamine, phenmetrazine and methylphenidate are another example for mainly central acting indirect sympathetic compounds. All these substances have been used as stimulants and for doping purposes. They can induce addiction and play a greater role in forensic medicine than in drug therapy.

This holds true especially for the alkaloid cocaine from *Erythroxylon coca*. Cocain has various mechanisms of action: it is a local anaesthetic and an indirect, central acting sympathomimetic. It increases the effects of released or externally applied catecholamines but reduce the effect of other indirect sympathomimetic drugs.

In contrast to the indirect acting compounds, which always stimulate α_1-, α_2- and β_1-adrenoceptors, direct acting drugs can selectively activate particular subtypes, for example the α_1-adrenoceptors. The drugs in this group, phenylephrine, methoxamine, xyolmetazoline, oxymetazoline or naphazoline are commonly used topically in the therapy of conjunctivitis and rhinitis. The reduction of the blood flow by constriction of the small vessels in the mucosa results in decongestant effect. Various circulatory side effects have been described as well as urinary retention. Centrally-induced shock and coma have occurred in new-born infants, most probably by the penetration of the drugs into the central nervous system across an immature blood–brain barrier.

High doses can induce hypotension especially with compounds showing an affinity for α_2-adrenoceptors like oxymetazoline.

III.b.2. β-Sympathomimetics

While the inhibition of noradrenaline re-uptake exerts predominantly an α-adrenergic effect, a selective β-adrenergic effect can not be obtained by such an indirect mechanism. All selective β-sympathomimetics activate the receptors, β_1-, β_2- or both subtypes, directly. The first pure β-sympathomimetic in clinical use was isoproterenol which is structurally identical to adrenaline except the methyl-moiety at the N-position in the side-chain is replaced by an isopropyl-group. All effects produced by isoproterenol are due to either β_1- or β_2-adrenoceptor stimulation: tachycardia, increased stroke volume, decreased vascular resistance, broncho dilatation and, in pregnancy, uterus relaxation. The metabolic effects of isoproterenol are less pronounced than those of adrenaline.

The indications are bronchial asthma, cardiogenic or septic shock, cardiac arrest and premature labor.

III.b.3. β_2-Sympathomimetics

For all indications without an involvement of the heart the β_1-effects are unwanted. Therefore efforts have been made to develop selective β_2-sympathomimetic. By further increasing the size of the substituent at the N-position in the side-chain (beyond isopropyl) and altering the position of the hydroxyl-moieties at the phenylring, compounds emerge with a much higher affinity towards β_2- than β_1-adrenoceptors, for example orciprenaline, salbutamol, fenoterol and terbutaline. These drugs, which have all have a much longer duration of action than isoproterenol, are used in the therapy of bronchial asthma and to inhibit uterine motility in obstetrics.

Although the cardiac side effects are considerably reduced, metabolic effects occur under the therapy with this β_2-sympathomimetics: increased plasma levels of free fatty acids, glucose and ketones. In diabetic patients a hyperglycaemic ketoacidosis can be induced. All β_2-sympathomimetics reduce the potassium plasma level.

III.b.4. Tocolytics

Ritodrine was the first β_2-adrenergic agonist to be used as a tocolytic in late pregnancy. It was infused i.v. while carefully monitoring maternal and fetal cardiovascular and metabolic parameters. Terbutaline, salbutamol, isoxsuprine and other substances have been used as tocolytics since then. They have been developed to prolong action by metabolic stability but in spite of a long half-life the β-mimetics use to loose efficacy within 48 hours due to tachyphylaxis. The reduction in receptor density as a result of continous stimulation is the reason for this phenomenon. Pulsatile application of short acting β-adrenoceptor agonists might overcome this problem but there exists little experience with this form of treatment. Although these drugs have been given orally there is little evidence that they are effective when applied via this route. Preterm labor can be delayed for 48–72 hours by these drugs. The main problem of the therapy with β_2-mimetics are the extra uterine effects of these agonists. The lack of absolute uterine selectivity is due to the fact that these drugs always keep a certain β_1-activity and that β_2-adrenoceptors are located in other tissues as well. Therefore maternal hypotension, as a result of a peripheral vasodilatation, and maternal and fetal tachycardia are common side effects which actually cause considerable discomfort in the patients. The increased hepatic glycolysis results in an increased insulin secretion and cellular potassium uptake. The hypokalaemia can cause cardiac dysrhythmias. Fetal hypoglycaemia might result from prolonged maternal hyperinsulinaemia. In combination with salt-retaining glucocorticoides β-mimetics can induce pulmonary edema with potentially fatal consequences. The fluid intake must be restricted under these conditions.

Inhibitors of the prostaglandin synthesis like indomethacin have been used as tocolytics as well. Since prostaglandin E_2 is necessary to maintain patency of the ductus arteriosus of the unborn child, at least in the last trimester, their use should be restricted to maximally 48 hours. There seems to be an increased incidence of intracranial hemorrhage and necrotizing enterocolitis in neonates receiving indomethacin. Concerning the mother, the side effects of cyclooxigenase inhibitors are the typical NSAID-like: gastrointestinal bleeding, nausea and headaches. If at all, cyclooxigenase inhibitors are applied as rectal suppository followed by oral maintenance therapy.

Magnesium sulfate, applied intravenously is often used as tocolytic. The mechanism of action is not completely clear but might involve a competition with calcium on the cellular level. Precautions in the sense of magnesium plasma level monitoring must be taken in patients with renal insufficiency since this divalent kation is eliminated by the kidneys. Relatively high plasma concentrations are necessary to achieve a sufficient tocolysis. The relatively frequent side effects are respiratory depression, depressed reflexes, headaches, palpitation and skin flushing in the mother and muscle relaxation and, rarely, CNS depression in the fetus.

A recent Cochrane review failed to demonstrate the advantage of oxytocin receptor antagonists for women with preterm labour as a form of tocolytic therapy. Possible side effects are nausea, vomiting and headache in the mother. Oxytocin receptor antagonists for preterm labour do not improve infant outcomes more than placebo or other tocolytics.

III.c. Sympatholytics

Under various pathological conditions the inhibition of the sympathetic nervous system is therapeutically useful, like the reduction of the vascular resistance and the reduction in heart rate.

There are two types of sympatholytics: those with a direct and an indirect mechanism of action. The direct sympatholytics act via the inhibition of adrenoceptors by competing as antagonists with the transmitters for the binding site. The indirect acting drugs, the so-called antisympathotonics, interfere with the central regulation and/or the peripheral mechanisms of sympathetic transmitter release.

III.c.1. α-Adrenoceptor Blockers

The main indication for an inhibition of α-adrenoceptors is an increased blood pressure. Drugs like prazosine, doxazosine or terazosine block selectively α_1-adrenoceptors, resulting in a relaxation of resistance arteries, arteriols and venules. This subtype selectivity, leaving the α_2-mediated autofeedback control unaltered, may be the cause for

the lesser degree of reflex tachycardia when compared to unselective α_1-, α_2-adrenoceptor blockers such as phenoxybenzamine and phentolamine. Phenoxybenzamine is an irreversible blocker of both α-adrenoceptor subtypes. Its duration of action is determined by the *de novo* synthesis of receptor proteins. Drugs without subtype selectivity are used mainly in the therapy of conditions associated with an exaggerated catecholamine release such as pheochromocytoma. α-Blocking drugs can induce postural hypotension. Other, less frequent side effects are a reduced pupillary dilator tone, decreased adrenergic sweating and nasal stuffiness. The urinary bladder sphincter is inhibited resulting in a decreased resistance to the flow of urine, an effect that is used in the therapy of urinary obstruction. Tamsulosine and alfuzosine are newer α_1-adrenoceptor blockers mainly used in the treatment of benign prostatic hyperplasia.

III.c.2. β-Adrenoceptor Blockers

The sympatholytics of this type interfere with the β_1- and β_2-adrenoceptor subtypes. Via this mechanism the stimulating influence of the sympathetic nervous system on the heart and the metabolism and its inhibiting influence on smooth muscle is blocked. β-Adrenoceptor blocking agents, or β-blockers, mostly have a typical isoproterenol-like structure with an isopropylamine or a tertiary butylamine group and a substituted phenoxy moiety bound to the isopropanol backbone. The substituents determine the physicochemical properties of the particular drug and thereby its pharmacokinetic profile.

Some of the compounds, like propranolol, labetalol, pindolol and metoprolol, have membrane-stabilizing, local anaesthetic properties, which can, at high concentrations, induce a catecholamine-insensitive cardiodepressant effect.

Due to the numerous indications for these type of drugs a large number of compounds have been introduced into therapy. Differences between these drugs concern their affinity profile towards the β_1- and β_2-adrenoceptors, the lipophilicity and the ability to partially activate the receptor (intrinsic sympathomimetic activity, ISA). One isomer of the racemic mixture of labetalol and carvedilol are α-blocker as well. Although this might be therapeutically useful in the treatment of conditions like hypertension and heart failure, there is no real evidence for a contribution of this property to the overall beneficial effect of these compounds.

Pindolol, oxprenolol, acebutolol and alprenolol are β-blocker ISA. A weak sympathomimetic effect can be seen in the heart if almost all β-adrenoceptors are occupied by these compounds. The advantage of ISA might be that a basal β-adrenergic stimulus is left. In some vessel beds a reduction of the vascular activity and thereby a reduction in resistance has been observed with pindolol which might be beneficial in the therapy of hypertension. The pharmacodynamic and -kinetic properties of some frequently used β-blocker are shown in Table 2.

Most of the indications for β-blockers concern the β_1-adrenoceptor. This subtype is predominantly present in the heart, mediating all typical cardiac effects like positive inotropy, chronotropy and dromotropy. The main indications are hypertension, ischemic heart disease, cardiac arrhythmias and some forms of congestive heart failure. The mechanism by which β-blocker, when administered chronically, can reduce the blood pressure is not completely understood yet. Most probably several mechanisms,

Table 2. Properties of various β-blocker

Compound	Selectivity	ISA	Local anaesthetic	Half-life	Bioavailability (in %)	Remarks
Acebutolol	β_1	Yes	Yes	3–4 h	50	
Atenolol	β_1	No	No	6–9 h	40	
Carvedilol	None	No	Yes	4–8 h	25	α-blocker
Esmolol	β_1	No	No	10 min	–	
Labetalol	None	No	Yes	5 h	30	α-blocker
Metoprolol	β_1	No	Yes	3–4 h	50	
Nadolol	None	No	No	14–24 h	33	
Pindolol	None	Yes	Yes	3–4 h	90	
Propranolol	None	No	Yes	3.5–6 h	30	
Sotalol	None	No	No	13 h	90	Class III antiarrhythmic
Timolol	None	No	No	4–5 h	50	

like the reduction of the stroke volume and the reduced renin-release from the juxta-glomerular apparatus, are responsible for this effect. In ischemic heart diseases, like angina pectoris, β-blocker can prevent the imbalance between oxygen supply and oxygen demand which often is the result of an increased sympathetic stimulation of the heart. The effectiveness of this therapy, for example as secondary prevention, has been proven in large scale clinical trials investigating the mortality of patients who survived a first myocardial infarction.

β-Blockers are antiarrhythmics of class II according to the Vaughan–Williams classification, effective in the treatment of both supraventricular and ventricular tachyarrhythmias. These drugs can also reduce ectopic beats, especially if they are a result of sympathetic activity. Sotalol is a racemic mixture of the β-blocking L-isomer and the class III antiarrhythmic D-isomer. This racemic mixture as well as D-sotalol are used as class III-antiarrhythmic.

The use of β-blocker in congestive heart failure is a relatively new therapeutic approach which seems to be a paradox. Patients with heart failure, at least in the advanced stages, have a high sympathetic outflow. The β-adrenoceptor stimulation was though of being necessary to keep the heart going. However, clinical trials have shown that β-adrenoceptor blockade is beneficial in terms of survival and reduced morbidity which might be due to the fact that under these conditions the number of receptors, which have been down-regulated by excessive sympathetic stimulation, is restored. This re-gained sensitivity as well as the reduced velocity of ventricular ejection might be the explanation for this phenomenon. However, β-blocker should be used with great caution in this indication.

Beside the cardiac indications β-blockers can be used in the therapy of glaucoma. Systemic but also the local application of these compounds can reduce intraocular pressure. The mechanism of this action is a reduced production of aqueous humor by the ciliary body. Although applied locally, β-blockers might be absorbed in sufficient amounts to induce systemic side effects in susceptible individuals.

Hyperthyroidism is characterized by an enhanced sympathetic activity, especially in the heart. The salutary inhibition of β-adrenoceptors under these conditions can be achieved by all β-blocker alike. Some of the clinically used compounds are able to reduce the conversion (de-iodination) of thyroxine (T_4) to the active 3,5,3′-Triiodothyronine (T_3) as well. This effect might be especially beneficial in the treatment of thyroid storm. In the case of the racemic propranolol it has been shown that the (+)-isomer inhibits the de-ionidation whereas the β-adrenoceptor blocking (−)-propranolol does not.

There are various neurologic disorders which can be treated with β-blockers like migraine, certain forms of tremor and alcohol withdrawal syndrome. Somatic manifestations of anxiety respond well to β-adrenoceptor blockade. β-Blockers with a selectivity for the β_1-subtype might be useful to avoid extracardial side effects.

It has to be realized that adrenergic receptor sensitivity as well as the pharmacokinetics of the compounds that interact with these receptors are under genetic control. Genetic polymorphism of the metabolism of e.g. propranolol is of clinical importance as is probably also the sensitivity for e.g. β_2 mimetics.

In general the side-effects of β-blockers result from an imbalance of the autonomic innervation. In the heart this might lead to an inhibition of the excitation propagation resulting in AV-block and arrhythmia, especially when given in combination with other antiarrhythmics and non-dihydropyridine calcium-antagonists. After acute myocardial infarction or under conditions of a compensated congestive heart failure β-blockers may induce cardiac decompensation by removing a necessary stimulus. The blockade of the β_2-subtype leads to a vasoconstriction especially in the skin which can induce the sense of cold hands and feet. In rare cases it can provoke Raynaud-like symptoms, the exacerbation of psoriasis or an induction of psoriasis-like exanthema. Several central side effects have been described for β-blockers like depression, with or without insomnia, sedation, hallucinations and agitation. Hydrophilic compounds seem to induce central side effects less frequently.

Since the bronchial tonus is under the relaxant influence of β_2-adrenoceptor stimulation, especially unselective β-blockers increase the respiratory resistance. In susceptible patients this might induce airway obstruction or even acute asthma. The blockade of β_2-adrenoceptors inhibits the mobilization of free fatty acids and glucose. This might result in hypoglycemia in diabetic patients. Furthermore, these patients will be not aware of the danger since most of the sympathetically mediated alerting symptoms like tachycardia are suppressed by the β-blockers as well. β_1-Selective blockers show this type of side-effect less pronounced than unselective compounds.

III.c.3. Antisympathotonics

Since the main clinical use for antisympathotonics is in the treatment of essential hypertension, such drugs will be discussed in Chapter 20 in more detail. The alkaloid reserpine from *Rauwolfia serpentina* was the first drug used clinically to reduce sympathetic tone. Reserpine reduce the ability of storage and release of various transmitters (adrenaline, noradrenaline, serotonine and dopamine) by an irreversible destruction of the axonal vesicle membranes. The duration of the reserpine effect is actually determined by the de novo synthesis of these structure. Beside various central side effects like sedation, depression, lassitude and nightmares the pattern of unwanted effects of reserpine is determined by the shift of the autonomic balance towards the parasympathetic branch: myosis, congested nostrils, an altered saliva production, increased gastric acid production, bardycardia and diarrhea. As a consequence of the inhibition of central dopamine release, reserpine infrequently shows Parkinson-like disturbances of the extrapyramidal system.

Like reserpine guanethidine interferes with the ability of vesicular transmitter storage. In contrast to reserpine, guanethidine is unable to enter the central nervous system and is therefore void of any centrally mediated side effects.

The activation α_2-adrenoceptors is particularly important in the negative feedback control of adrenergic outflow, centrally in the vasomotor centers and peripherally at the presynaptic axonal membrane of adrenergic neurons.

Clonidine is an agonist at α_1- and α_2-adrenoceptor subtypes. It reduce the sympathetic tonus and is thereby a useful antihypertensive drug. Clonidine can induce sedation, depression and peripheral side effects like a dry mouth. Unspecific α-adrenoceptor blocking agents like tricyclic antidepressants can reduce the antihypertensice effect of clonidine.

Methyldopa is an false substrate for the dopamine-β-hydroxylase resulting in α-methylnoradrenaline. This metabolite is an α_2-adrenoceptor agonist an induce, like clonidine, a centrally mediated reduction of sympathetic tonus.

Another, new group of compounds act via the same central mode of action: the imidazoline receptor agonists. The central regulation of sympathetic tone in the medulla oblongata is sensitive not only to α_2-adrenoceptors but to so called imidazoline receptors as well. Two drugs with high affinity towards this type of receptor have found their way into therapy: moxonidine and rilmenidine. Although claimed to be more specific the pattern and incidence of side effects is comparable to clonidine.

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Chapter 19

Autacoids

Martin Pfaffendorf

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I. INTRODUCTION

The word Autacoids comes from the Greek "Autos" (self) and "Acos" (drug) and the general meaning is self-remedy. They are naturally occurring substances which do not normally circulate and are localized in tissues. Their sites of action are thus restricted to the synthesis area. They have diverse physiological and pharmacological activities with a short duration of action which primarily involve responses to injury. Of general importance are effects on smooth muscle contraction. With respect to vascular smooth muscle, there are both vasoconstrictor and vasodilator autacoids. Vasodilator autacoids can be released during periods of exercise. Their main effect is seen in the skin, allowing for heat loss.

Autacoids are a chemically diverse group of substances which are released in response to various types of stimulation. An imbalance in their synthesis, release or in the transduction system contributes significantly to pathological conditions such as inflammation, allergy, hypersensitivity and ischaemia.

The autacoids comprise histamine, serotonin, angiotensin, neurotensin, NO (nitric oxide), kinins, platelet-activating factor, endothelins and the four families of traditional eicosanoids – the leukotrienes and three types of prostanoids i.e. prostaglandins, prostacyclins, and thromboxanes. Several other natural occurring molecules are sometimes called eicosanoid, including the hepoxilins, resolvins, isofurans, isoprostanes, lipoxins, epoxyeicosatrienoic acids (EETs) and some endocannabinoids. However, not all the substances which can be categorized as autacoids have a direct bearing on our pharmacotherapeutic armamentarium.

II. HISTAMINE

Histamine (2-(4-imidazolyl)ethylamine) is a biogenic amine present both, in animals and plants. It is a component of the venom of many insects. The tissues of mammals contain species-dependent various amounts of histamine. In humans the lungs, skin and gastrointestinal tract contain the highest concentrations (∼0.01 mg/g). The biogenic amine is stored in a biologically inactive form in mast cells of tissues and blood which normally contain large amounts of heparin as well. As a result of antigen–antibody interactions histamine and other vasoactive substances are released from the mast cells.

In the mucosa of the gastrointestinal tract histamine is present in enterochromaffin cells. These cells are thought to contain the histamine which is involved in the stimulation of gastric acid secretion. In the central nervous system there are histaminergic neurons.

Mechanical destruction of cells, as it occurs as a result of a trauma, is the most unspecific way of histamine release. Another important mechanism are allergic reactions. The triggering reaction is the binding of an antigen at immunoglobulin E (IgE) antibodies present at the surface of mast cells. A series of reactions, one of which is a calcium influx, leads

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Table 1. Histamine receptors, agonists and antagonists

	H_1	H_2	H_3	H_4
Agonist	2-methyl-histamine	Dimaprit	R-(α)-methylhistamine	4-methylhistamine
Antagonist	Pyrilamine	Cimetidine	Thioperamide	Cinnarizine

to the exocytosis of histamine-containing vesicles. The symptoms of allergic reactions on a local but also on the level of the whole organism are mainly determined by the histamine release. As a dangerous side effect some drugs, like D-tubocurarine, can directly induce a histamine release.

Histamine is rapidly degraded by oxidative desamination by the diaminooxidase histaminase, acetylation of the NH_2-group, methylation of the ring and oxidation of the methylhistamines by the monoaminoxidase. The main metabolites are the N-methyl-imidazole acetic acid and the imidazole acetic acid. Histamine interacts with at least four different specific receptors H_1 to H_4 (see Table 1).

H_1-receptors mainly mediate the constriction of large and relaxation of small blood vessels, contractions of the bronchial, intestinal and uterine smooth muscle and contractions of vascular endothelial cells with the result of an increased capillary permeability. The lymphatic flow is augmented by H_1-receptor stimulation. H_2-receptor stimulation induce a dilatation of pulmonary arteries, a positive inotropic and chronotropic effect on the heart and an increased glandular secretion, especially in the mucosa of the stomach.

H_3-receptors have been identified in the central nervous system. They are located on presynaptic membranes and serve as inhibitory autoreceptors at histaminergic neurons. They are also found on certain human autonomic nerve endings and in atrial tissue where they may inhibit norepinephrine release during ischemia.

The histamine H_4-receptor which was discovered in 2001 has been shown to have a role in chemotaxis and mediator release in various types of immune cells including mast cells, eosinophils, dendritic cells and T cells. H_4-receptor antagonists have been shown to have anti-inflammatory properties and efficacy in a number of disease models, such as those for asthma and colitis *in vivo*. Cinnarizine has a high affinity for the H_4-receptor. Recently other H_4-receptor antagonists have been developed with high receptor affinity and specificity. The first few studies into the function of H_4-receptors suggested that their blockade would be of benefit to allergic diseases with an eosinophilic and/or mast cell component.

The vasodilatory effect of H_1-receptor stimulation is mainly due to an endothelial release of nitric oxide, which is able to activate the soluble guanylate cyclase in vascular smooth muscle cells. This effect is mainly responsible for the erythema seen after injection (insect sting) of histamine. Furthermore, it is responsible, together with the increased capillary permeability, for the cardiovascular symptoms seen in anaphylactic or allergic shock.

II.a. Inhibitors of Histamine Release

Cromoglycate and nedocromil are known to stabilize the outer cell membrane of mast cells and thereby inhibiting the release of histamine and leukotrienes. Their antiallergic effect might be due to more than one mechanism, for example by additionally reducing the sensitivity of inflammatory cells towards histamine.

Sodium cromoglycate does not penetrate the tissue very well and only after chronic application the desired effect on mast cells can be observed. Therefore, this type of drugs can only be used for a prophylaxis but not in the treatment of an acute situation. This profile of action makes cromoglycate most suitable for topic application for example as inhalation for allergic asthma or hey fever and, orally applied for the therapy of food allergy. Systemic side effects are rare since cromoglycate is hardly absorbed. The application via inhalation might result in a mechanical irritation of the mucosa in the bronchial tract. The efficacy of a therapy with cromoglycate is mainly determined by the contribution of histamine to the respective symptoms.

II.b. H_1-Antagonists

There are numerous compounds which act as competitive antagonists at the H_1-receptor. They all have a common structure which more or less resembles that of histamine. Most of the classic compounds show antagonistic actions, not only at the

H_1-receptor but also at muscarinic cholinoceptors, serotonin receptors, and adrenoceptors. This explains the atropine-like side effects of those drugs. The cationic amphophilic structure of these substances resemble that of antiarrhythmic agents which might explain the arrhythmogenic properties seen with some of these H_1-antagonists.

The indications for H_1-antihistaminics are derived from their mechanism of action: all conditions in which a histamine release, mainly as sequel of an allergic reaction (bronchial asthma, hey fever, urticaria, allergic reactions to food or drugs), dominates the clinical symptoms. They can be used prophylactically or in acute situations, even by intravenous application.

The choice of a suitable drug depends on the individual characteristics of the drugs. Most of the classic compounds with atropine-like properties induce sedation, tachycardia, dry mouth, gastro-intestinal disorders and an obstruction of micturition. Due to their amphophilic character some of the compounds have local anaesthetic properties, which might be useful in the topical treatment of allergic itching (diphenhydramine, promethazine). In some cases the sedative effect is so pronounced that the compounds can be used as 'sleep aids' (diphenhydramine, pyrilamine, doxylamine). H_1-antagonists (diphenhydramine, promethazine) are used to prevent motion sickness, while they are less effective in treating this condition if it is already present. Doxylamine have been used in the treatment of nausea and vomiting. The atropine-like effect can be used in the therapy of nonallergic rhinorrhea (chlorpheniramine).

Newer developments are astemizole, cetirizine, loratadine, mequitazine and terfenadine which are basically devoid of central side effects and effects on the autonomic transmission. This is not due to an inability of the drugs to pass the blood brain barrier, since these drugs are quite lipophilic but probably to their selectivity towards H_1-receptors. These drugs can be used in the chronic treatment of allergic disorders.

Astemizole and terfenadine are known to aggravate cardiac arrhythmic disorders especially of the prolonged QT-interval type. Their use should be avoided at least in susceptible patients.

II.c. H_2-Antagonists

The gastric acid secretion can be stimulated by the transmitters acetylcholine, histamine and the hormone gastrin. Histamine, acting via H_2-receptors, plays a key role in this process. There are several conditions in which a reduction of gastric acid secretion is desirable and which therefore are indications for H_2-antagonists like hyperacidic gastritis, ulcus duodeni, hyperacidic ulcus ventriculi, reflux esophagitis, gastric mucosa lesions in patients at intensive care or subsequent to major surgery and gastrin-producing tumors (Zollinger–Ellison syndrome).

H_2-antagonists competitively interact with the H_2-receptor. They are very specific for the H_2-subtype of the histamine receptor.

Cimetidine is a weak base which is absorbed rapidly with a presystemic elimination of about 40%. The compound is excreted mainly via the kidneys, two thirds of it unchanged the rest as oxidized metabolites. The elimination half-life is about 2.5 h but shows large interindividual variations. In patients with renal insufficiency the half-life is prolonged which makes an adaptation of the dosage necessary. The dosage of cimetidine depends on the condition to be treated. To prevent the reoccurrence of a hyperacidic gastric mucosa lesion 400 mg per day might be sufficient, whereas 800–1200 mg per day, taken as a single dose at night, are necessary to treat an active ulcus. For the therapy of a Zollinger–Ellison syndrom even higher doses are needed.

In general side effects are rare and mainly occur at higher doses e.g. in patients with renal insufficiency. Central side effects are dizziness, disorientation, double vision, dyskinesia, and, especially with high doses, hallucinations. Furthermore, galactorrhea, gynecomastia and reversible impotence have been reported. Blood dyscrasias, reversible cholestasis and abnormalities in liver enzymes occur. On intravenous injection bradycardia or extrasystoles accompanied by hypotension have been reported. Cimetidine is a potent inhibitor of the cytochrome P-450-catalyzed oxidative drug metabolism pathway that prolongs and enhances the effect of drugs such as: warfarin, phenytoin, propranolol, metoprolol, labetalol, quinidine, caffeine, lidocaine, theophylline, alprazolam, diazepam, flurazepam, triazolam, chlordiazepoxide, carbamazepine, ethanol, tricyclic antidepressants, metronidazole, calcium channel blockers and sulfonylureas. Ranitidine, famotidine, nizatidine and roxatidine are if at all, much less potent inhibitors of the cytochromes P-450. All these newer compounds are more potent that cimetidine, although qualitatively the therapeutic effects are identical. They do not show the endocrine side effects of cimetidine and induce less frequently an increase in liver enzymes.

III. SEROTONIN

Serotonin (5-hydroxytryptamine; 5-HT) acts as transmitter and mediator on several locations in the body with quite different effects. There are multiple sub-types of the serotonin receptor. This offers the possibility of a selective therapeutic interference using subtype specific agonists or antagonists.

Ninety percent of all serotonin is located in enterochromaffin cells in the gastrointestinal tract where it is synthesized from the amino acid L-tryptophan by hydroxylation of the ring and decarboxylation. It is stored in reserpine-sensitive vesicles. The physiological role of this cell type is not fully understood yet. They can release serotonin on mechanical and neuronal stimuli. A neoplasm of these cell type is called a carcinoid. It is characterized by a periodically occurring excessive serotonin release which results in vasomotoric reactions (flush), asthma-like symptoms, and diarrhea. In the blood serotonin is present in platelets where it is accumulated by an active carrier mechanism. The release of serotonin from these cells result in an increased platelet aggregation and vasoconstriction. In the central nervous system it is present in the brain stem (nucleus raphé) and other regions (hypothalamus, nucleus caudatus) where it is involved in temperature regulation, sleep, pain perception, appetite and blood pressure regulation. Serotonin has an influence on the mood, disturbances of the serotonin metabolism might result in depression, anxiety and migraine. In the gut serotoninrgic neurons modulate intestinal motility.

Excess serotonin in the central nervous system leads to a condition commonly referred to as the serotonin syndrome. There are several drug mechanisms that can cause serotonin toxicity. Serotonin toxicity can be a medical emergency characterised by rapid onset of severe hyperthermia, muscle rigidity and multiple organ failure.

One important mechanism of serotonin elimination is the (re-) uptake, e.g. by platelets. Furthermore, serotonin is metabolized by monoaminoxidase to 5-hydroxyindoleacetaldehyde and, subsequently, by an aldehyde dehydrogenase to 5-hydroxyindolacetic acid. The vascular effects of serotonin are complex. The direct interaction with vascular smooth muscle induces a vasoconstriction, whereas the stimulation of 5-HT-receptors on the endothelium induces the release of vasorelaxant factors with a dilatation as a result. An intravenous application of serotonin increases the pressure in the pulmonary circulation. A continuous infusion results in a stable blood pressure reduction. The effect of serotonin on the circulation strongly depends on its actual condition. Beside vascular smooth muscle, serotonin contracts bronchial, intestinal and uterine smooth muscle. Skeletal and cardiac muscle are hardly influenced by this transmitter.

The classification of 5-HT-receptors is still an ongoing field of research. 5-HT_1, 5-HT_2, 5-HT_4, 5-HT_6 and 5-HT_7 subtypes belong to the superfamily of G-protein coupled receptors whereas the 5-HT_3 subtype is a ligand-gated ion channel. The activation of 5-HT_1-receptors induces excitatory or inhibitory effects in the periphery as well as in the central nervous system. There are presynaptic 5-HT_1-autoreceptors. 5-HT_2-receptors in the periphery are located postsynaptically, their stimulation induce only excitatory effects.

5-HT_3-receptors in the central nervous system are located on various types of neurons. On activation these receptors induce a release of the respective transmitter (noradrenaline, substance P). Due to this mechanism this subtype is involved in many reflex processes.

In the heart the rate and force of contraction of atria is increased by 5-HT_4-receptor stimulation.

For therapeutical purposes selective and unselective 5-HT-receptor agonists and antagonists are used. Furthermore, the serotonin metabolism can be influenced by drugs like re-uptake inhibitors and the substrate of 5-HT synthesis, L-tryptophan.

III.a. 5-HT_1 Agonists

The selective partial 5-HT_{1A} agonist buspirone is used in the therapy of anxiety and premenstrual syndrome. Buspirone has a slow onset of action (1–2 weeks) and is devoid of sedation and physical or psychological dependence. It is used as an alternative for benzodiazepines.

Sumatriptan is a partial to full agonist at 5-HT_{1D}-, HT_{1B}- and HT_{1F}-receptors. It is used in the therapy of acute migrain where it is supposed to contract the abnormally dilated cranial arteriols and inhibits the release of substance P and the calcitonin-gene related peptide. Although mostly well-tolerated sumatriptan can potentially induce coronary spasms and dysrhythmias in susceptible patients. Other triptans are naratriptan, rizatriptan and zolmitriptan. Ergot alkaloids, like partial agonist–antagonist methysergide and the partial to full agonists ergotamine and dihydroergotamine are used in the therapy and

prophylaxis of migraine. Methysergide is more effective in resistant cases of migraine with a high attack frequency. It is a 5-HT_2-receptor antagonist and a 5-HT_1-receptor agonist. These compounds are potent vasoconstrictors and may exacerbate peripheral vascular diseases, coronary artery diseases, and hypertension. They are contraindicated in pregnant woman since they may cause fetal harm. Dihydroergotamine is a venous vasoconstrictor and should not be used where there is a history of venous thrombosis.

The triptans should be used with caution in patients on lithium, monoamine oxidase inhibitors or selective serotonin reuptake inhibitors, due to the rare occurrence of the serotonin syndrome.

III.b. 5-HT_4 Agonists

Metoclopramide is a partial 5-HT_4-agonist with antagonistic properties at the D_2-dopamine-receptor. It displays a prokinetic effect which is used therapeutically in the treatment of gastroparesis and gastroesophageal reflux diseases. Metoclopramide is an effective antiemetic. Due to its dopamine antagonism it can induce dystonis and Parkinson's disease-like side effects. Furthermore, metoclopramide increase the prolactin release resulting in typical symptoms of a hyperprolactinemia like gynecomastia, galactorrhea and breast tenderness.

The newer 5-HT_4-agonists like cisapride and tegaserod are, due to the lack of dopamine antagonism, devoid of extrapyramidal side effects. They can be used in the therapy of constipation-predominant irritable bowel syndrome (IBS). These drugs can relieve the abdominal discomfort, bloating and constipation of IBS and are useful to treat chronic idiopathic constipation. However, in many countries cisapride is no longer registered due to of risks of life-threatening arrhythmias secondary to prolongation of the QT interval. This can be especially the case if cisapride is co-administered with drugs that are metabolized via the same cytochrom P450 3A4 pathway like ketoconazole, fluconazole, erythromycin or clarithromycin.

III.c. 5-HT_2 Antagonists

5-HT_2 antagonists like trazodone, nefazodone, clozapine and risperidone are used in the treatment of schizophrenia and depression. They block adrenoceptors and H_1-histamine-receptors as well. Hypotension, drowsiness and weight gain can occur.

Ketanserine, which is an 5-HT_2- and α_1-adrenoceptor-antagonist as well, is used in the therapy of hypertension. The interaction with both receptor systems contributes to its therapeutic effect.

III.d. 5-HT_3 Antagonists

With the exception of cilansetron, which is used in the treatment of irritable bowel syndrome, all 5-HT_3-antagonists are antiemetics, used in the prevention and treatment of nausea and vomiting. Antagonists at the 5-HT_3-receptor, like ondansetron, granisetron and tropisetron are very potent antiemetics, used in the therapy of postoperative and cancer therapy-induced nausea and vomiting. In this indication they are often combined with glucocorticoids. Ondansetron and tropisetron can be given orally whereas granisetron has to be given parenterally. It has been demonstrated that ondansedron also has anti-itching activity.

Newer agents in this group are dolasetron and palonosetron.

With 5-HT_3-antagonists headaches, flushing and visual disturbances may occur. They can cause severe constipation and therefore should be used briefly and only where they are clearly more clinically effective than alternatives.

III.e. Monoamine Oxidase Inhibitors

The pharmacological inhibition of the serotonin eliminating enzyme MAO is used in the therapy of depression and hypertension. Tranylcypromine is an irreversible unselective MAO inhibitor which displays numerous interactions with amine-containing food and monoamine-related drugs, resulting in eventually fatal hypertensive crisis, cranial hemorrhage, arrhythmias and seizure can occur. The coadministration with specific serotonin reuptake inhibitors (SSRI) can result in similar effects and is therefore contraindicated. Moclobemide, on the other hand, is a reversible inhibitor of MAO_A, one of the two enzyme subtyppes (MAO_A, MAO_B) which is void of most interactions see with tranylcypromine.

MAOIs had been reserved as a last line of treatment, used only when other classes of antidepressant drugs had failed, because of the mentioned potentially lethal dietary and drug interactions. However, in 2006 a patch form of the drug selegiline, called Emsam, was approved for use by the FDA. When applied transdermally the drug does

not enter the gastro-intestinal system as it does when taken orally, thereby decreasing the dangers of dietary interactions associated with MAOIs.

III.f. SSRIs

Due to the frequent unwanted effects and, in case of tranylcypromine, the numerous and dangerous interactions MAO-inhibitors are more and more replaced by the much less problematic SSRIs. Compounds belonging to this group are citalopram, escitalopram, fluoxetine, paroxetine and sertraline. They are used clinically in the therapy of depression, bulimia and obsessive–compulsive disorders. All SSRIs show a slow onset of action (1–2 weeks). They may induce insomnia and weight loss. The antidepressant venlafaxine inhibits both, serotonin and noradrenaline re-uptake and might therefore additionally induce hypertension.

Fenfluramine and its active isomere dexfenfluramine act by stimulating the release of serotonin and inhibiting its re-uptake. Dexfenluramine lacks the amphetamine-like properties of the racemic mixture which are due to L-fenfluramine. Both isomers have antiobesity activity but they were taken from the market, at least in several Western countries, because of rare but very serious cardiotoxicity.

The SSRIs are particularly helpful in heading off depression in the early stages, before it becomes deeply rooted.

Paroxetine increases the risk of birth defects in women taking the drug during their first trimester of pregnancy. Evidence from case studies, epidemiological studies, experimental research, and theory supports the view that SSRIs increase suicide risk for some patients.

All drugs inducing a constantly increased serotonin level may induce pulmonary hypertension on the basis of a hypertrophic smooth muscle layer of small pulmonary arteries.

L-tryptophane is the precursor of serotonin and other biological substances like tryptamine, kynurenine and quinolinic acid. Furthermore, it is an essential substrate in the protein synthesis. The dietary intake of L-tryptophane might increase the production of serotonin. For this reason the aminoacid is used for the therapy of light sleeping disorders.

IV. ANGIOTENSIN

As a response to an increased sodium excretion and a low kidney perfusion specialized cells located at the contact region of the efferent arterioles in the capsule of Bowman and the distal tubulus (juxtaglomerular apparatus) secrete a glycoprotein into the blood stream: the acid protease renin. It is a enzyme of a molecular weight of 35,000–42,000 from the same group as pepsin and cathepsin D. Another potent stimulus of renin release is coming from the sympathetic nervous system via the activation of β_1-adrenoceptors. Vasopressin, potassium and the final product and effector of the cascade, angiotensin II, inhibit the renin release. The only known substrate of renin is the glycoprotein angiotensinogen (MW 52,000–66,000), which is mainly synthesized and secreted by the liver. It is permanently present in the plasma although in concentrations below the K_m (concentration needed for 50% of the reaction rate). Renin cleaves a decapeptide from the amino terminal end of angiotensinogen which is angiotensin I. This decapeptide is biologically inactive but forms the substrate for another peptidase: the dipeptidyl carboxypeptidase angiotensin converting enzyme (ACE). This enzyme, which is much less substrate specific then renin, catalyzes the cleavage of the last two aninoacids histidine and leucine from the carboxyterminal end of angiotensin I resulting in the biologically active end product of the cascade angiotensin II. Beside the angiotensin I conversion ACE catalyzes the inactivation of bradykinin (here called kininase II) and other active transmitters and hormones such as substance P and enkephalines. It is located with high activity in the vascular endothelium, especially in the pulmonary circulation. It has been shown that all components of the cascade can be present in a variety of tissues, including the heart and the vascular vessel wall. The extent to which these local renin–angiotensin contributes to the overall effect of this system is not clear yet.

While the rate limiting step of the cascade is the renin release, the biological active component is the octapeptide angiotensin II. It is an essential regulator of fluid and electrolyte balance as well as blood pressure. It exerts its actions on various structures like blood vessels, adrenal cortex, kidney and central nervous system. Although at least two different receptor subtypes for angiotensin II have been identified (AT_1 and AT_2) the AT_1-subtype is responsible for most of the cardiovascular effects of the agonist.

With a half-life of 15–60 seconds angiotensin II is removed from the blood. It is cleaved at various positions of the molecule by different an-

giotensinases, resulting mostly in inactive fragments, except the heptapeptide angiotensin III ([des-Asp^1]angiotensin II) which is able to activate AT_1-receptors as well.

Angiotensin II is a very potent vasoconstrictor by a direct interaction with AT_1-receptors on vascular smooth muscles as well as by facilitating the sympathetic stimulation of this structure. The release and the postsynaptic effect of noradrenaline is enhanced by angiotensin II. Furthermore, this octapeptide stimulates the secretion of the mineralocorticoid aldosterone from the zona glomerulosa of the adrenal cortex, resulting in a water and sodium retention. Beside this indirect, aldosterone mediated effect, angiotensin II effects the renal function directly by inducing renal vasoconstriction and increased proximal tubular sodium reabsorption. In the central nervous system angiotensin II induce thirst and salt appetite and increase the secretion of the antidiuretic hormone (ADH) vasopressin and of adrenocorticotropic hormone (ACTH). Angiotensin II is also a growth factor which can induce or at least contribute to vascular and cardiac hypertrophy and remodeling as a long term adaption to an increased pressure.

Taken together under physiological conditions the renin angiotensin system maintains volume and electrolyte homeostasis as well as the blood pressure. Under pathological conditions, like heart failure, it increases blood pressure and fluid retention, thereby enhancing pre- and afterload of the heart.

Under various pathological conditions, including heart failure and essential hypertension, a reduction of the activity of this system is desirable.

IV.a. ACE Inhibitors

The first attempt which actually lead to a therapeutically useful drug was the development of orally active AEC inhibitors (see also Chapter 22). These compounds, of which captopril was the first, resemble the structure of two or more carboxyterminal amino acids of angiotensin I, thereby showing a high affinity towards ACE. All actions of angiotensin II can be blocked by ACE inhibitors including vasoconstriction and fluid retention. Under the therapy with theses drugs the renin and angiotensin I levels are elevated. Since ACE is not a very substrate specific enzyme various other systems are influenced as well by these drugs. The most important of those is the bradykinin system. Bradykinin is a vasodilatory pepitde formed in the plasma by cleavage from high molecular weight kiniogen by the enzyme kallikrein. This kinin is eliminated by two carboxypeptidases: kininase I and II. Kininase II is identical with the ACE. Inhibition of this enzyme results in an accumulation of bradykinin. While the inhibition of the synthesis of the vasoconstrictive hormone angiotensin II and the inhibition of the elimination of the vasodilatory bradykinin are potentially synergistic effects concerning the blood pressure reduction, most of the side effects of ACE-inhibitors are believed to be bradykinin dependent, like angioneurotic edema and cough.

Quite a number of ACE-inhibitors have been introduced with different chemical structures: sulfhydryl-containing agents like captopril, dicarboxylate-containing agents like enalapril, ramipril, quinapril, perindopril, benazepril and lisinopril and phosphonate-containing agents like fosinopril. The main difference is the affinity towards the enzyme ACE. Qualitatively there is no major difference. For sake of a better bioavailibility, most of these compounds are prodrugs in the form of esters. After resorption of the relatively lipophilic prodrug the ester moiety is hydrolyzed by serum esterases liberating the active free acide. Examples are benazepril, cilazapril, enalapril, fosinopril, moexipril, perindopril, quinapril, ramipril, spirapril and trandolapril. Examples for direct acting ACE-inhibitors being no prodrugs are captopril and lisinopril.

The main side effects of ACE-inhibitors are cough, hypotension and angioneurotic edema, hypokalemia. Contraindications are stenosis of the renal arteries, kidney transplantation and pregnancy.

IV.b. AT_1-Receptor Antagonists

Although ACE-inhibitors are in general effective and well tolerated, another group of drugs has been developed to inhibit the action of angiotensin II: the AT_1-receptor antagonists.

This group of drugs are non-peptide antagonists at the AT_1-receptor, competing with angiotensin II for the main binding site. Depending on the species and type of tissue the antagonism is surmountable or unsurmountable, that is it can not be fully reversed by increasing angiotensin II concentrations. The first drug of this group was losartan a diphenylimidazole derivative which is orally active and transformed *in vivo* to a even more potent metabolite.

Other compounds are candesartan, eprosartan, irbesartan, telmisartan, vaslartan and olmesartan. AT_1-receptor antagonists have been proven in large,

randomised, double-blind, placebo-controlled and comparative studies to be safe, well tolerated and effective in treating hypertension and heart failure. AT_1-receptor have few side effects. Potential, but infrequent effects include angioedema, dizziness and elevated liver function values.

There are three major differences when compared to ACE-inhibitors; AT_1-blockers do not interfere with the bradykinin metabolism and therefore do not induce a bradykinin accumulation. This might explain the lower incidence of cough and edema. The renin release in the kidney is sensitive to a negative feedback by angiotensin II. This mechanism is effectuated by AT_1-receptors. The blockade by specific antagonists inhibits the feedback loop with the result of a markedly increased renin release and, as a consequence, high angiotensin II levels. Although the vast majority of all known cardiovascular effects are mediated by AT_1-receptors, which are blocked by the antagonists, there are other subtypes, like the AT_2-receptor, which are exposed to this high concentrations of the hormone. Apparently, this does not negatively influence the therapeutic effect of AT_1-blockers but should be kept in mind.

IV.c. Renin-Inhibitors

A rather new development is the orally available renin inhibitor aliskiren. It was approved by the U.S. Food and Drug Administration in 2007 for the treatment of hypertension. As mentioned above renin is a protease released on various stimuli from the juxtaglomerula apparatus in the kidney. Its release is the limiting step in the whole renin–angiotensin cascade. Since renin is highly substrate-specific its inhibition can be expected to have very little unspecific side effects. The result of an effective blockade of this enzyme is a reduced angiotensin I and angiotensin II formation. In contrast to ACE-inhibition or AT_1-receptor blockade, the plasma concentrations of both peptides stay low. No interaction with other systems like the Kallikrenin–Bradykinin system seems to take place.

As with ACE inhibitors, renin inhibitors should not be used in pregnancy, specifically the second and third trimesters, during which they will interfere with fetal kidney development.

V. EICOSANOIDES

A large number of local hormones are derived from polyunsaturated C_{18}–C_{22} fatty acids. These are the prostaglandins, thromboxanes, hydroperoxyeicosatetraenoic acids (HPETE), hydroxyeicosatetraenoic acids (HETE), the leukotriens and the lipoxines. They exert complex control over many bodily systems, especially in inflammation, immunity and as messengers in the central nervous system. The most important substrate is the arachidonic acid, which is a organic, in four positions unsaturated C20 fatty acid: 5,8,11,14-eicosatetraenoic acid. The arachidonic acid is a component of phospholidids which form the skeleton of cell membranes of higher animals. Usually it is situated in the 2 position of the glycerol backbone of the phospholipid where it can be cleaved by the activity of the enzyme phospholipase A_2. Furthermore, it can be cleaved by a specific lipase from the diacylglycerol which is a product of the phospholipase C reaction with phosphatidylinositol.

Those lipase reactions can be the result of unspecific or specific stimuli or can even form a constitutive part in the signal transduction cascade of receptors.

The free acid forms the substrate for two distinct enzyme systems: the cyclooxigenase and the lipoxigenase.

V.a. Prostaglandines

The cyclo-oxigenases (COX-1 and COX-2) or prostaglandin endoperoxide synthase, which are membrane bound hemoproteins, catalyze the oxygenation and cyclization of a pentane ring, resulting in the unstable prostaglandin G_2. The same enzyme is responsible for the reduction of the C_{15} hydroperoxy group to a hydroxyl group resulting in prostaglandin H_2. COX-1 is responsible for the baseline levels of prostaglandins while COX-2 produces prostaglandins through stimulation. However, while COX-1 and COX-2 are both located in the blood vessels, stomach and the kidneys, prostaglandin levels are increased by COX-2 in scenarios of inflammation.

COX-1 and COX-2 are the targets of the nonsteroidal anti-inflammatory drugs (NSAID, see Chapter 28). Indirectely the effect of these enzymes is also inhibited by corticosteroids (see also Chapter 26) through a decrease of the availibility of its substrate arachidonic acid by inhibition of phospholipase A_2. Relatively new drugs, known as COX-2 selective inhibitors or coxibs (celecoxib, rofecoxib and others), are used as specific inhibitors of COX-2.

The development of these drugs allowed the circumvention of the negative gastrointestinal effects while effectively reducing inflammation. However, it was subsequently shown that both NSAIDs and Coxibs can raise the risk of myocardial infarction, when taken on a chronic basis for at least 18 months. In 2004 rofecoxib was taken off the market for this reason.

Specific enzymes use the endoperoxide prostaglandin H_2 as substrate to synthesize the prostaglandins D_2, E_2, $F_{2\alpha}$ as well as thromboxane A_2 (TxA_2) and prostacycline (PGI_2). The prostaglandines differ by the number and position of keto- and hydroxyl-groups. Prostaglandin E_2 is particularly important in pathophysiological processes like inflammation, nociception, and pyrogen-induced fever. PGE_2 release by a certain stimulus, increases the blood flow by vasodilatation, enhances the extravasation of plasma and induce a hypersensitivity of nociceptors. This results in the typical local signs of inflammation: swelling, erythema, increase of temperature and pain. Certain components of the cell membrane of numerous bacteria act as an endotoxin (lipopolysaccharide, *exogeneous pyrogen*) and induce the release of interleukin-1 (*endogenous pyrogen*) which is a stimulus for a PGE_2-release in the preoptic region of the hypothalamus. Under the influence of this prostaglandin the normal value of the body temperature is increased. This is a purely pathophysiological mechanism since the inhibition of the prostaglandin synthesis is able to prevent or inhibit fever but does not affect the normal body temperature.

The enumeration of these effects of prostaglandins makes it understandable that the inhibition of the cycloxigenases will result in antiinflammatory, analgesic and antipyretic effects. Another important function of PGE_2 is the vasodilatation it can induce in the renal circulation. Locally produced PGE_2 increases the renal perfusion.

PGE_2 and $PGF_{2\alpha}$ increase the production of mucus and reduce the acid secretion in the gastric mucosa. They stimulate the motility of the gastrointestinal tract. $PGF_{2\alpha}$ induces vasodilatation and bronchoconstriction and a stimulation of uterine smooth muscle, independent of the hormonal status. This effect is used therapeutically for the activation of the uterus. Intra-amniotic injection of $PGF_{2\alpha}$ is used to induce second-trimester abortion. $PGF_{2\alpha}$ analogs are also used in glaucoma to reduce intraocular pressure. PGE_2 stimulates the uterus as well. Dinoproston is the naturally occurring PGE_2 and is marketed for use in obstetrics under the trademarks Cervidil and Prepidil. Cervidil is a vaginal insert used for the starting or continuing of cervical ripening to induce labour in every state of pregnancy. Prepidil gel is used for the same indication. PGD_2 is of less importance although it can induce bronchodilatation, increased mucus secretion in the gastrointestinal tract and an inhibition of platelet aggregation.

Since prostaglandins are subjected to an efficient metabolism their half-life is very short. Therefore one goal in the effort to use prostaglandins as therapeutics was to find derivatives which are more stable. Misoprostol is a synthetic analog of PGE_1 that is used to protect against haemorrhagic-risks in chronic NSAID users. Gastrointestinal and gynecological adverse events are frequent. Sulprostone is a metabolism resistant synthetic analog of PGE_2. It is used for the stimulation of the uterus and it reduces the need for manual removal of the placenta in patients with retained placenta. The second goal, an increased organ selectivity, was not achieved; the naturally occurring as well as the synthetic prostaglandins induce a variety of side effects like nausea, overstimulation of gastrointestinal motility, diarrhea as well as bronchoconstriction, hypotension and bradycardia.

In contrast to the other prostaglandins, prostacycline (PGI_2) has two pentane rings, one of those containing a oxygen atom. It is formed by the vascular endothelium and has a half-life of about 5 minutes. It is a potent, cAMP-dependent vasodilator and inhibitor of platelet aggregation. Under physiological conditions PGI_2 is an important regulator of the peripheral perfusion and microcirculation. A chemically stable derivative is iloprost which is currently available as a therapeutic for the indication Buerger's disease to improve peripheral perfusion and oxygenation. It is contraindicated for patients with coronary artery disease, heart failure or important haemorrhagic-risks.

Thromboxane A_2 is synthesized and released mainly by platelets. Its half-life is around 30 seconds. It is a potent vasoconstrictor and enhances platelet aggregation. Apparently, a functional antagonism exists between PGI_2 and TXA_2, guarding the vascular integrity. Any tissue damage will result in a decreased endothelial PGI_2 production and effect, giving way to the TXA_2-induced vasoconstriction and platelet aggregation to stop bleeding and initiate wound closure. Under pathological conditions where the endothelium is damaged or, at least

dysfunctional without a mechanical damage of the vessel, like atherosclerosis, thromboxane can induce thrombosis and vasospasm.

V.b. Leukotriens

The biologically very active leukotriens are formed directly by the enzyme 15-lipooxygenases using arachidonic acid as substrate. Inhibition of phospholipase A_2 by corticosteroides (see also Chapter 26) decreases the availability of this substrate. Neutrophils, mast cells, monocytes, macrophages and creatinocytes can synthesize leukotriens in the lung, spleen, brain, and heart. Leukotriens are derivatives of the arachidonic acid which are oxidized to different degrees and in different positions. Furthermore, the leukotriens can be coupled to glutathion (LTC_4), a complex from which either glycine (LTE_4) or glutaminic acid (LTD_4) can be cleaved. This results in a large number of different closely related substances. In inflamation especially the leukotrien B_4 (of which five isomers are known) is of importance, since it enhances the chemokinetic and chemotactic activity of leukocytes. By this mechanism leukotriens contribute to the infiltration of leukocytes to the inflammatory region. Among the leukotriens substituted with glutathione at the 5-position are the so called 'slow reacting substances' which play a major role in anaphylaxis. These compounds dilate blood vessels, increase vascular permeability and induce bronchoconstriction. They are involved in anaphylactic shock, various forms of bronchial asthma and in inflammation. They have a very short half-life. Unlike prostaglandines their formation is not influenced by cyclooxigenase inhibitors. However, substances, like corticosteroids, which inhibit the liberation of the common substrate arachidonic acid from the phospholipids by decreasing the phospholipase A_2 activity, will inhibit both, the cyclo-oxigenase and lipo-oxigenase pathway. A number of compounds that are either 5-lipo-oxygenase inhibitors (zileuton), which block leukotriene formation, or cysteinyl leukotrien receptor antagonists, which block receptor function are in different stages of clinical evaluation. Many of these are being tested for their utility in asthma and related conditions and recently montelukast, the first leukotriene receptor antagonist for the use in asthma, has been approved for marketing. Others, like iralukast, pranlukast, and zafirlukast are expected to follow soon.

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Chapter 20

Drugs Affecting Cardiovascular and Renal Functions

Pieter A. van Zwieten

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I. α-ADRENOCEPTOR ANTAGONISTS (α-BLOCKERS)

I.a. General Profile

α-Adrenoceptor antagonists (α-blockers) are competitive inhibitors at the level of α-adrenoceptors. These receptors are found in many organs and tissues, but their predominant functional importance is to mediate the vasoconstrictor effects of endogenous catecholamines (noradrenaline, adrenaline) released from the sympathetic nerve endings. Conversely, α-adrenoceptor antagonism by means of an α-blocker will inhibit this constrictor activity and hence cause vasodilatation. This vasodilator effect occurs in both resistance vessels (arterioles) and capacitance vessels (veins), since α-adrenoceptors are present in both types of vascular structures. Accordingly, both cardiac afterload and preload will be lowered, in particular when elevated.

α-Adrenoceptor antagonists may be used as antihypertensives and occasionally in the treatment of heart failure as unloading drugs. Their side-effects, such as orthostatic hypotension, headache, flush, and reflex tachycardia, are readily explained on the basis of vasodilatation. Vasodilatation will enhance sympathetic nervous activity via the baroreceptor system and hence induce a rise in heart rate (reflex tachycardia). At present, selective α_1-adrenoceptor antagonists, such as doxazosin and prazosin, are preferable to the older, non-selective ($\alpha_1 + \alpha_2$)-blockers, such as phentolamine, for the following reasons: The blockade of presynaptic α_2-adrenoceptors will cause an enhanced release of noradrenaline from the nerve endings, thus substantiating tachycardia. The selective α_1-blockers, however, do not influence presynaptic receptors, since these are virtually only belonging to the α_2-subtype. For this reason, the selective α_1-blockers cause much less tachycardia than non-selective antagonists with an α_2-component.

Selective α_1-adrenoceptor antagonists are among the few antihypertensive agents that moderately improve the plasma lipid profile, glucose tolerance

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and insulin resistance. Both prazosin and doxazosin (see below) increase plasma HDL-levels and the ratio HDL/total cholesterol. It is difficult to judge whether these effects are clinically relevant. Progress in fundamental research has led to the distinction between α_{1A}, α_{1B} and α_{1D}-receptor subpopulations and the development of selective antagonists with respect to these receptor subtypes. So far this distinction between α_1-adrenoceptor subtypes has not led to clinically relevant therapeutics.

I.b. Clinically Useful α-Blockers

Prazosin was the first example of a selective α_1-blocker. Its main application is hypertension, usually in combination with a β-blocker and/or a diuretic. Orthostatic hypotension readily occurs as a result of venous dilatation. The problem may be avoided by a gradual increase of the dosage. The drug has a short duration of action and must be administered 2–3 times daily in order to achieve adequate control of blood pressure.

Doxazosin, also a selective α_1-blocker, resembles prazosin in most aspects, but it has a better pharmacokinetic profile, at least for long-term use as in essential hypertension. Owing to its slow onset of action, doxazosin causes far less orthostatic hypotension and reflex tachycardia than prazosin. As a result of its long duration of action, it can be administered once daily in the long-term treatment of essential hypertension.

Phentolamine and phenoxybenzamine are older α-adrenoceptor antagonists, which may be used occasionally in course of the surgical removal of phaeochromocytoma, with the aim to suppress the vasoconstrictor effects of noradrenaline/adrenaline released from the tumor as a result of surgical manipulation.

Urapidil is a selective α_1-adrenoceptor antagonist with an additional central antihypertensive mechanism, mediated by the stimulation of serotonergic (5-HT_{1A}) receptors in the brain. It may be used in the treatment of essential, but also acute, peri-operative hypertension. The intravenous administration in the treatment of acute, peri-operative hypertension is not associated with a rise of intracranial pressure, in contrast to various other vasodilators. For this reason, urapidil may be used in neuro-surgical interventions.

Ketanserin is a serotonin (5-HT_2) receptor antagonist with additional α_1-adrenoceptor blocking activity. Its antihypertensive mechanism is not understood in detail. When administered intravenously its hypotensive action is explained by α_1-receptor antagonism.

α_1-Receptor blockade may be beneficial in conditions of benign prostate hyperplasia (BPH). The blockade of α_1-adrenoceptors at the smooth muscle associated with the prostate gland causes relaxation and thus facilitates urinary outflow. The α-blockers alfuzosine, terazosine and tamsulosine may be used for this purpose. Hypotension is a logical side-effect of such compounds.

I.c. Choice of an α-Adrenoceptor Antagonist

In the treatment of hypertension a selective α_1-adrenoceptor agent is preferable to the older, non-selective ($\alpha_1 + \alpha_2$)-blockers. Doxazosin is preferable to prazosin, because it has a slower onset and longer duration of action. It therefore causes less or no reflex tachycardia and orthostatic hypotension.

Urapidil may be used in neurosurgery in order to suppress peri-operative hypertension. Ketanserin is used in cardiothoracic surgery for the suppression of peri-operative hypertension.

II. β-ADRENOCEPTOR ANTAGONISTS (β-BLOCKERS)

II.a. General principles

Adrenoceptors of the β-subtype are important mediators of the sympathetic activation of the heart, kidney, and bronchi. β-Adrenoceptors are also found in other organs and tissues such as blood vessels and the central nervous system. Accordingly, β-adrenoceptor antagonists or β-blockers inhibit the stimulating influence of the endogenous catecholamines (noradrenaline, adrenaline) on the various organs and tissues which are subject to sympathetic innervation. In cardiovascular medicine the β-blockers are used in particular to blunt the sympathetic activation of the heart and kidneys. These effects are mediated by the β_1-subtype of the β-adrenoceptors. The currently used β-blockers are all competitive antagonists of the β_1-adrenoceptor, which is the basis of their therapeutic application.

β_1-Adrenoceptor antagonism by means of a β-blocker causes the following cardiovascular effects: reduction in heart rate, AV conduction and cardiac output; reduction of renin release by the kidney.

Adrenoceptors of the β_2-subtype are also available in particular organs and tissues, such as the

bronchi and blood vessels, and on the enzyme adenylate cyclase. β_2-Receptor blockade by non-selective β-blockers therefore causes bronchoconstriction and (mild) vasoconstriction, as well as hypoglycaemia.

β-Blockers are used as therapeutics in the treatment of hypertension, myocardial ischaemia (angina pectoris), tachyarrhythmias, and in the secondary prevention following myocardial infarction. More recently the cautious use of β-blockers has been found to be of potential benefit in the treatment of congestive heart failure (NYHA stages II and III).

Topically applied β-blockers are used to reduce elevated intraocular pressure in patients with open-angle glaucoma simplex.

All of the aforementioned beneficial effects of the β-blockers are caused by the blockade of β_1-adrenoceptors. The beneficial effect of β-blockers in the treatment of angina is largely caused by the reduction of heart rate and the concomitant decrease in myocardial oxygen consumption, thus improving the imbalance between oxygen supply and consumption which underlies myocardial ischaemia.

The mechanism of the blood pressure-lowering activity of the β-blockers, which have been used as antihypertensives for several decades on a very large scale, is still not understood in full detail. Myocardial and renal factors play a role, whereas it is also presumed that on long-term treatment moderate vasodilatation and a reduction in peripheral resistance will occur.

The therapeutic efficacy in the treatment of tachyarrhythmias is based upon the reduction of the influence of endogenous catechol-amines on the sinus node and the AV node.

The well-defined beneficial effect of β-blockers as secondary prevention post-MI patients is probably based upon the impairment of sympathetic activation and concomitant rises in blood pressure and heart rate, and possibly also on an anti-arrhythmic effect.

Severe congestive heart failure (CHF) is associated with sympathetic activation and down-regulation of β-adrenoceptors. The beneficial effect of cautiously used β-blockers in CHF is believed to be based upon the suppression of tachycardia and tachy-arrhythmia. Upregulation of β-adrenoceptors can also be thought of as a beneficial factor, although the evidence for this is meagre.

The therapeutic effect of β-blockers (topically applied) in open angle glaucoma is based upon the reduction of the production of aqueous humor, via a mechanism which is not known in detail.

Blockade of β_2-adrenoceptors by non-selective β-blockers causes side-effects such as bronchoconstriction, vasoconstriction and hypoglycaemia. β_2-Adrenoceptor blockade is sometimes used in the treatment of migraine or particular forms of tremor.

II.b. Pharmacokinetic Properties

The kinetic properties of the various β-blockers may be summarized as follows: all of the so far available β-blockers are readily absorbed after oral administration. Most drugs of this type are subject to hepatic degradation, usually leading to inactive metabolites.

Esmolol, a short acting β-blocker which is used intravenously in anaesthesiology and cardiac surgery is metabolised and inactivated via esterases in the blood or other tissues.

More hydrophilic β-blockers, such as atenolol, bisoprolol, celiprolol, pindolol and sotalol are predominantly eliminated via the kidney. In elderly patients this may require adaptation of the dosage. Most of the shorter acting β-blockers are available as slow release preparations. Accordingly, when used as antihypertensives β-blockers are usually administered once daily. For other applications such as angina pectoris a twice daily dosage may be required.

II.c. Different Types of β-Blockers

Over the years numerous β-blockers with different ancillary properties have been developed.

(a) β_1-*selectivity* indicates that the drug has a much stronger affinity for the β_1-adrenoceptor than for the β_2-subtype and therefore causes fewer or no side-effects based upon β_2-receptor blockade;

(b) *intrinsic sympathomimetic activity (ISA)* indicates that a β-blocker with this property is able to activate the β-adrenoceptor, although it prevents the effects of endogenous catecholamines (as achieved by all β-blockers). From a haemodynamic point of view this implies that ISA-β-blockers (e.g. pindolol, oxprenolol) cause little or no reduction in heart rate, as well as a weak vasodilator effect with a reduction in peripheral vascular resistance;

(c) *lipophilic* β-blockers will penetrate more readily into the central nervous system and therefore cause more frequently side-effects such as sleep disturbance and vivid dreams than hydrophilic β-blockers;

(d) *the duration of action* of the various β-blockers differs. Those with a short action are usually available as slow-release preparations;

(e) *β-blockers with an additional vasodilator component* are now becoming available. From a haemodynamic point of view this would appear an attractive profile. Unfortunately, the vasodilator component of such preparations is very weak and usually attenuates or disappears on long-term use. ISA-β-blockers (with β_2-receptor ISA) were the first examples of such agents. Labetalol is a ($\beta_1 + \beta_2$) non-selective blocker with weak α_1-adrenoceptor blocking activity. In fact it is a mixture of 4 different stereoisomers with different pharmaco-dynamic and pharmacokinetic properties. Celiprolol, carvedilol and nebivolol are newer examples of β-blockers with an additional although weak vasodilator component;

(f) *sotalol* is a β-blocker which is predominantly used as an anti-arrhythmic agent. The racemic mixture, which is administered as tablets, consists of the following two compounds: L-isomer: β-blocker + class III antiarrhythmic (in 1 molecule); D-isomer: class III-antiarrhythmic, virtually devoid of β-blocking activity;

(g) *esmolol* is a very short-acting β-blocker, administered intravenously in the context of anaesthesiology and cardiac surgery.

The most important β-blockers and their characteristics are listed in Table 1.

Table 1. Various β-blockers and their characteristics

Drugs	β_1-Selectivity	ISA
Acebutolol	$\beta_1 > \beta_2$	+
Alprenolol	$\beta_1 + \beta_2$	+
Atenolol	$\beta_1 \gg \beta_2$	–
Betaxolol	$\beta_1 \gg \beta_2$	–
Bevantolol	$\beta_1 \gg \beta_2$	–
Bisoprolol	$\beta_1 \ggg \beta_2$	–
Celiprolol	$\beta_1 \gg \beta_2$	+ (β_2)
Carvedilol	$\beta_1 + \beta_2 \gg \alpha_1$	–
Esmolol*	$\beta_1 > \beta_2$	–
Labetalol	$\beta_1 + \beta_2 > \alpha_1$	–
Metoprolol	$\beta_1 \gg \beta_2$	–
Nebivolol	$\beta_1 \gg \beta_2$	– + vasodilator component
Oxprenolol	$\beta_1 + \beta_2$	++
Penbutolol	$\beta_1 + \beta_2$	+
Pindolol	$\beta_1 + \beta_2$	+++
Propranolol	$\beta_1 + \beta_2$	–
Sotalol	$\beta_1 + \beta_2$	–
Tertatolol	$\beta_1 + \beta_2$	– vasodilator component (renal)
Timolol	$\beta_1 + \beta_2$	–

*ultrashort effect (i.v., anaesthesiology).

ISA = intrinsic sympathomimetic activity; $\beta_1 + \beta_2$: non-selective; $\beta_1 \gg \beta_2$: β_1-selectivity.

The β-blockers used in ophthalmology (treatment of open-angle glaucoma) are not discussed here.

II.d. Choice of a β-Blocker

In the treatment of hypertension it seems preferable to choose a selective β_1-blocker with a sufficiently long duration of action, thus allowing once daily administration.

Angina pectoris requires a β-blocker which clearly lowers heart rate. For this reason ISA-β-blockers should not be used in this condition. As in the treatment of hypertension a β_1-selective blocker seems preferable.

Tachy-arrhythmias may be treated with a β_1-selective blocker. Sotalol may be used in the treatment of postoperative atrial fibrillation, which is observed frequently following cardiac surgery.

Secondary prevention in post-MI patients should preferably be performed with a β-blocker which has been found to be beneficial in an appropriate trial. Accordingly, metoprolol, timolol or propranolol can be considered. β-Blockers with ISA (pindolol, oxprenolol) should not be used for this purpose. Neither should sotalol be used in this condition.

Congestive heart failure treatment may be improved by *cautiously* adding a β-blocker to conventional management with ACE-inhibitors and diuretics. Bisoprolol and carvedilol are the preferable β-blockers, since their beneficial effect has been convincngly demonstrated in appropriate clinical trials. Bisoprolol is a highly selective β_1-blocker. Carvedilol has additional properties to its β-receptor blocking activity, such as a weak vasodilator component and anti-oxidant activity. The beneficial effect is very likely to be caused by β_1-adrenoceptor blockade.

Migraine, glaucoma simplex (open angle glaucoma) and certain forms of tremor are other diseases where β-blockers can be used. These conditions will not be discussed here.

III. PERIPHERAL BLOCKERS OF THE SYMPATHETIC NERVOUS SYSTEM

Apart from the α- and β-adrenoceptor antagonists, dealt with in separate paragraphs of this chapter, the influence of the sympathetic nervous system on the cardiovascular system can be suppressed at the ganglia as well as at the postganglionic sympathetic neurons. The drugs which bring about this suppression are the ganglionic blocking agents (ganglioplegic drugs), and also reserpine, bretylium, and guanethidine. Drugs of this type have been used as antihypertensives from the nineteenfifties onwards. Although they are effective blood pressure-lowering agents, they have been largely abandoned because of their severe subjective side-effects. Reserpine in low dosage may still be used because of its low cost.

These drugs will be briefly discussed here, for the sake of completeness, for historical reasons and because they have been very useful as tools for the analysis of sympathetic nerve transmission.

III.a. Ganglion Blockers (Ganglioplegic Drugs)

Ganglion blockers are competitive antagonists of the nicotinic cholinergic receptors in the ganglia of both the sympathetic and the parasympathetic nervous system. The inhibition of sympathetic nervous transmission explains the effective lowering of blood pressure provoked by such compounds. Since both sympathetic and parasympathetic ganglia are blocked the side-effects are considerable and very disturbing for the patient. Orthostatic hypotension, constipation, retention of urine, male sexual dysfunction and ocular side-effects (impaired accomodation, and pupillary adaptation) may occur and all of these disturbing adverse reactions can be explained on the basis of both sympathetic and parasympathetic blockade.

III.b. Guanethidine, Bretylium and Reserpine

Guanethidine inhibits the uptake of noradrenalin by sympathetic neurons. Guanethidin also blocks the influx of extracellular Na^+-ions and therefore impairs conduction in postganglionic sympathetic neurons. Treatment with guanethidine is associated with serious and subjectively disturbing side-effects such as orthostatic hypotension, vertigo, congestion of the nasal mucosa and male sexual dysfunction.

Bretylium is also an adrenergic neuron blocker which lowers blood pressure effectively, but it is also associated with unpleasant adverse reactions.

The *Rauwolfia* alkaloid reserpine was originally used as a neuroleptic/antipsychotic agent. It was then discovered to be an effective antihypertensive agent. Reserpine causes depletion of the noradrenaline stores in peripheral postganglionic sympathetic neurons. In addition it causes depletion of noradrenalin in central nervous structures involved in the regulation of blood pressure.

In comparison with more modern antihypertensives reserpine causes unpleasant side-effects, such as sedation, depression and various effects reflecting a dominant parasympathetic system (nasal congestion, diarrhea and exacerbation of peptic ulcers). Reserpine should be considered as an antihypertensive of second choice, although in certain countries it is still used because of its low price.

IV. CENTRALLY ACTING ANTIHYPERTENSIVE DRUGS

IV.a. General Principles

Since blood pressure and various other cardiovascular parameters are subject to regulation by the central nervous system (CNS) it seems a logical approach to search for antihypertensive drugs which primarily influence the CNS. Although complex there exists a relationship between hypertensive disease and the sympathetic nervous system, which offers an important target for antihypertensive drugs, both in the central nervous system and in the periphery. Centrally acting antihypertensives have indeed been developed and introduced in clinical practice. However, until very recently such agents were limited to agonists of central α_2-adrenoceptors, in spite of the wide variety of other central receptors as potential drug targets. Well-known examples of centrally acting α_2-adrenoceptor agonists are clonidine (and a variety of related agents) and α-methyl-DOPA. The latter is a pro-drug, which *in vivo* is converted into its active metabolite α-methylnoradrenaline. Both clonidine and α-methylnoradrenaline stimulate central α_2-adrenoceptors in the brain stem and concomitantly induce peripheral sympathoinhibition and a reduction in (elevated) blood pressure and sometimes also in heart rate.

These centrally acting antihypertensives have been widely used in clinical practice in the nineteenseventies and -eighties. Their haemodynamic profile and antihypertensive efficacy are without any doubt favourable. However, their profile of side-effects

is problematic when compared with more modern drugs such as low dose diuretics, β-blockers, ACE-inhibitors, calcium antagonists and angiotensin II (AT_1)-receptor antagonists. For this reason the older centrally acting α_2-adrenoceptor agonists have lost much of their priority in antihypertensive treatment. In spite of this development the concept of centrally acting antihypertensives remains of interest and potentially attractive for both patho-physiological and haemodynamic reasons.

A newer approach is offered by the discovery of central imidazoline (I_1)-receptors in the rostro-ventrolateral medullary region (RVLM). When stimulated with I_1-receptor agonists peripheral sympathoinhibition occurs, thus resembling the mechanistic sequelae of central α_2-adrenoceptor activation by the classic drugs.

Moxonidine and rilmenidine are the only examples of moderately selective I_1-receptor stimulants which have been developed clinically. Since moxonidine and rilmenidine have much lower affinity for α_2-receptors than for I_1-receptors it may be hoped that they will display a more favourable pattern of side-effects than classic α_2-adrenoceptor stimulants such as clonidine, guanfacine and α-methyl-DOPA.

IV.b. Reserpine

Reserpine lowers elevated blood pressure as a result of neuro-transmitter depletion in peripheral postganglionic sympathetic neurons, as discussed in detail in a separate paragraph. In addition, reserpine also causes neurotransmitter depletion in central neurons involved in the regulation of sympathetic activity and blood pressure. For this reason it may be assumed that this central mechanism contributes to the antihypertensive activity of reserpine. The mechanism of the central antihypertensive action of reserpine has not been analysed in detail.

IV.c. α-Methyl-DOPA

After oral ingestion the prodrug α-methyl-DOPA is converted into its active metabolite α-methylnoradrenaline, a rather selective α_2-adrenoceptor stimulant. Accordingly, α-methyl-DOPA via its active metabolite causes peripheral sympathoinhibition as a result of α_2-adrenoceptor stimulation in the brain stem. α-Methyl-DOPA is an effective antihypertensive, which has been used on a very large scale for decades. Its efficacy and safety are beyond doubt. It is one of the very few drugs which are known to be safe in the treatment of hypertension in pregnancy. However, the tolerability of α-methyl-DOPA is poor when compared with that of other antihypertensives. Sedation, dry mouth, male sexual impotence and various symptoms indicating the domination of the parasympathetic system (nasal congestion, nausea, etc.) are frequently observed. Allergic reactions, characterised by a positive Coombs' test have been reported.

In summary, α-methyl-DOPA may be considered as a second choice antihypertensive. In spite of this it is still used on a moderately large scale in certain countries because of its low cost. Its documented safety in pregnant women explains why it is sometimes used by obstetricians in such patients.

IV.d. Clonidine

Clonidine has been put forward for many years as the prototype of selective agonists of central α_2-adrenoceptor agonists. More recently it has been shown to be a mixed agonist of both α_2- and I_1-receptors in the central nervous system. It is an effective antihypertensive which has been used on a large scale for several decades. Its use has greatly declined in recent years because of its poor tolerability when compared with more modern antihypertensives. Sedation, dry mouth and sexual impotence are the most obvious side-effects.

The sudden cessation of treatment with clonidine, especially when applied in high doses for prolonged periods, has been shown to cause a withdrawal phenomenon, characterised by general symptoms of sympathetic hyperactivation.

In anaesthesiology clonidine may be used to suppress perioperative hypertension.

In conclusion, the concept of centrally acting drugs causing peripheral sympathoinhibition has been investigated in depth and indeed led to the development of a few clinically useful agents. The relatively poor tolerability of these agents when combined with more modern therapeutics has reduced the priority of α-methyl-DOPA, clonidine and guanfacine to second choice therapeutics in hypertension, notwithstanding the theoretically favourable mode of action and haemodynamic profile.

The discovery of the centrally acting imidazoline receptor stimulants moxonidine and rilmenidine theoretically offers the same haemodynamic advantages as the α_2-adrenoceptor agonists. However, it may be hoped that their profile of side-effects is more favourable, owing to their lower affinity for

α_2-adrenoceptors. Moxonidine and rilmenidine are far from perfect compounds and it would be feasible and desirable to develop more selective compounds based on the same principle.

V. VASODILATOR DRUGS WITH A DIRECT ACTION

A few older drugs are directly acting vasodilators, which means that vasodilatation is induced without an interaction with the autonomic nervous system. Vasodilatation is brought about by a complex mechanism involving calcium movements, whereas for some of these drugs potassium channel opening may play a role. The clinical application of this type of vasodilators is limited. Monotherapy of hypertension cannot be carried out satisfactorily, since drugs of this type provoke a reflectory activation of both the sympathetic nervous system and the renin–angiotensin–aldosterone system (RAAS). Accordingly, reflex tachycardia and fluid retention will occur. These problems may be compensated, at least in part, by adding a β-blocker and a diuretic agent. Other drugs of this type may be used intravenously in order to induce a rapid and transient fall in blood pressure. This procedure, however, may be dangerous in particular in elderly patients and it is performed rarely at present. The individual drugs of this category will be briefly discussed here.

Hydralazine and *dihydralazine* are predominantly arterial vasodilators which cause a reduction in peripheral vascular resistance but also reflex tachycardia and fluid retention. They were used in the treatment of hypertension, in combination with a β-blocker and a diuretic. Long-term use of these compounds may cause a condition resembling lupus erythematodes with arthrosis, dermatitis and LE-cells in the blood. This risk is enhanced in women and in patients with a slow acetylator pattern. When combined with the venous vasodilator isosorbide (an organic nitrate) hydralazine was shown to be mildly beneficial in patients with congestive heart failure (V-HEFT I Study). Hydralazine and dihydralazine have been replaced by other therapeutics, both in hypertension treatment and in the management of heart failure.

Minoxidil is a potent vasodilator predominantly with respect to resistance vessels. Vasodilatation is brought about, at least in part, by the opening of potassium channels, thus causing hyperpolarisation and the inhibition of calcium influx. Minoxidil has a proloned duration of action of 3–4 days, as a result of strong binding to vascular smooth muscle tissues. Reflex tachycardia and fluid retention are provoked by minoxidil. It is therefore unsuitable for monotherapy of hypertension. If at all used as an antihypertensive minoxidil should be combined with a β-blocker and a diuretic. Hypertrichosis is an unpleasant adverse reaction, in particular in women. Conversely, this effect may be used deliberately as an attempt to treat alopecia, by the topical application of minoxidil.

Diazoxide is a potassium channel opener with a rapid antihypertensive action after intravenous administration. Diazoxide causes hyperglycaemia which may underlie side-effects such as nausea and vomiting, cardiac dysrhythmia and ketosis. Diazoxide was used occasionally in the management of hypertensive emergencies, but it is now largely abandoned for this indication. Diazoxide is an alternative for glucagons in patients with hypogycaemia.

Sodium nitroprusside (SNP) is both a venous and an arterial vasodilator. An important part of its vasodilator action is caused by the release of nitric oxide (NO), similarly as for the organic nitrates. SNP can only be administered via the intravenous route. It is a rapidly and short acting vasodilator. It has been used in the treatment of hypertensive emergencies and in the management of myocardial ischaemia. In spite of its vasodilator action it hardly influences heart rate, in contrast to hydralazine and minoxidil. The dosage of SNP should not be higher than 3 µg/kg/min within 48 h, in order to avoid the rise of cyanide ions and thiocyanate in the blood.

VI. ORGANIC NITRATES (NITRO COMPOUNDS)

VI.a. General Principles

Organic nitrates (nitro compounds) are vasodilators with a predominant effect on the venous vascular bed (capacitance vessels) and a concomitant reduction of the cardiac preload. In higher doses, arterial vasodilatation at the level of resistance vessels (arterioles) may occur as well, thus leading to cardiac afterload reductions. Higher doses may also cause some coronary arterial dilatation. The reduction of cardiac preload and at higher doses also of cardiac afterload, will reduce myocardial oxygen consumption, leading to the improvement of angina pectoris. In addition, coronary arterial dilatation at higher doses

will somewhat enhance myocardial oxygen supply. This effect becomes particularly relevant when coronary spasm is present, as in Prinzmetal's or variant angina. These haemodynamic changes in the periphery (preload and afterload reduction) and to a lesser degree also at the cardiac level, will lead to an improvement of the imbalance of cardiac oxygen consumption/supply, which is characteristic for ischaemic heart disease.

In clinical practice, nitrates are used on a large scale in the treatment of ischaemic heart disease, in particular stable angina. Although very effective as a symptomatic measure, it remains unclear so far whether the prognosis of patients with stable angina is improved by nitrate treatment. Clinical trials addressing this question are ungoing.

Vasodilatation explains both the therapeutic efficacy of the nitrates in angina (see above) and their well-known side-effects, such as headache, facial flush, reflex tachycardia, and (in higher doses) hypotension.

Nitrates (with nitroglycerin as their prototype) have been known for well over a century. It was only very recently, however, that their mode of action at the cellular level has been established. Nitrates are known to release *in vivo* the simple but very reactive compound nitric oxide (NO), which enhances the formation of the endogenous vasodilator cyclic guanosine monophosphate (cGMP; Fig. 1). It has been demonstrated that the vascular endothelium, when stimulated appropriately, for instance, by endogenous acetylcholine, releases the endothelium-derived relaxing factor (EDRF), which causes vasodilatation. Since a few years, it is known that EDRF consists of nitric oxide (NO), synthesized *in vivo* from L-arginine. In fact, the nitrates, by releasing NO, are imitating this physiological principle. The vasodilator effect of the nitrates is endothelium-independent, since it persists in vessels with damaged or absent endothelium. After the successful therapeutic use of nitroglycerin for more than a century, it has suddenly become clear which cellular mechanism is underlying the drug's beneficial vasodilator effects.

Short-acting nitrates, such as nitroglycerin, are predominantly used for the suppression of acute anginal symptoms. The well-known sublingual (oromucosal) route of administration is characterised by

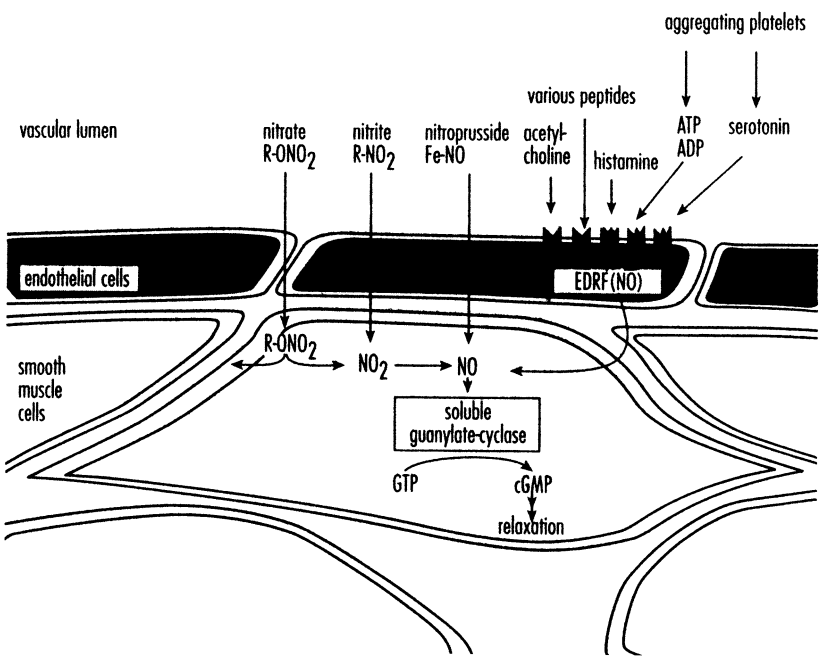


Fig. 1. The EDRF/NO pathway in vascular smooth muscle. Vasodilatation by nitrates at a cellular level. Nitrates, nitrites, and nitroprusside-Na are able to release nitric oxide (NO), which stimulates the conversion of GTP into cyclic guanosine monophosphate (cGMP), thus causing vasodilatation. The release of EDRF (=NO) from endothelial cells can be stimulated by various endogenous compounds. Endogenous EDRF (=NO) then causes vasodilatation, similar to the NO released by nitrates et cetera via the formation of cGMP.

rapid relief of symptoms, owing to the rapid absorption of the drug in this densely vascularised region. A further advantage of the sublingual route of administration may be the avoidance of the hepatic circulation (as after oral ingestion), thus precluding rapid hepatic degradation. Longer acting nitrates are obtained by means of slow-release preparations. Sprays, ointments, and transdermal preparations are also available. Apart from their well-established use in the treatment of angina, nitrates may also be used to reduce cardiac preload, in particular in conditions of heart failure.

VI.b. Preparations

Nitroglycerin, the prototype of the nitrates is characterized by a rapid onset and short duration of action. It is usually administered sublingually (via the oromucosal route), which allows a rapid and efficient absorption and avoids the strong first pass effect after oral administration. Nitroglycerin is available as tablets, capsules (for sublingual administration) but also as transdermal preparations, sprays, and ointments.

Isosorbide is available as the di- and mononitrate, respectively. The mononitrate is known to be the active form, which is generated by biodegradation of the dinitrate. On theoretical grounds, the mononitrate as a drug would therefore be preferable, but a relevant clinical benefit for the mononitrate remains to be demonstrated. Accordingly, both preparations may be used. Isosorbide's action develops somewhat slower than that of nitroglycerin and its duration is longer. Isosorbide may be used for the suppression of an acute attack of angina, but nitroglycerin is probably preferable because of its more rapidly developing action. Isosorbide is the drug of choice for long-term lowering of cardiac preload in conditions of myocardial ischaemia.

VI.c. Tolerance

Tolerance to nitrates may be observed when these agents are used repeatedly with short intervals. The loss of therapeutic efficacy thus observed may be attributed to two different mechanisms:

- the inactivation of SH-groups;
- reflex activation, as a response to nitrate-induced vasodilatation, of the sympathetic nervous system. The tachycardia thus induced, counteracts the beneficial effects of the nitrates with respect to the imbalance of the ratio myocardial oxygen consumption/supply.

Attempts have been made to suppress or circumvent the tolerance to nitrates:

- by adding SH-group donors, such as N-acetylcysteine, to the therapeutic regimen;
- by applying nitrate-free intervals by means of intermittent application of such drugs.

So far, the solution to this problem remains unsettled.

VII. CALCIUM ANTAGONISTS

VII.a. General Principles

Calcium antagonists (CA), also known as calcium entry blockers or calcium channel blockers, have acquired and maintained an important position in the drug therapy of cardiovascular diseases, in particular hypertension, angina pectoris, and supraventricular tachy-arrhythmias (verapamil only). The chemical structures of the various preparations are largely heterogeneous. The most important CA used in the treatment of cardiovascular diseases belong to the subgroups of phenylalkylamines (verapamil and gallopamil), dihydropyridines (nifedipine and others), and benzothiazepines (diltiazem), respectively. In spite of this chemical heterogeneity, all CA have the same mode of action at the cellular level, that is the competitive blockade of the influx of extracellular calcium ions via specific calcium channels of the L-type in the cell membrane (Fig. 2). Accordingly, there will be less activation of intracellular structures and particles by calcium ions, resulting in vascular smooth muscle relaxation, reduction in cardiac contractile force, heart rate, AV conduction, etc. The patterns of the haemodynamic changes brought about by the CA are largely different for the three major groups of compounds, as shown in Fig. 3. These patterns may be summarized as follows:

Verapamil and a few newer drugs of this category are vasodilator agents, which in addition impair AV conduction, reduce heart rate and cardiac contractile force. Verapamil was initially developed for the treatment of supraventricular tachycardia and it continues to be an important drug for the management of this condition, also postoperatively. Verapamil is the CA of choice in the management of hypertrophic cardiomyopathy. Verapamil is also used in the treatment of stable angina and, less frequently, essential hypertension.

Dihydropyridines are predominantly vasodilator drugs at the level of resistance vessels (precapillary arterioles) and to a certain degree also in the

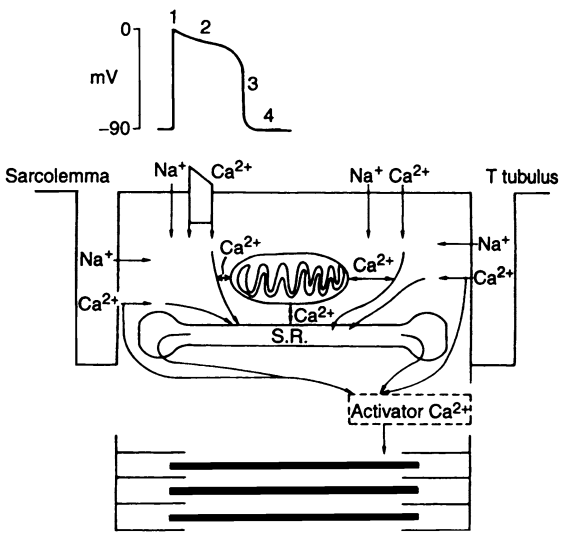


Fig. 2. Effect of calcium antagonists (CA) on a cardiac cell. Top: typical cardiac action potential. The calcium (slow) inward current flows during the characteristic plateau phase (phase 2) of the action potential. This calcium influx is selectively inhibited by CA. Activation of the sarcoplasmic reticulum (SR) and other cellular calcium pools occurs via Ca^{2+} and Na^{+} ions which flow into the cell. The SR and other pools donate activator Ca^{2+} ions which stimulate the contractile proteins. The presence of tubular systems (invaginations), which are characteristic of cardiac tissues, results in considerable enlargement of the cellular surface, thus enabling an effective influx of Na^{+} and Ca^{2+} ions. Inhibition of the calcium inward flux by a CA causes diminished activation of the contractile proteins.

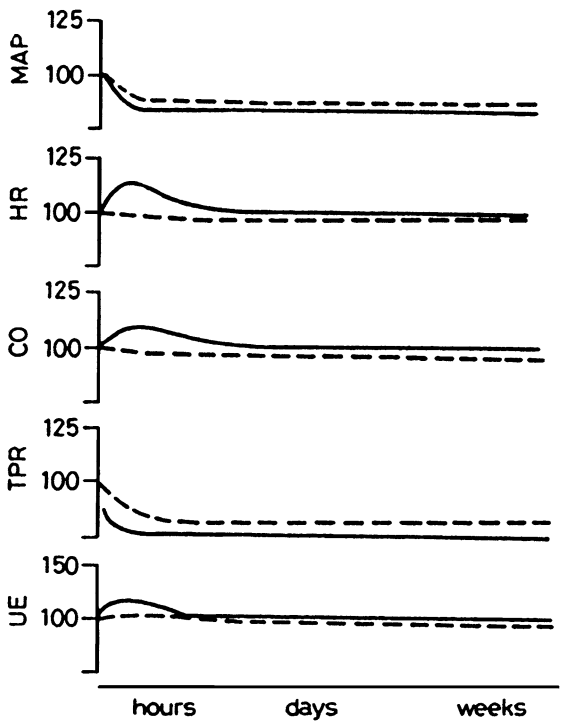


Fig. 3. Haemodynamic effects of different types of calcium antagonists. Drawn lines: nifedipine and other rapidly an short-acting dihydropyridines. Dotted lines: verapamil and diltiazem. MAP = mean arterial pressure; HR = heart rate; CO = cardiac output; TPR = total peripheral resistance; UE = urinary excretion of Na^{+} and H_2O. Note the reflex tachycardia, provoked by nifedipine.

coronary system, in particular if coronary spasm is present. In therapeutic doses they do not directly influence the venous system (capacitance vessels). Neither do they directly influence the nodal systems in the heart, at least in therapeutic doses. The moderate, usually transient tachycardia caused by dihydropyridine-CA is secondary to the reflex activation of the sympathetic nervous system via the baroreceptors (reflex tachycardia). The dihydropyridines possess weak natriuretic activity, probably as a result of a direct tubular effect in the kidney. This activity explains why dihydropyridine-CA, although potent vasodilators, do not cause systemic fluid retention. The adverse reactions to dihydropyridine-CA also reflect vasodilation: headache, flush, palpitations. The ankle edema observed during the use of these compounds is probably the result of a direct effect on the regional microcirculation and/or the lymph vessels; ankle edema is not a reflection of systemic fluid retention and it responds poorly or not at all to treatment with diuretics. Dihydropyridine-CA are predominantly used for the treatment of essential hypertension or stable angina pectoris. Rapidly and short-acting compounds (nicardipine, nifedipine) may be used for the peri-operative treatment of hypertension or for the management of a hypertensive emergency. The newer dihydropyridines will be dealt with in a separate paragraph.

Diltiazem, a benzothiazepine, has a pharmacodynamic and side-effect profile that is intermediary between those of nifedipine and verapamil. Diltiazem is mostly used in the treatment of stable angina. It also displays antihypertensive activity, although it is not widely used in antihypertensive treatment. In certain countries diltiazem is used as an antiarrhythmic agent with the same type of applications as verapamil.

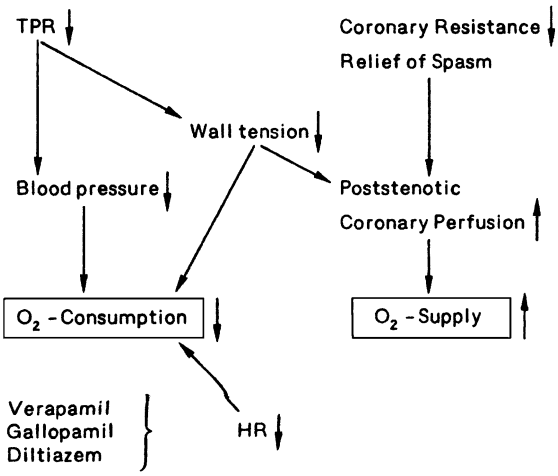


Fig. 4. Schematic presentation of the mechanism of calcium antagonists with respect to their beneficial effect in angina pectoris. The final result is an improvement of the imbalance between myocardial oxygen demand and supply. TPR = total peripheral resistance; HR = heart rate.

The various haemodynamic changes underlying the beneficial effects of CA may be summarized as follows:

1. Antihypertensive activity: Vasodilation of the resistance arteries (precapillary arterioles).
2. Antiischaemic activity (Fig. 4):
   - Dihydropyridine-CA: reduction of cardiac afterload → reduction of coronary spasm and coronary vasodilatation: improved myocardial oxygen supply.
   - Verapamil and diltiazem: as for the dihydropyridines. In addition: reduction in heart rate → reduced myocardial oxygen consumption.
3. Antiarrhythmic activity (verapamil, possibly also diltiazem): impairment of AV conduction and to a lesser degree also that of sinus node activity.
4. Reduction of the left ventricular outflow obstruction and antiarrhythmic activity underlying the beneficial effect of verapamil.

VII.b. Adverse Reactions

Most of the adverse reactions to CA can be readily explained on the basis of their haemodynamic actions.

Nifedipine and other dihydropyridines:

- vasodilatation, as reflected by flush, headache, and reflex tachycardia (palpitations),
- negative inotropic activity (weak, and attenuated by vasodilation),
- ankle edema, based on interference with the local micro-circulation and not as an expression of systemic fluid retention,
- the newer dihydropyridines cause less or no reflex tachycardia, whereas the negative inotropic effect is weak or absent.

Verapamil and related drugs:

- constipation,
- impaired AV conduction, risk of AV block,
- negative inotropic and chronotropic activity,
- vasodilation, as reflected by headache and flush, although milder than observed with nifedipine,
- no reflex tachycardia but, in contrast, a reduction in heart rate,
- no ankle edema.

Diltiazem: as for verapamil and also: vertigo, headache, bradycardia and blurred vision.

VII.c. Relevant Interactions with Other Drugs

Nifedipine: β-blockers suppress reflex tachycardia (favourable), but enhance the negative inotropic activity.

Verapamil: additive cardiodepressant activity when combined with a β-blocker; additive impairment of AV conducton when combined with digoxin.

Diltiazem: as mentioned for verapamil.

VII.d. New Calcium Antagonists

Several new calcium antagonists (CA) have been registered in the past decade. The following trends draw attention:

1. Virtually all of the newly introduced CA are dihydropyridines.
2. Most new CA are characterized by an improved pharmacokinetic profile when compared with the classical compound nifedipine. Accordingly, the newer compounds are characterized by a slow-developing and longer lasting vasodilator activity. The slow-developing action implies that less or no reflex tachycardia is elicited, in contrast to nifedipine. Owing to the persistence of the effect, once-daily administration is sufficient to achieve satisfactory control of blood pressure or angina. Amlodipine, lacidipine, lercanidipine, and manidipine are examples of such compounds. Sophisticated pharmaceutical preparations may be used to develop slow- and long-acting compounds, which, in their basic, simple form, are rapidly and short-acting. Examples are the slow-release forms of felodipine, isradipine, nifedipine (nifedipine-GITS), nicardipine and nisoldipine.

3. Dihydropyridine-CA have been developed with a certain degree of vascular selectivity, which implies that at therapeutic doses such compounds would have less negative influence on cardiac contractile force or none at all. Indeed, a few of such compounds are devoid of cardiodepressant (negative inotropic) activity. Examples of such compounds are amlodipine, felodipine, isradipine, lacidipine, lercanidipine and manidipine.
4. For a few compounds claims have been made that they may even be selective for a particular vascular bed. Examples are nimodipine (cerebral vessels), nisoldipine (coronary arteries), and manidipine (renal vascular bed). Although potentially attractive, the clinical evidence for such a selectivity is so far not convincing.
5. Mibefradil is a verapamil-like agent with a potentially attractive haemodynamic profile. It is a vasodilator, which also causes a reduction in heart rate, whereas it is devoid of negative inotropic activity. Some of its properties are attributed to its influence of calcium channels of the T- and N-types. Unfortunately, the compound has been withdrawn because of multiple interactions with various other drugs.
6. Antiatherogenic activity of CA has been observed in animal and biochemical experiments and this antiatherogenic activity cannot be explained by changes in the plasma lipid profile, which remains unaffected by CA-treatment. It has been extremely difficult to prove antiatherogenic activity of CA in patients and the evidence so far put forward is not convincing. A few clinical trials addressing this matter are ongoing.

VIII. POTASSIUM CHANNEL OPENERS

Potassium channel openers (PCO) are a new group of vasodilator/antiischaemic drugs with a certain pharmacological similarity to the calcium antagonists, at least at the cellular level. PCO, as indicated by their nomenclature, will enhance the outflow of cellular potassium ions, thus causing hyperpolarisation of the cell membrane. Accordingly, the influx of extracelular calcium ions will be impaired, a mechanism greatly resembling the effect of calcium antagonists. In addition, PCO display strong antiischaemic effects. Although potent vasodilator drugs, the PCO are unsuitable for the monotherapy of hypertension or angina, because of the strong reflex tachycardia provoked by these compounds. This unwanted effect can be suppressed by the addition of a β-blocker. Examples of PCO drugs include the anti-hypertensive agents, minoxidil, diazoxide and pinacidil, as well as a variety of benzopyran derivatives such as levcromakalim, bimakalim, and rilmakalim. Only the benzopyran derivatives have been profiled as therapies for asthma. The application of PCO may be considered in the treatment of myocardial ischaemia. In cardiopulmonary surgery, PCO are the subject of investigation concerning their usefulness as additives to cardioplegic solutions.

VIII.a. Well-Known Potassium Channel Openers

Nicorandil is the only PCO so far registered in a few countries, aiming at the treatment of stable angina pectoris. However, this agent is a hybrid drug, since apart from being a PCO it is also a nitrate (comparable with nitroglycerin and related compounds). Nicorandil may be considered in angina if there exists resistance against conventional drugs, such as β-blockers, nitrates and calcium antagonists.

Cromakalim, aprakalim and bimakalim are examples of experimental PCO.

IX. ACE-INHIBITORS

IX.a. General Principles

Inhibitors of the angiotensin I-converting enzyme (ACE-inhibitors) have been introduced into cardiovascular medicine, in particular for the treatment of hypertension and congestive heart failure (CHF).

They are inhibitors of the enzyme ACE, which is predominantly present in the lungs but also in blood vessels and the central nervous system. Accordingly, the conversion of the inactive decapeptide angiotensin I into the biologically active angiotensin II (Ang II) is reduced. Angiotensin II is the main effector of the renina–ngiotensin–aldosterone-system (Fig. 5). Angiotensin II induces a series of effects which are assumed to be unfavourable for the organism, such as: vasoconstriction and a rise in blood pressure; release of aldosterone from the adrenal cortex; enhancement of sympathetic stimuli; enhanced cellular growth and hence the stimulation of vascular and myocardial hypertrophy. All of these effects are mediated by specific receptors, called angiotensin II (AT)-receptors.

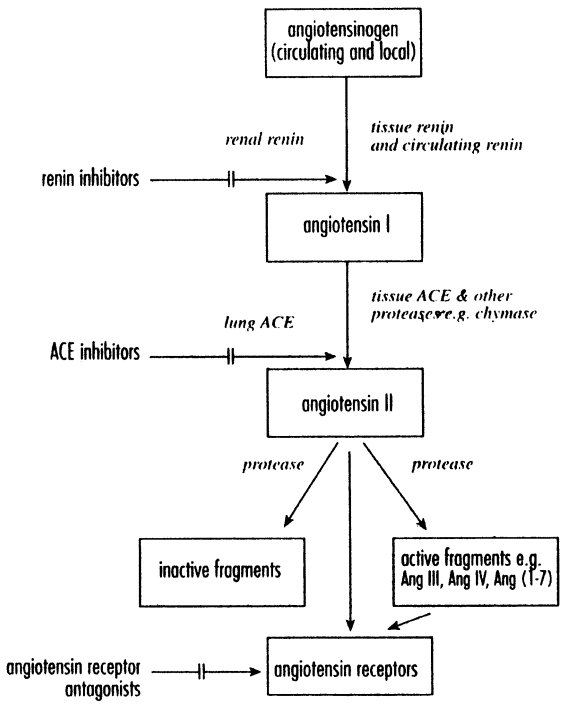


Fig. 5. The renin–angiotensin system. Catalyzed by the enzyme renin, the inactive decapeptide angiotensin I is split off from the substrate angiotensinogen. Angiotensin I is converted into the active octapeptide angiotensin II, under the influence of the angiotensin I-converting enzyme ACE. In the human heart the enzyme chymase also catalyzes the formation of angiotensin II. Angiotensin II is considered the main effector of the renin–angiotensin system. The various sites of action of drugs interacting with the renin–angiotensin system are shown as well. Renin inhibitors inhibit the biosynthesis of angiotensin II in an early stage. Inhibitors of the angiotensin I-converting system (ACE-inhibitors) also suppress the formation of angiotensin II. However, the enzyme chymase is not influenced by ACE-inhibitors. Accordingly, the angiotensin II-formation via the chymase pathway is not depressed by ACE-inhibitors. Angiotensin II-receptor antagonists inhibit the various effects of angiotensin II at the receptor level.

Conversely, the suppression of the biosynthesis of Ang II via ACE-inhibition will lead to vasodilatation, reduced release of aldosterone, blunting of sympathetic stimuli, and impairment of myocardial and vascular hypertrophy. The antihypertensive effect of the ACE-inhibitors is readily explained on the basis of vasodilatation, which occurs predominantly in the resistance vessels (arterioles) and, to a lesser extent, also in the venous system. Vasodilatation by ACE-inhibition will cause a reduction of cardiac afterload and preload in patients with heart failure. In addition, the ACE-inhibitors exert a favourable effect on the neuro-endocrine activation process associated with chronic heart failure. They are more effective than classic vasodilators such as hydralazine and isosorbide, which do not influence these neuro-endocrine mechanisms in a favourable manner.

ACE-inhibitors are known to cause regression of left ventricular and vascular hypertrophy. This phenomenon is important in the long-term treatment of hypertension, where cardiac hypertrophy is known to be an important, virtually independent risk factor. Data that are beginning to emerge, which indicate that ACE-inhibitors may be beneficial as secondary prevention in postinfarct patients, especially if signs of heart failure occur. This favourable influence of the ACE-inhibitors may be the result of haemodynamic effects, a favourable effect on neuro-endocrine mechanisms, and also a beneficial influence on the process of remodeling of the heart, secondary to a myocardial infarction.

Long-term treatment with ACE-inhibitors is associated with a significant rise in plasma renin activity (PRA), but not of plasma angiotensin II. The relevance of the rise in PRA is not clear. Since the enzyme ACE is identical with kininase II there occurs an accumulation of the endogenous vasodilator bradykinin. Bradykinin is assumed by certain investigators to significantly contribute to the therapeutic effect of ACE-inhibitors, although this hypothesis is subject to debate. ACE-inhibitors inhibit both the conversion of plasma angiotensin I and that in tissues, and both effects are assumed to underlie the therapeutic effects of these drugs. More recently the ACE-inhibitors have been recognized as beneficial in the prevention of diabetic nephropathy. The antihypertensive action of these drugs contributes to this beneficial effect, but probably also the regression of vascular remodeling in the glomerular structures.

Hypotension, in particular in combination with diuretics, is a well-known adverse reaction to ACE-inhibitors when used in patients with heart failure. Dry cough, possibly mediated by the accumulation of bradykinin, is also a well-known side-effect in 5–15% of the patients treated with an ACE-inhibitor. Impaired renal function may be worsened by ACE-inhibitors. Allergic reactions, sometimes rather intense, may be observed occasionally. In rare cases angioneurotic edema has been described. ACE inhibitors should be avoided in women who are likely

to become pregnant. There is a risk of birth defects when taken during the second and third trimester. It has also been found that use of ACE inhibitors in the first trimester is associated with a risk of major congenital malformations.

The following interactions with other drugs are relevant:

- hyperkalemia may occur when an ACE-inhibitor is combined with a potassium-sparing diuretic;
- classical diuretics (thiazides, loop diuretics) potentiate the hypotensive effect of ACE-inhibitors and their combination should be applied cautiously;
- additional use of NSAID's with an ACE-inhibitor may diminish the hypotensive action of the ACE-inhibitor, and the combination of both drugs may enhance renal dysfunction.

IX.b. Pharmacokinetic Properties

Most of the so far available ACE-inhibitors with the exception of captopril and lisinopril are prodrugs, which are converted in the liver into an active metabolite.

The relationship between plasma levels of the ACE-inhibitors and their duration of action is hardly relevant, since the binding of the ACE-inhibitor to the target enzyme (ACE) plays an important role. Tissue ACE is probably a relevant target of the ACE-inhibitors. Most ACE-inhibitors are eliminated via the kidney, in the unchanged form or (at least in part) as active metabolites. Fosinopril, quinapril and trandolapril are eliminated both via the kidney and via the liver.

IX.c. Choice of an ACE-Inhibitor

Three groups of ACE-inhibitors can be distinguished. Captopril, the first ACE inhibitor, is a sulfhydryl-containing agent. The group dicarboxylate-containing agents, the largest group, include enalapril, ramipril, quinapril, perindopril, lisinopril and benazepril. The only member of the phosphonate-containing agents is fosinopril.

Captopril and enalapril are the standard examples of ACE-inhibitors, which have been used on a large scale for almost two decades. The differences between the two preparations are predominantly based on pharmacokinetic parameters. Enalapril is a prodrug, which is converted into its active compound enalaprilate after oral ingestion; captopril is active as such. Enalapril can be given once daily, whereas captopril is administered 2–3 times per 24 h. The presence of an SH-moiety in the captopril molecule does not imply particular toxicological problems, in contrast to earlier speculations on this matter. In conclusion, the practical differences between both drugs are largely irrelevant, apart from the differences in dosage schedule.

Since the differences between the various newer ACE-inhibitors are marginal captopril and enalapril continue to be the drugs of choice, also because of the wide experience acquired with these agents.

X. ANGIOTENSIN II-RECEPTOR ANTAGONISTS (AT_1-BLOCKERS)

X.a. General Principles

Peptidergic antagonists of angiotensin II-receptors, such as saralasin, became available in the nineteen-seventies. Because of their poor bioavailability such compounds could not be used in the long-term treatment of hypertension and congestive heart failure.

Non-peptidergic antagonists of the angiotensin II-receptor were then introduced in the treatment of hypertension. These compounds inhibit virtually all of the detrimental effects of Ang II at the receptor level (Fig. 5), such as vasoconstriction, enhanced release of aldosterone, vascular hypertrophy, etc. Ang II-receptors are subdivided into AT_1- an AT_2-receptors, respectively. All detrimental effects of Ang II, outlined in the paragraph on ACE-inhibitors, are known to be mediated by the AT_1-receptor subtype. Concomitantly, the beneficial effect of AT-receptor blockers are all mediated by AT_1-receptor blockade. The haemodynamic effects of the AT_1-blockers so far available are very similar to those of the ACE-inhibitors. They are vasodilators in the arterial vascular bed (resistance vessels) but also, although less actively, in the venous bed (capacitance vessels). Heart rate remains unchanged. Long-term treatment with an AT_1-blocker is associated with a rise in plasma renin activity and angiotensin II concentrations.

High levels of circulating angiotensin II will stimulate the AT_2-receptor and this mechanism may counteract the noxious process of vascular and myocardial remodeling. A potential theoretical advantage of the AT-receptor blockers over the ACE-inhibitors may be the inhibition of all Ang II effects at the AT-receptor level. ACE-inhibitors suppress a major portion of the Ang II synthesis, but the

Ang II generated via the chymase pathway (in particular in the human heart, see Fig. 5) is uninfluenced, since the chymase pathways remain unaffected by treatment with ACE-inhibitors. Combination of an ACE-inhibitor and an AT_1-receptor antagonist can be thought of as potentially beneficial.

The therapeutic efficacy of AT_1-receptor blockers in hypertensive disease is well documented. The AT_1-blockers are assumed to be as effective as various classes of well-known antihypertensives, such as β-blockers, diuretics, ACE-inhibitors and calcium antagonists. A major advantage of the AT_1-blockers may be their favourable pattern of side-effects, which so far does not appear to differ from the use of placebo. In particular the fact that AT_1-blockers do not cause cough (in contrast to the ACE-inhibitors) appears to be an advantage.

Epidemiological data concerning the protective effect of AT_1-blocker treatment on the sequelae of hypertensive disease (coronary heart disease, stroke, renal disease) are so far not available, but appropriate trials addressing this question are on the way.

Losartan is the prototype of the non-peptidergic AT_1-receptor antagonists. Losartan is a prodrug which is converted into a more active metabolite which largely contributes to the antihypertensive activity. Numerous new AT_1-blockers have recently been introduced as antihypertensives. Candesartan, eprosartan, telmisartan, irbesartan and valdesartan are examples of these newer compounds. Their position in the management of hypertension remains to be established. All of the AT_1-blockers so far available can be used in a once daily schedule of antihypertensive treatment. Pharmacological differences between AT_1-receptor blockers are reflected in clinically important differences in maximal antihypertensive effect, response rate, and duration of action. There is currently no evidence that differences in receptor binding between AT_1-receptor blockers translate into differences in tolerability. AT_1-receptor blockers show placebo-like tolerability at all doses evaluated in clinical trials.

Data are beginning to emerge indicating that AT_1-blockers may be useful in the treatment of congestive heart failure, in particular of the patients who do not tolerate ACE-inhibitors (mostly because of cough).

X.b. AT_1-Receptor Blocker or ACE-Inhibitor?

The question whether AT_1-blockers may offer relevant advantages over the well-established ACE-inhibitors is an obvious one. For theoretical reasons the direct blockade of AT_1-receptors, as the target of angiotensin II, appears to be a logical approach, even more so since the ACE-inhibitors can only partially suppress the formation of angiotensin II. In spite of this the antihypertensive action of the AT_1-blockers is not more pronounced than that of the ACE-inhibitors. As far as can be judged the haemodynamic profile of the AT_1-blockers and the ACE-inhibitors are comparable. The major difference between both categories of drugs therefore appears to be the profile of adverse reactions, which is more favourable for the AT_1-blockers, in particular with respect to the absence of cough.

XI. DIRECT RENIN INHIBITORS

Direct renin inhibitors, a new class of antihypertensive drugs, block the RAS pathway at the point of activation. Inhibition of renin prevents the downstream production of the potent vasoconstrictor angiotensin II, which is responsible for increasing blood pressure. Clinical trials demonstrate direct renin inhibitors reduce systolic and diastolic blood pressure comparable with other commonly used antihypertensive drugs, including angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. Aliskiren, a direct renin inhibitor of a novel structural class, inhibits the activity of the renin produced and, thus, its capacity to form angiotensin I, as measured by plasma renin activity. Aliskiren has been shown to be efficacious in hypertensive patients at once-daily oral dosing.

XII. POSITIVE INOTROPIC AGENTS

XII.a. Catecholamines and Related Agents (Sympathomimetic Drugs)

Drugs of this type can only be administered intravenously. Their effects, based on the stimulation of cardiac β_1-adrenoceptors, develop rapidly and are rather short, thus requiring continuous intravenous administration. A rise in heart rate and the risk of tachy-arrhythmia are logical side-effects of such agents, also mediated by β-adrenoceptor stimulation.

Dobutamine is the most frequently used drug of this category. It is considered to be a selective β_1-adrenoceptor stimulant, although it displays weak β_2- and α_1-adrenoceptor stimulation as well. It

may be used in advanced stages of congestive heart failure as an inotropic agent. In order to avoid further downregulation of β-adrenoceptors its period of administration should be shorter than 3 weeks. The use of dobutamine in congestive heart failure offers no more than palliative treatment. In higher doses dobutamine may cause a rise in blood pressure, in particular in hypertensives.

Dopamine stimulates dopaminergic (DA_1), β_1- and α-adrenoceptors. Accordingly, it is an inotropic agent that may also stimulate the kidney function. In higher doses, dopamine may cause vasoconstriction as a result of α_1-adrenoceptor stimulation. Dobutamine and dopamine may be combined, although this combination is hardly rational.

Dopexamine, an agonist of cardiac β_2-adrenoceptors and renal DA_1-receptors, may be considered an inotropic drug with additional renal and peripheral vasodilator activities. Its duration of action is rather short and the drug is rarely used at present.

Noradrenaline and adrenaline are the classic catecholamines and neurotransmitters in the sympathetic nervous system. Noradrenaline stimulates the following subtypes of adrenoceptors: $\beta_1, \alpha_1, \alpha_2$. It has positive inotropic and chronotropic activities as a result of β_1-receptor stimulation. In addition, it is a potent vasoconstrictor agent as a result of the stimulation of both subtypes (α_1, α_2) of α-adrenoceptors. After intravenous infusion, its effects develop within a few minutes, and these actions disappear within 1–2 minutes after stopping the infusion. It may be used in conditions of acute hypotension and shock, especially in patients with very low vascular resistance. It is also frequently used as a vasoconstrictor, added to local anaesthetics. Adrenaline stimulates the following subtypes of adrenoceptors: β_1, β_2, α_1, α_2. Its pharmacological profile greatly resembles that of noradrenaline (see above), as well as its potential applications in shock and hypotension. Like noradrenaline, its onset and duration of action are very short, as a result of rapid inactivation *in vivo*. Both noradrenaline and adrenaline may be used for cardiac stimulation. Their vasoconstrictor activity should be kept in mind. A problem associated with the use of β-adrenoceptor stimulants is the tachyphylaxis of their effects, explained by the β-adrenoceptor downregulation, which is characteristic for heart failure.

Isoprenaline, a $\beta_1 + \beta_2$-receptor agonist, is sometimes used in paediatric cardiac surgery. It causes a rise in cardiac contractile force and heart rate (both via β_1) as well as vasodilatation (β_2-effect).

XII.b. Phosphodiesterase (PDE) Inhibitors

The enzyme phosphodiesterase (type III) catalyzes the biode-gradation of cyclic AMP (cAMP). Inhibition of this enzyme will cause accumulation of the nucleotide cAMP and hence induces an increase in cardiac contractile force. This effect does not involve cardiac β-adrenoceptors and will therefore persist after downregulation of these receptors associated with heart failure.

Piroximone and enoximone (imidazalone derivatives) and Milrinone (a bipyridine mderivative) are well-known PDE III-inhibitors, used for the short-term treatment of cardiac failure. Clinically these drugs mimic sympathetic stimulation and increase cardiac output. The inotropic effect is associated with peripheral vasodilatation, which as such is usually considered unwanted in the treatment of acute heart failure. The long-term treatment of *chronic* CHF with milrinone was found to be disappointing, as reflected by the enhanced mortality of milrinone-treated patients (compared with placebo) in the PROMISE study. The enhanced mortality of milrinone-treated patients has led to the assumption that PDE III-inhibitors are contra-indicated in patients with chronic CHF. The beneficial effects of milrinone and enoximone in *acute* heart failure, as observed in connection with cardiac surgery and anaesthesiology, however, are widely accepted and beyond reasonable doubt. The enzyme PDE III occurs in various subtypes and isozymes, with a differential pattern of distribution in various tissues and organs. Several compounds that are more or less selective inhibitors of some of these subtypes have been developed and investigated. Apart from the moderately selective PDE III-inhibitors milrinone and enoximone, this development has so far not led to relevant clinical innovation.

The moderately selective PDE type V-inhibitor sildenafil (Viagra®) has been introduced in the treatment of erectile dysfunction. On the basis of cyclic GMP accumulation sildenafil is claimed to be a selective vasodilator in erectile tissues in the penis because of the high concentration of PDE type V in this region. Several of its adverse reactions (headache, flush, hypotension) reflect its vasodilator actions in other vascular beds than that of the penis. The drug will not be further discussed here.

XII.c. Cardiac Glycosides

XII.c.1. General Principles

Cardiac glycosides display positive inotropic activity by a direct effect on the myocardial cells, trig-

gered by an increase in the intracellular concentration of calcium ions. The rise in intracellular calcium concentration is assumed to be caused by a complex interaction between the cardiac glycosides and the enzyme Na^+/K^+-ATP-ase. The inhibition of this enzyme also implies that the action potential is widened. Accordingly, impulse conduction in the nodal tissues, in particular the AV-node, is impaired.

In summary, cardiac glycosides increase contractile force and reduce heart rate and AV conduction. In addition, cardiac glycosides suppress the sympathetic hyperactivity which occurs in advanced stages of congestive heart failure via a complex mechanism involving the central nervous system.

Digoxin and ouabain are the only cardiac glycosides which are clinically used at present, although a large number of glycosides have been identified. Digoxin is used in the long-term treatment of congestive heart failure (CHF). There exists doubt with respect to its beneficial effect in patients with sinus rhythm. A therapeutic effect of digoxin in CHF is attributed to its mild positive inotropic action which is not accompanied by a rise in heart rate as found with numerous other inotropic drugs, such as β-adrenoceptor agonists and PDE-inhibitors. The negative chronotropic action of digoxin is considered as beneficial in CHF-patients. In addition, the aforementioned suppression of sympathetic hyperactivity in CHF-patients is assumed to contribute significantly to a beneficial action of digoxin.

Another important, in fact more convincing indication for the use of digoxin is atrial fibrillation, in particular when occurring after cardiac surgery. The beneficial effect of digoxin is caused by impairment of the AV conduction, leading to the dissociation of the electrical activities of the atria and the ventricles. The inotropic effect, although weak, is potentially useful.

Ouabain can only be administered via the intravenous route because of its very low bioavailability after oral ingestion. Ouabain is occasionally used as a cardiotonic (cardiostimulant) agent in intensive care medicine.

The side-effects of cardiac glycosides are mostly caused by electrophysiological/neuronal phenomena. Gastro-intestinal adverse reactions are probably triggered by effects on the central nervous system. Various types of cardiac arrhythmias are caused by the influence of the drugs on nodal tissues in the heart. The risk of arrhythmia is strongly enhanced by low plasma potassium concentrations.

Ophthalmologic problems, frequently involving impaired accomodation, photosensitivity, xanthopsia, etc. are also caused by electrophysiological phenomena, probably initiated in the central nervous system.

Cardiac glycosides are known to have a narrow therapeutic range, which means that adverse reactions readily occur at moderate degrees of overdosage. The monitoring of plasma levels of digoxin may be helpful to avoid overdosage, but it is not suitable to judge the therapeutic efficacy.

XII.c.2. Pharmacokinetic Properties

After oral ingestion digoxin shows an acceptable bioavailability in the range of 55–75%. As already mentioned ouabain can only be administered intravenously. The pharmacodynamic effects of digoxin develop slowly and are maintained for approximately 60 hours and even longer in patients with an impaired renal function. Ouabain acts rather rapidly (within 30 min) and its effects are reduced or disappear after 6–10 h. The elimination of digoxin occurs via the kidney only. Accordingly, the dosage of digoxin should be adapted in patients with an impaired renal function. This applies in particular to elderly patients. Ouabain is also excreted via the kidney, in the unchanged form.

XII.c.3. Overdosage

As a result of the narrow therapeutic range overdosage of digoxin readily occurs, in particular in patients with low plasma potassium levels. Special attention should therefore be paid to the combination of digoxin with drugs causing hypokalemia, such as diuretics.

The treatment of an overdosage of digoxin requires monitoring of cardiac rhythm in order to detect arrhythmias.

Antiarrhythmic treatment with intravenously administered phenytoin as well as correction of the electrolyte balance (K^+, Ca^{2+}, Na^+) should be performed. AV block may require a temporary pacemaker. Digitalis antibodies may be used as a specific antidote.

XIII. ANTIARRHYTHMIC DRUGS

XIII.a. General Principles

Antiarrhythmic drugs are used with the aim to prevent or suppress those conditions of cardiac arrhythmias which are considered harmful or dangerous,

or cause unpleasant subjective symptoms to the patient. As such the clinical indication for these agents has been considerably narrowed when compared with a decade ago, in particular as a result of the CAST Study. In this study increased mortality was observed in patients with class Ic-antiarrhythmics (for details see below), in spite of a significant improvement of the ECG-aberrations characteristic for supraventricular arrhythmias.

The various types of antiarrhythmic drugs owe their therapeutic activity to changes in the passage of Na^+, K^+ and Ca^{2+} ions across the cell membranes of the nodal tissues in the heart. The classification and subdivision of antiarrhythmic drugs continue to be subject of considerable debate. The frequently used classification according to Vaughan-Williams is certainly far from perfect, but it has so far not been replaced by one that is preferable from a clinical point of view. We therefore follow this classification, which is based on the electrophysiological characteristics of the drugs involved. The various electrophysiological properties are visualized in Fig. 6 and listed in Table 2, where well-known examples of each class of drugs are mentioned.

Inhibition of the rapid influx of sodium ions is the most characteristic electrophysiological effect of the class I-agents. Class I-antiarrhythmics are ever increasing in number, although genuinely new preparations are hardly introduced. Fine-tuning of the class I-drugs is obtained by their subclassification into I_A, I_B and I_C-agents, respectively. Most of the class I-drugs belong to the I_A-subtype, with quinidine and disopyramide as well-known examples. Lidocaine, frequently used to treat arrhythmias associated with acute myocardial infarction, is the prototype of I_B-agents. Flecainide is a well-known example of I_C-agents. Since the publication of the results of the CAST Study the I_C-agents are used only with great reluctance. β-Adrenoceptor (β-blockers) are designated as class II-agents in the Vaughan-Williams scheme. Their antiarrhythmic activity is based on the impairment of heart rate and AV conduction, thus reflecting the potentially proarrhythmogenic effects of noradrenaline, released from the sympathetic nerve endings.

Class III-agents, used clinically, are rare, with amiodarone as the best-known example. Several experimental preparations are the subject of clinical investigation. Amiodarone has shown to be effective in the treatment of various ventricular tachyarrhythmias and one of its major advantages is

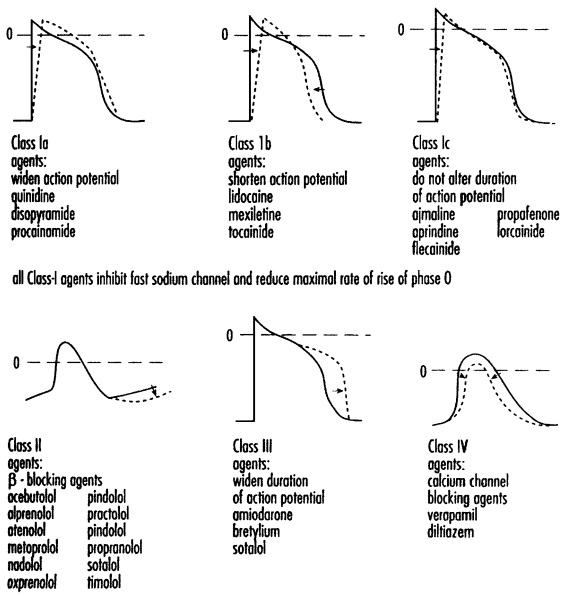


Fig. 6. Influences of different types of antiarrhythmic agents (Vaughan-William's classification) on the shape of cardiac action potentials. First row: Class I-agents; action potentials of ventricular myocardial cells. Second row (from left to right): Action potential of SA-node cells; influence of a β-blocker (class II). Action potential of ventricular myocardial cells; influence of a class III-antiarrhythmic. Action potential of AV nodal cells; influence of a class IV-antiarrhythmic (verapamil, diltiazem).

Table 2. Examples of antiarrhythmic drugs (Vaughan-William's classification)

Class Ia (action potential wider)	Procainamide Disopyramide Cibenzoline Quinidine
Class Ib (action potential narrower)	Lidocaine Mexiletine Tocaine
Class Ic (action potential unchanged, apart from the impaired upstroke)	Flecainide Propafenone
Class II	β-Blocker (e.g. metoprolol, propranolol)
Class III	Amiodarone D,L-sotalol
Class IV	Verapamil Diltiazem

the virtual absence of negative inotropic activity, which is characteristic for most other antiarrhythmic agents. In spite of this, amiodarone is associated with numerous adverse reactions. It is by no means certain that the beneficial effects of amiodarone are only the result of class III-activity (widening of the action potential), since this agent is also a calcium antagonist and a blocker of sodium channels. In a few countries, amiodarone is used in the management of stable angina. Furthermore, some interest exists for amiodarone as a potential drug in the secondary prevention following myocardial infarction (EMIAT and CAMIAT studies). Special attention must be paid to the kinetic properties of amiodarone. As a result of its lipophilicity, it slowly but substantially accumulates into various lipid structures in the organism. This property of the drug implies that after cessation of its administration, the effects and adverse reactions may persist for several weeks or months, because of the slow disappearance of amiodarone from the lipid depots.

Sotalol, as the racemate (a 1:1 mixture of the d- and l-enantiomers), has a well-documented class III-antiarrhythmic activity, without showing the various side-effects of amiodarone. The β-adrenoceptor blockade by this agent, however, limits its use in patients with heart failure. Dofetilide is an example of a newer, rather "pure" class III-antiarrhythmic, virtually devoid of other pharmacological properties.

The basic electrophysiologic effect brought about by class III-antiarrhythmics is the inhibition of the outflow of K^+-ions through the cell membrane. Accordingly, these drugs widen the duration of the action potential and therefore prolong the refractory period.

The class IV-antiarrhythmics are the calcium antagonists, but remain limited to verapamil and possibly also diltiazem. The dihydropyridines (nifedipine and related compounds) are unsuitable for antiarrhythmic therapy. The antiarrhythmic activity of verapamil and diltiazem is based upon the impairment of AV conduction and heart rate. A few compounds may be considered to act as antiarrhythmics, but they are not included in the Vaughan-Williams classification.

Digoxin, prototype of the cardiac glycosides, is frequently used postoperatively for the management of atrial fibrillation. This effect is based on the impairment of AV conduction and unrelated to digoxin's positive inotropic activity. In the treatment of post-operative atrial fibrillation digoxin may be combined with the calcium antagonist verapamil. Atropine, a classic parasympatholytic (vagolytic agent), may be used to increase heart rate via pharmacological mechanisms, although this does not occur frequently in clinical practice. Atropine is less hazardous than the use of β-adrenoceptor stimulants for this purpose.

Adenosine reduces heart rate and AV conduction, although it is not a calcium antagonist. It is administered intravenously for the acute treatment of paroxysmal supraventricular tachycardia. Adenosine displays a rapid onset and short duration of action. Apart from its antiarrhythmic activity it is also a vasodilator, in particular in the coronary system.

XIII.b. Choice of Antiarrhythmic Drugs

Although antiarrhythmic drugs may offer reasonable or even good results in the symptomatic treatment of cardiac arrhythmias, the rational choice of the optimal drug remains an unsolved problem. In spite of the sophisticated knowledge of their electrophysiological characteristics, the application of such data to a particular clinical situation remains problematic and uncertain. The suggestions for the choice of a particular agent in particular conditions are therefore mostly empiric and do not surpass the level of global empirism (Table 3). *Warning: Virtually all antiarrhythmic agents may display proarrhythmogenic activity under particular conditions*.

Table 3. Application of antarrhythmic drugs

Class Ia	Supraventricular tachyarrhythmias Certan ventricular tachyarrhythmias
Class Ib	Ventricular tachyarrhythmias (in particular during the management of acute myocardial infarction: lidocaine)
Class Ic	Ventricular tachycardia Tachycardia associated with the Wolff–Parkinson–White (WPW) syndrome AV-nodal re-entry tachycardia
Class II	Ventricular tachycardia WPW syndrome Postoperative atrial fibrillation (i.v. amiodarone)
Class IV	Supraventricular tachycardia Reduction of ventricular frequency during atrial fibrillation WPW syndrome

XIV. DIURETIC AGENTS

XIV.a. General Principles

Modern diuretics (natriuretics, saluretics), as used in the treatment of hypertension and heart failure, are administered with the aim to enhance the renal excretion of sodium ions and water. Older diuretics, such as the osmotic diuretic agents, are of little interest in the treatment of the aforementioned cardiovascular disorders, but may be used to lower intracranial pressure associated with brain edema.

The potassium sparing diuretics are predominantly used in conjunction with thiazides or loop diuretics, with the aim to counteract the hypokalemia induced by the aforementioned types of diuretics. Enhanced natriuresis caused by thiazides or loop diuretics will lead to the following therapeutic benefits.

1. Reduction in plasma volume secondary to the enhanced excretion of sodium ions and water and the regression of edema, if present. These effects are accompanied by a reduction in cardiac preload. During long-term treatment most of these effects are counteracted by various regulatory mechanisms, such as a persistent rise in plasma renin and aldosterone.
2. Reduction of peripheral vascular resistance and cardiac afterload, probably because the enhanced loss of the sodium ions leads to a blunted vasoconstrictor response to endogenous catecholamines. This effect is relevant in the long-term treatment of essential hypertension with thiazide diuretics.

XIV.b. Thiazide Diuretics

These agents inhibit sodium reabsorption at the level of the distal tubulus (Fig. 7). They are rather mild and slow-acting diuretics, mainly used in the long-term treatment of essential hypertension. The various compounds available all act via the same principle. There exist differences in the onset and duration of action. In practice very few drugs are sufficient, such as hydrochlorothiazide, a well-known example. Other thiazides are chlorthiazide, chlortalidon and indapamide.

Side-effects of thiazide diuretics predominantly consist of metabolic changes, such as hypokalaemia and rise of plasma uric acid levels, glucose, and lipids (total cholesterol and triglycerides). These metabolic changes are clearly less pronounced when

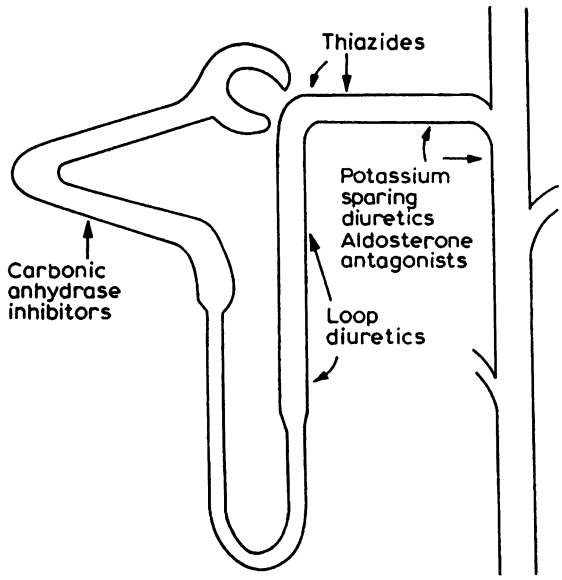


Fig. 7. Sites of action of the major classes of diuretic drugs used in fluid retention states and in hypertension.

the thiazides are administered in low doses, such as 12.5 or 25 mg hydrochlorothiazide daily, which is sufficient to achieve blood pressure control in hypertensive adults. In this connection it seems useful to mention the very flat dose response curve for the antihypertensive effect of thiazide diuretics, which implies that an increase in dosage has usually little additional benefit with respect to antihypertensive efficacy. The dose response curve for the various metabolic side-effects is much steeper, indicating that an increase in dosage greatly enhances the problem of metabolic side-effects, without offering much additional antihypertensive benefit.

XIV.c. Loop Diuretics

These potent diuretic agents interact with almost the entire nephron, including Henle's loop (Fig. 7). Their primary effect is probably the inhibition of the active reabsorption of chloride ions, which then leads to the enhanced excretion of sodium ions and water. Plasma volume is reduced as a result of these effects, whereas in the long-term both cardiac preload and afterload will diminish. The metabolic side-effects of the loop diuretics are globally the same as those of the thiazides, with some incidental differences. Plasma renin activity increases by loop diuretic treatment and it can be well imagined that this effect is noxious in the long-term management of heart failure. The loop diuretics provoke a clearly

more intensive and rapid natriuresis and diuresis than the thiazides. With respect to the practical use of loop diuretics, furosemide is the preparation of choice, with bumetanide as a good alternative. Both preparations are usually administered orally but they can also be given intravenously if necessary, in particular in patients with congestive heart failure when gastrointestinal absorption is impaired because of backward failure phenomena. Torasemide, a newer preparation of this category, has a longer duration of action than the aforementioned two diuretics and in most cases it can be given once daily. Unlike the other loop diuretics, ethacrynic acid is not a sulfonamide and thus, its use is not contraindicated by sulfa allergy.

XIV.d. Potassium-Sparing Diuretics

The following two groups of potassium-sparing diuretics may be used in clinical practice:

1. *Aldosterone receptor antagonists*. These drugs inhibit the effect of endogenous aldosterone at the receptor level. Accordingly, they induce a weak natriuretic effect, whereas the plasma potassium level is increased. Spironolactone, the prototype of such agents, may be added to loop diuretics in order to avoid the concomitant loss of potassium ions. Eplerenone may be more specific for the mineralocorticoid receptor. As monotherapy, spironolactone and related drugs are less suitable because of their weak natriuretic effect, although recent studies have shown beneficial effects in hypertension and heart failure.

   Gynaecomasty in males is a well-known adverse reaction to such compounds.
2. *Potassium-sparing diuretics, such as amiloride and triamterene*. These agents reduce at the tubular level the reabsorption of sodium and water, whereas the excretion of potassium is diminished. Their primary effects are independent of aldosterone. They are slow-acting and weak diuretics, which are unsuitable as monotherapy of hypertension or heart failure. For this reason, they are always combined with thiazide or loop diuretics. Several combined preparations are commercially available.

XIV.e. Osmotic Diuretics

Osmotic diuretics such as mannitol are readily filtered in the glomeruli, but they are hardly subject to tubular reabsorption. For this reason the osmotic reabsorption of water is impaired, thus leading to osmotic diuresis with enhanced excretion of water, but a hardly increased excretion of sodium ions. Accordingly, mannitol and related agents increase the osmolality of the plasma, thus leading to a reduction of intracranial and intraocular pressures. Mannitol may be used to lower intracranial pressure in patients with cerebral edema. It is occasionally used in conditions of acute glaucoma.

XV. LIPID-LOWERING (HYPOLIPAEMIC) DRUGS

The lowering of elevated plasma lipids by means of a diet, possibly combined with drug treatment, has proved useful in reducing the risk of coronary heart disease. An appropriate diet continues to be the cornerstone of the management of hyperlipidaemia. This intervention may be supported by lipid-lowering drugs and some of the newer ones have proved to be beneficial with respect to the outcome of ischaemic heart disease. Fibrates, resins, nicotinic acid and derivatives, and the more recently introduced HMG-CoA reductase inhibitors (statins) are the most important groups of hypolipaemic drugs. Their effects on the various plasma lipid fractions are listed in Table 4. A beneficial rise in HDL-cholesterol, associated with a reduction in plasma triglycerides, is seen in particular for the fibrates and the nicotinic acid-like drugs. Plasma HDL is considered an inverse risk factor. In other words, a high HDL-level appears to be favorable.

The statins are considered as a major breakthrough in the development of hypolipaemic drugs. These agents inhibit the biosynthesis of cholesterol (Fig. 8) and also increase the density of LDL-receptors. They induce a potent lowering of total cholesterol, LDL, and a weak lowering effect on the triglycerides. The plasma HDL-cholesterol level is moderately enhanced.

Apart from their lipid-lowering activity these agents are thought to improve endothelial dysfunction in various cardiovascular diseases.

Side-efects of these agents are marginal and they are usually very well tolerated. However, potentially live threatening rhabdomyolyis can occur, especially when statins are combined with other lipid lowering drugs like gemfibrozil. Several studies have shown not only the lowering of elevated plasma lipides, but also a protective effect against acute coronary

Table 4. Most important lipid-lowering drugs available at present. An indication is given of the most relevant changes in the plasma lipoprotein fractions caused by these agents

Group	Drugs	Changes in plasma lipoprotein fractions				
		Total cholesterol	LDL	VLDL	HDL	Triglycerides
Fibrates	Clofibrate Bezafibrate Fenofibrate Gemfibrozil	↓	↓	↓	↑	↓
Resins	Colesyramine Colestipol	↓	↓	↑	=	↓
Nicotinic acid and derivatives	Nicotinic acid Nicotinic alcohol Acipimox	↓	↓	↓	↑	↓
HMG-CoA-reductase inhibitors (statins)	Simvastatin Pravastatin Fluvastatin Lovastatin Atorvastatin Rosuvastatin	↓↓	↓↓	↓	↑ weak effect	↓
Probucol	Probucol	↓	↓	=	↓	=

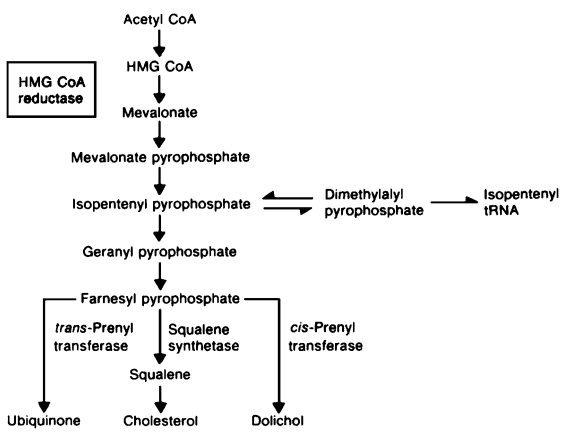


Fig. 8. Most important steps in the biosynthesis of cholesterol. The reduction of 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) to yield mevalonic acid is an important rate-limiting step and also the site of attack of the HMG-CoA-reductase inhibitors (statins).

events, both as secondary post-MI prevention, but also as primary prevention in high-risk patients.

Several compounds of this type are now available, such as simvastatin, pravastatin, fluvastatin, atorvastatin and lovastatin. Cerivastatin was withdrawn from the market in 2001 because of the high rate of serious side-effects. As of 2004, rosuvastatin had been approved in 154 countries.

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Chapter 21

Drugs Acting on the Central Nervous System

Chris J. van Boxtel

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I. PSYCHOTROPIC AGENTS

I.a. Sedative–Hypnotic and Anxyolytic Agents

I.a.1. Benzodiazepine Derivatives

Benzodiazepines have four main effects, i.e. sedation and hypnosis, anxyolysis, antiepileptic activity and muscle relaxation. There are differential activities for these four actions among the various agents within this group. Only some benzodiazepines block seizures or produce muscle relaxation. The most important indications for benzodiazepines as a whole are anxiety states and insomnia. Mainly for the short acting agents indications also include sedation and even light anesthesia in peri-operative states. Longer acting benzodiazepines are used for the management of alcohol withdrawal. Some are specifically used in epilepsy, sometimes in combination with other anticonvulsant therapy or alone for the discontinuation of status epilepticus. Diazepam is especially useful for the relief of muscle spasms in various disorders.

The effects on sleep are a decrease of sleep latency, a diminished number of awakenings with, as an overall effect an increase in total sleep time. However in many patients partial tolerance to the effects on sleep develop in a few nights.

For the induction of sleep a higher dose and through that a more pronounced inhibition of the central nervous system is necessary than for the induction of sedation. These drugs have effects on the $GABA_A$ receptor. This receptor has a receptor operated chloride channel that can be open or closed. Benzodiazepines potentiate the action of GABA by concomitant GABA agonist opening and benzodiazepine agonism. GABA is the primary inhibitory neurotransmitter within the CNS. The binding site of GABA on the $GABA_A$ receptor complex is modulated by the benzodiazepines. The chloride channel is closed at rest. The benzodiazepines potentiate the GABA-ergic neurotransmission through stimulation of the $GABA_A$ receptors in the limbic, neocortical and mesencephalic reticular systems and through that enhance the inhibitory activity of this neurotransmitter. The benzodiazepine receptor lies within the $GABA_A$ receptor. Used as hypnotics benzodiazepines produce drowsiness and sleep, decrease sleep latency, the number of awakenings and the time spent awake.

Discontinuation of a hypnotic after a month of continued use can cause a rebound of REM (rapid eye movement) sleep. The duration of action of a hypnotic is determined not only by the half-life of the mother substance but especially by their biological half-life determined by the half-life of the mother substance and the biological active metabolites. On this basis the benzodiazepines can be divided in four different groups: ultra short-acting with a half-life < 6 hours such as midazolam and triazolam, short-acting with half-lives between 6 and 12 hours like lormetazepam, loprazolam, oxazepam and temazepam. Alprazolam, bromazepam

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and lorazepam belong to the intermediate-acting benzodiazepines with half-lives of 12–24 hours and the long-acting benzodiazepines (half-life > 24 hours) are chlordiazepoxide, clobazam, clonazepam, clorazepate, diazepam, flurazepam, ketazolam, medazepam, nitrazepam and prazepam. However it should be realized that there exists a considerable overlap between these groups and that there are some important exceptions on these generalizations. There is some evidence that the short-acting benzodiazepines produce more withdrawal symptoms and thus more dependence than the longer-acting analogues.

The most common adverse effects are drowsiness, ataxia and reduced psychomotor performance.

However, adverse effects also include dependence and thus drug abuse. Tolerance develops within 3 months for anxiety. However considerable interindividual variability exists for the development of this tolerance. Benzodiazepines have very little effect on respiration which is not seen with sedative doses. In cases involving benzodiazepine intoxication, respiratory assistance has only been needed in patients who had also taken another CNS depressants.

Long-term use can result in a withdrawal symptoms such as insomnia, anxiety, tinnitus, tremor, perceptual disturbances and loss of appetite.

Contraindication are myasthenia gravis, chronic obstructive pulmonary disease and severe hepatic disease. Both in the elderly and in children paradoxical reactions were described. In the elderly the use of benzodiazepines is strongly correlated with falls and hip fractures.

Related hypnotics that also act at benzodiazepine receptors are the newer agents zolpidem, a imidazopyridine, zaleplon a pyrazolopyrimidine and the cyclopyrrolone zopiclone. Zopiclone might have a role for the treatment of benzodiazepine addiction. In patients in whom zopiclone was substituted for a benzodiazepine for 1 month and then itself abruptly terminated, improved sleep was reported during the zopiclone treatment, and withdrawal effects were absent on discontinuation of zopiclone. A series of non-sedating anxiolytic drugs derived from the same structural families as the above mentioned non-benzodiazepines, have been developed, such as alpidem and pagoclone.

Flumazenil is a benzodiazepine antagonist and is used to accelerate the recovery from the sedative actions of benzodiazepines in overdosed patients or after the use of short acting benzodiazepines in anesthesia. It has a short duration of action and therefore multiple doses are often necessary.

I.a.2. Aldehydes and Derivatives

Chloral hydrate and triclofos are of some use as hypnotics for children. However these compounds are largely superseded by the benzodiazepines and are not recommended other than for exceptional cases. Chloral hydrate has a low therapeutic index. These agents have an unpleasant taste and odor. The hypnotic effect has a rapid onset but a short duration. Tolerance appears to occur rapidly with a loss of sleep-inducing and sleep-maintaining effects after about 2 weeks.

All chloral derivatives are similar with respect to their therapeutic effects as they are all converted to the same active intermediate. They irritate the skin and mucous membranes and should therefore not be taken on an empty stomach. They are widely distributed throughout the body. In therapeutic doses there is little effect on respiration and blood pressure. In patients with hepatic or renal impairment chloral derivatives are contraindicated. They have no analgesic activity of any importance. The undesirable CNS effects of these drugs are light headiness, malaise, nightmares and ataxia.

Paraldehyde, although not a drug of first choice, can be used for sleep induction. It is also still considered to be of some value in the treatment of status epilepticus.

I.a.3. Azaspirodecanedione Derivatives

Buspirone is the first representative of this group. It is a partial agonist for the inhibitory presynaptic 5-HT1A receptors. This results in decreased firing of 5-HT neurons. Buspirone does not affect the GABA neurotransmitter system. It is a non-sedating anti-anxiety agent. Buspirone is poorly bioavailable (5% or less), is largely protein-bound in plasma (95%) with an apparent volume of distribution of 5 l/kg. Its duration of action is much longer than the short half-life of 2–3 hours indicates.

It does not cause cognitive impairment and has a low potential for abuse. It does not show withdrawal reactions and has no anticonvulsive, hypnotic, muscle relaxant and sedative effects. The anxiolytic effect gradually evolves over 1–3 weeks, it does not potentiate the sedative effects of alcohol and is indicated for the short-term management of generalized anxiety disorder.

There is no cross-tolerance of buspirone with benzodiazepines or other sedative medications. Withdrawal symptoms, occurring for example after stopping benzodiazepine use are influenced by buspirone only to a minor extend. Adverse effects include dizziness, light-headiness, agitation, headache, tinnitus and nausea but those reactions are generally mild.

I.a.4. Miscellaneous Sedative–Hypnotic Drugs

Several histamine H1 antagonists, e.g. hydroxyzine, promethazine, and mepyramine, display considerable sedative effects and they are sometimes used as sedative/hypnotics. Symptoms after withdrawal are usually less severe than those seen with the above mentioned hypnotics and sedatives. Especially in the elderly caution with these agents is warranted as.

Meprobamate is a carbamate derivative which is also used as a sedative–hypnotic drug. However, it has less anxiolytic activity than the benzodiazepines and it may cause serious CNS depression. Meprobamate induces some hepatic microsomal enzymes and large doses increase the elimination of warfarin, estrogens and oral contraceptives. Although it has some analgesic effects, these are negligible with clinical doses. It does however enhance the analgesic effects of other drugs. Major unwanted effects are drowsiness, ataxia and has largely been superseded by them. Drug dependence is not a rare problem.

Pregabaline is primarily an antiepileptic. Although it is an analogue of the neurotransmitter GABA it is not a GABA-agonist. It is mentioned here because it is also approved for use in generalized anxiety states.

I.b. Antipsychotics

The antipsychotics as a whole are not a homogeneous group as various classes exist. In general they block both dopamine (D2) and 5-hydroxytryptamine (5-HT2) receptors, however the pharmacological basis for antipsychotic therapy is not well understood. Administration of antipsychotic drugs decreases dopamine activity by blocking D2 receptors in both the limbic system which supposedly leads to normalizing of behavior. However blocking D2 receptors in the striatum is the cause of extrapyramidal side effects. Since Parkinsonian-like symptoms are due to a relative excess of acetylcholine, they may be reduced by the administration of anticholinergic agents.

Antipsychotics also affect cholinergic, alpha-adrenergic and histamine receptors to varying degrees and different affinities for these receptors determine to a major extend differences in their major adverse effects. They can be given by intramuscular, intravenous or oral routes and also depot preparations are frequently used. In general the pharmacokinetic behavior of antipsychotic agents is characterized by complete or almost complete hepatic metabolism, large distribution volumes despite high protein binding and elimination half-lives with respect to total concentrations in plasma are typically 20–40 hours. Many have a low oral bioavailability due to extensive first-pass metabolism in the liver and/or gut wall. Sulpiride is a notable exception in this respect with slow and incomplete oral absorption, a low volume of distribution of only 0.65–1.4 l/kg; low protein binding of 14–40% and a relatively short half-life of 6–8 hours. Of this drug 90–95% is excreted unchanged in urine.

Indications include a wide variety of psychiatric disorders, in the first place schizophrenia, organic psychoses and other acute psychotic illnesses. However they are also of use for the manic phase of bipolar affective disorder and for psychotic depression. Under antipsychotic drug therapy patients become less agitated and restless, withdrawn and autistic patients may become more communicative, aggressive and impulsive behavior diminishes and hallucinations and disordered thinking disappear.

The conventional antipsychotics have little effect on the negative psychotic symptoms such as autism, stupor and emotional withdrawal. The so-called atypical antipsychotics, or second-generation antipsychotics, like the heterocyclic compound risperidone, the benzamide sulpiride and several dibenzepines of which clozapine is the best known, have a broader spectrum which means that they also have an effect on the negative psychotic symptoms. Most share a common attribute of working on serotonin receptors as well as dopamine receptors. They have a low risk of extrapyramidal side effects.

Antipsychotic agents are also used for a diversity of other indications like hiccups, Tourette's syndrome, aggressive behavior in children and the elderly and alcohol withdrawal syndrome. Some of them are also used in anesthesia as they can potentiate the sedative, analgesics or anesthetic effects of other agents. Antipsychotics which are mainly active by blocking dopamine activity have also an effect on chemoreceptor trigger zone and may therefore be used as anti-emetics.

Some degree of physical dependence may occur with withdrawal after abrupt discontinuation.

Most antipsychotics and especially the piperazines and the butyrophenones can cause extrapyramidal symptoms. Blockade of dopamine receptors mainly in the corpus striatum is held responsible for these extrapyramidal effects. They may become manifest as a variety of clinical symptoms and it should be noted that within 24–48 hours after the beginning of treatment acute dystonic reactions like torticollis, facial grimacing and opisthotonos may occur. Parkinsonism-like symptoms such as bradykinesia, rigidity and tremor occur after weeks or months of therapy and are more common in the elderly. Motor restlessness, i.e. akathisia, also mostly occurs not before weeks or months after starting therapy. The tendency of an antipsychotic agent to produce extrapyramidal symptoms appears to be inversely related to its ability to block cholinergic receptors.

Tardive dyskinesia presents itself as involuntary movements that involve the face but sometimes also the extremities or trunk. One has to bear in mind that in a large segment of these patients the symptoms are not reversible and there are estimates that 10–20% of hospitalized psychiatric patients and 40% of the elderly on long-term antipsychotic therapy display some signs of tardive dyskinesia.

Neuroleptic malignant syndrome is a rare condition which can occur even after the single administration of antipsychotics. It manifests itself with hyperpyrexia, muscle rigidity, autonomic symptoms, clouding of consciousness and it has a mortality rate of over 10%. The aetiology is unknown but dopamine blockade may play a role.

Other adverse events can manifest themselves in different organ systems. Endocrine effects which may occur in both sexes include inappropriate ADH secretion (SIADH), loss of libido, increased prolactin release and weight gain. In males gynecomastia may occur and amenorrhea and galactorrhoea in females. Anti-histaminergic effects in the CNS can induce sedation. Tolerance usually develops to these sedative effects over a period of days or weeks. Orthostatic hypotension can occur as a result of alpha-adrenergic blockade. Well-known anticholinergic effects are dry mouth, constipation, blurred vision and urinary retention. Some antipsychotics are known to decrease seizure threshold and thus can promote seizures. Dermal reactions like discoloration of the skin, urticaria, dermatitis and rashes may occur.

Retinitis pigmentosa and agranulocytosis are rare idiosyncratic reactions. During treatment with clozapine leucocyte counts should be carried out frequently, especially the first few month, as there is a considerable risk of agranulocytosis.

There are some clinically important pharmacodynamic drug–drug interactions to be mentioned. Antipsychotics will potentiate the central depressant effects of sedatives and of alcohol. They will also increase the risk of respiratory-depressant effects of opiates. Inducers of drug metabolic enzymes like for example rifampicin and several antiepileptics, may increase the elimination rate of antipsychotic agents and thus decrease their efficacy.

I.b.1. Phenothiazines

Phenothiazine antipsychotics can be divided in the aliphatic phenothiazines with a dimethylaminopropyl group, those with a piperazine structure and agents with a piperidine structure.

Chlorpromazine is the best known representative of the aliphatic phenothiazines. Although it is considered to be a low potency agent it is still frequently used. It is one of the most sedative antipsychotic agents and is therefore very effective in the treatment of agitated and violent patients. Extrapyramidal effects are seen with a rather low incidence. However it displays marked anticholinergic activity. There have been reports of hepatotoxicity, also in patients with previously normal hepatic function, due to chlorpromazine. Alimemazine and triflupromazine are other representatives from this group.

The piperazines include fluphenazine, trifluoperazine, prochlorperazine, perazine and perphenazine. They are agents with a high antipsychotic potency with less pronounced anticholinergic effects. However their potential to produce extrapyramidal effects is more pronounced.

Fluphenazine is a short acting agent. For the management of agitated and potentially violent patients its hydrochloride formulation is frequently used for parenteral administration. Fluphenazine decanoate is a widely used depot preparation. Although its principal pharmacological activities are similar to those of the other phenothiazines fluphenazine displays only weak sedative action and it shows little anticholinergic and hypotensive effect.

Trifluoperazine is also a more potent antipsychotic than chlorpromazine with only minor sedative, anticholinergic and cardiovascular activity.

The piperidines, e.g. thioridazine, pipothiazine and pericyazine, have the lowest potential to cause extrapyramidal effects. Thioridazine is one of the most sedative phenothiazines. It may decrease the inotropic activity of digitalis by its quinidine-like action, which can cause myocardial depression, decreased efficiency of repolarization, and increased risk of tachyarrhythmias. With thioridazine drug induced sexual dysfunction and especially cardiotoxicity with prolongation of the QT-interval are more frequently seen than with other phenothiazines. For the above reasons thioridazine is withdrawn from the market in many countries.

Anticholinergic properties are highest in the aliphatic and piperidine groups, and lowest in the piperazine group.

I.b.2. Butyrophenones

Haloperidol, benperidol, droperidol, bromeperidol and pipamperon are representatives from this group. Except pipamperon they have high affinity for the postsynaptic D_2 receptor. Haloperidol has similar pharmacological properties as the piperazine phenothiazines. It also has the same indications as the phenothiazines. Haloperidol is considered the agent of choice for the management of acute psychotic states with agitation and possible violence. It has very little anticholinergic effects and it is also less sedating than chlorpromazine, for example.

Benperidol is used mainly to diminish libido in the management of anti-social sexual behavior. Droperidol is one of those antipsychotics that is used in anesthetic practice to potentiate analgesic and anesthetic effects of other agents.

Pimozide, penfluridol and fluspirilene are diphenylbutylpiperidine derivatives. Pimozide and penfluridol are antipsychotics with high potency but they give relatively few extrapyramidal problems and exhibit minimal other adverse effects. Fluspirilene has similar pharmacological activity although the risk for extrapyramidal reactions seems to be somewhat higher.

I.b.3. Thioxanthene Derivatives

The pharmacological profiles of flupenthixol and zuclopenthixol are similar to those of the piperazine-type phenothiazines. Patients with mild depression can have benefit from low dosages of flupenthixol.

Chlorprothixene has affinity for both dopamine-D_2 receptors and 5-HT_2 receptors but also for α-adrenergic and H_1 histamine receptors. It is used for the treatment of psychosis but also for sedation and for the management of manic states. Thiothixene is used for the same indications but is less sedative than chlorprothixene.

I.b.4. Benzamides

Benzamides are heterocyclic neuroleptics. These include the gastroenterologic agents metoclopramide and cisapride, which have antiserotonergic as well as anti-D_2 receptor dopaminergic actions and also the antipsychotic agents sulpiride and tiapride. Tachyarrhythmias have resulted in the withdrawal of cisapride from general use.

Sulpiride is a relatively selective dopamine-D_2 receptor antagonist. However, in low doses it is considered to have mild activating and antidepressant activity although it is of course mainly used for schizophrenia and for the management of acute organic psychosis. It is considered to be a atypical antipsychotic agent with also effects on negative psychotic symptoms. Because of its activating properties it is contraindicated in patients with suicidal tendencies. It has antiemetic activity like the phenothiazines.

Tiapride has weak antipsychotic activity. It has been used as a adjunct in patients with tardive hyperkinetic syndrome caused by other antipsychotics.

I.b.5. Dibenzazepines

The dibenzazepines are also tricyclic antipsychotic agents and they include drugs which are related to loxapine such as clothiapine, metiapine, loxapine and zotapine. They are typical antipsychotics with high antidopaminergic activity. Their pharmacological actions do not differ from those of the other neuroleptics and they are used for the same indications. Clothiapine is notorious for causing extrapyramidal reactions. Its parenteral use is only indicated for agitated schizophrenic patients and organic psychoses and for some patients with acute mania.

The other group within this class of dibenzazepines are formed by agents which are related to clozapine. Clozapine is an “atypical” antipsychotic which is used for the treatment of schizophrenia. It is primarily indicated for schizophrenic patients with predominantly negative symptoms. Its indication can be extended to those patients that have shown to be refractory to the conventional neuroleptics. It can also be substituted for other antipsychotics in

patients with serious extrapyramidal symptoms as it has little tendency to provoke these. Clozapine is a highly sedating agent. However it has a dose-related risk of inducing seizures in nonepileptic patients. Furthermore, with this drug the risk of bone marrow depression with life threatening agranulocytosis and neutropenia is considerably greater than with other neuroleptics and hematological monitoring is essential. There is also an increased risk for the development of diabetes. The clozapine-like antipsychotics such as fluperlapine and olanzapine have a lower potency and have a relatively low affinity at most dopamine receptors, but they do bind to muscarinic, 5-HT_2, α-adrenergic and H_1 histamine receptors. Olanzapine carries an increased risk for diabetes. Serious adverse events where reported after parenteral olanzapine including respiratory depression, hypotension and bradycardia, some of them fatal.

I.b.6. Miscellaneous Antipsychotics

The heterocyclic antipsychotic agent, risperidone, is a benzisoxazole derivative with antiserotonergic (5-HT_2) as well as antidopaminergic (D_2) activity. Risperidone is also considered to be a so-called "quantitatively atypical" antipsychotic agent because in low doses it has few extrapyramidal effects.

Quetiapine is an antipsychotic agent with a structure related to that of the benzodiazepines. It has high affinity for H_1 histamine receptors and intermediate affinity for 5-HT_2 and dopamine-D_2 receptors.

Sertindole is one of the newer antipsychotic medications available. It is classified chemically as a phenylindole derivative and has activity at dopamine and serotonin receptors. It is not associated with sedative effects. Sertindole was voluntarily withdrawn from the market late 1998 due to concerns over the risk of cardiac arrhythmia's. The European Commission recommended lifting the marketing restrictions on sertindole in 2005 with a regulatory requirement of ECG monitoring.

I.c. Antidepressants

Several mechanisms exist to explain the etiology of affective disorders all based on the hypothesis that certain levels of amine neurotransmitters (e.g., norepinephrine – NE, serotonin – 5-HT) and receptor sensitivity are necessary for normal mood. There is ample evidence that depression occurs if receptors are insensitive or if amine synthesis, storage or release are deficient. Mania occurs if the opposite situation exists. Increased beta-adrenergic activity in brain as can be induced with long term antidepressant therapy results in subsensitivity and decreased density of these receptors. This is not seen with Electro Shock Therapy (ECT) nor by the use of selective serotonin re-uptake inhibitors. Enhanced serotonin (5HT1A) receptor sensitivity is seen with all antidepressants and supposedly also occurs by ECT.

A period of at least 2 weeks' therapy with adequate doses of any of the antidepressants that are available at the moment is required before antidepressant action can be expected. When there is a therapeutic response antidepressant medication should be continued for a minimum of 6–12 months. It has to be realized that there are estimates that even under treatment 15–25% of the patients will continue to have symptoms of depression.

I.c.1. Tricyclic Derivatives

A considerable number of tricyclic antidepressants have been developed in the past, although with slight differences in their pharmacological activities, all with similar efficacy. They are primarily indicated for the treatment of endogenous depression. However this does not exclude efficacy in patients in whom the depression is associated with organic disease or in patients with reactive depression or depression combined with anxiety. They may also benefit patients during the depressive phase of manic-depressive disorder. For some also efficacy has been claimed in panic states, phobic disorders, and in obsessive–compulsive disorders.

Recently the tricyclic antidepressants are increasingly used for adjunctive analgesic effects to relieve intractable pain and in chronic pain situations such as malignancies.

In normal subjects the tricyclics only show anticholinergic and sedative activity but have no mood elevating action. In depressed subjects their mood elevating effect has a delay of 2–3 weeks. The reasons for this delay are unknown and could be both pharmacokinetic or pharmacodynamic in nature.

The neurochemical effects of the tricyclic antidepressants are blockade of the re-uptake of norepinephrine and for some drugs also serotonin by nerve terminals in the CNS and peripherally. This reuptake inhibition results in higher concentrations of the neurotransmitters at their receptors sites. There is little or no effect on DA neurotransmission. The tricyclic antidepressants have varying affinities for α_2

adrenoceptors, histamine H_1 receptors, α_1 adrenoceptors and muscarine receptors.

The tricyclic antidepressants show comparable pharmacokinetic behavior. They are well absorbed orally although absorption may be delayed due to slowing of gastric emptying as a result of anticholinergic activity. They have large distribution volumes of 15–20 l/kg, high protein binding to albumin and also to acid glycoprotein and long elimination half-lives ranging from 10 to 50 hours. They are extensively metabolized by hepatic microsomal cytochrome P450 enzymes. Metabolites of amitryptilyne, i.e. nortryptyline, and of imipramine, desipramine, are pharmacologically active.

Tricyclic antidepressants are cardiotoxic, inducing tachycardias and an increased tendency for ventricular arrhythmias with high doses. This dose dependent cardiotoxicity gives these agents a low therapeutic index. Overdoses are characterized by cardiac conduction disturbances, hyperpyrexia, hypertension, confusion, hallucinations, seizures and coma and there is a high mortality rate in suicide attempts. Depressed patients should therefore not be given more than one week supply of these drugs.

Other adverse effects include orthostatic hypotension, anticholinergic effects which may be severe in elderly patients and acute confusional states. Tolerance develops to the hypotensive and anticholinergic effects.

Tricyclic antidepressants are notorious for their risk to be involved in drug–drug interactions. Additive anticholinergic effects can be expected in combination with antihistamines, antipsychotics and anticholinergic-type anti-Parkinson agents. Hepatic enzyme-inducing agents increase their hepatic metabolism while enzyme inhibitors may potentiate the effects of tricyclics. Concomitant use with monoamine oxidase inhibitors will produce hypertension, hyperpyrexia and convulsions.

I.c.2. Selective Serotonin Re-uptake Inhibitors (SSRIs)

Agents from this class of antidepressants are selective blockers of the re-uptake of serotonin at presynaptic neurones and have little if any effects on muscarinic, histaminergic, adrenergic or serotonergic receptors. They are as effective as the tricyclic antidepressants in the management of depressive disorders, but have less cardiovascular effects. They have less anticholinergic activity and because of their lower risk of cardiotoxicity in overdose they are considered to be more safe than the tricyclic antidepressants.

They have a delayed onset of effect just like the tricyclics. Examples are fluoxetine, paroxetine, fluvoxamine, zimelidine, venlafaxine, citalopram and sertraline. Zimelidine was withdrawn worldwide in 1983 due to risk of Guillain–Barré syndrome.

Serotonin re-uptake inhibitors are readily absorbed after oral administration and widely distributed throughout the body. Elimination is mainly by hepatic metabolism. Fluoxetine, sertraline and venlafaxine are demethylated to active metabolites.

Venlafaxine, although its re-uptake inhibitory activity is not restricted to serotonin, is often classified as an SSRI because of its similar spectrum of adverse reactions. It has a short elimination half-life in contrast to the other serotonin re-uptake inhibitors. Fluoxetine, norfluoxetine and paroxetine are inhibitors of their own metabolism by CYP2D6 resulting in non-linear pharmacokinetic behavior.

Adverse reactions include nausea, nervousness, headache, insomnia, anxiety. Sexual dysfunction with loss of libido is a common complaint. Insomnia can be a problem. Urticaria and rashes have been described. Venlafaxine may significantly increase the risk of suicide and is therefore not recommended as a first line treatment of depression. The view that also fluoxetine and other SSRIs can lead to suicide is under debate for quite some time now. In most countries SSRIs are not approved for use in pediatric populations. In the UK and in the USA only fluoxetine can be prescribed for children.

Some selective serotonin re-uptake inhibitors are powerful inhibitors of cytochrome P450 enzymes and the metabolism of e.g. tricyclic antidepressants can be inhibited resulting in serious toxicity. Additive sedation can be expected when given in combination with CNS depressants such as benzodiazepines but also with alcohol. Selective serotonin re-uptake inhibitors should not be used in combination with monoamine oxidase inhibitors as fatal reactions have been reported.

I.c.3. Monoamine Oxidase Inhibitors

Monoamine oxidase (MAO) inhibitors block the oxidative deamination of monoamines, i.e. norepinephrine and serotonin by inhibiting monoamine oxidase type A (MAO-A) and dopamine also by monoamine oxidase type B (MAO-B) inhibition, thereby increasing these neurotransmittors at their receptors in the brain and in the periphery. MAO-A

is also located in the gut and liver and it metabolizes tyramine from the diet.

Examples of monoamine oxidase inhibitors are phenelzine, tranylcypromine, isocarboxazid and moclobemide. They are indicated for atypical depression. Changes in the neurotransmitter levels are seen in several days but the clinical effect may lag by several weeks. Phenelzine is a non-selective hydrazine-type monoamine oxidase inhibitor while the also non-selective inhibitor tranylcypromine is of the non-hydrazine-type. Phenelzine, tranylcypromine and isocarboxazid are irreversible inhibitors. Phenelzine is partly metabolized by acetylation and slow acetylators are more prone to toxicity. It has anxiolytic properties and superior efficiacy in treating severe anxiety.

Moclobemide increases concentrations of serotonin and noradrenaline by means of reversible inhibition of MAO-A. Although moclobemide has an elimination half-life of only 1–4 hours its duration of action is considerably longer.

Monoamine oxidase inhibitors have a low therapeutic index. Adverse effects include orthostatic hypotension, impotence and insomnia. Overdoses become manifest by symptoms of agitation, hyperreflexia followed by convulsions. Rare but serious cases of hepatotoxicity have been associated with the use of isocarboxazid and of phenelzine.

Interactions can be expected in all situations with risks for potentiation of sympathomimetic amine activity, particularly by indirect acting amines such as tyramine. Patients who are treated with MAO inhibitors must avoid food rich in tyramine e.g. aged cheese, red wine, beer and vegetables like beans. MAO inhibitors block the metabolism of tyramine resulting in adrenergic overstimulation which may result in a hypertensive crisis. Interactions with foods containing tyramine is reduced with selective MAO-A inhibitors such as moclobemide. Monoamine oxidase inhibitors can potentiate or prolong the action of tricyclic antidepressants but also of CNS depressants such as barbiturates. Accumulation of the epileptogenic metabolite of the opioid meperidine has been described.

I.c.4. Miscellaneous Antidepressants

These agents are effective in the treatment of a variety of depressive disorders like endogenous depression, depression associated with organic disease, reactive depression and depression combined with anxiety. The delay of the onset of the antidepressant effect of mianserin is similar to that of the tricyclic antidepressants. It has considerable sedative activity which is manifest almost immediately after the start of treatment. It has very little anticholinergic activity and it can therefore safely be used in patients for which anticholinergics are contraindicated like elderly men with benign prostatic hyperplasia or patients with glaucoma. Mianserin has no known cardiovascular effects and there are no absolute contraindications for patients with concomitant diseases of the cardiovascular system. Rarely blood dyscrasias have been reported.

Maprotiline and amoxapine are selective norepinephrine uptake inhibitors. They share most of the properties of the tricyclic antidepressants. Maprotiline has less sedating effect than mianserin and it is more epileptogenic than any other antidepressant. It shows considerable cardiotoxicity when taken in overdose.

The triazolopyridine trazodone does not have an appreciable effect on the re-uptake of the neurotransmittors dopamine or noradrenaline. It is a weak inhibitor of serotonin re-uptake but is a potent antagonist of the serotonin 5-HT2 receptor. Clinical experience has shown unpredictable efficacy. Trazodone has little antimuscarinic activity and has little if any action on cardiac conduction. Like mianserin it can therefore safely be used in patients for which anticholinergics are contraindicated and there are no absolute contraindications for patients with concomitant diseases of the cardiovascular system.

Bupropion belongs to the chemical class of aminoketones. It is an atypical antidepressant that acts as a norepinephrine and dopamine reuptake inhibitor, and nicotinic antagonist. Initially developed and marketed as an antidepressant, bupropion was subsequently found to be effective as a smoking cessation aid. If given to lactating women it can trigger convulsions in the newborn.

Although not an antidepressant also varenicline can be mentioned here. It is the first nicotinic receptor partial agonist approved to treat smoking addiction. As a partial agonist, it both reduces cravings for and decreases the pleasurable effects of cigarettes and other tobacco products.

I.c.5. Lithium

Lithium is best regarded as a mood stabilizer, with antimanic and antidepressant effects. Its indication

is the prevention of relapses in manic-depressive disorders and it is not effective for the management of acutely manic patients. Lithium is more useful for the prophylaxis of manic episodes than for depression but in manic-depressive disorders it can improve both. Unipolar depressions are not an indication for the use of lithium.

Its mechanism of action is not well understood. Some possible actions include inhibition of norepinephrine release and increased re-uptake of norepinephrine and serotonin. It also possibly increases the synthesis and turnover of serotonin. Lithium interferes with the production and release of the second messengers phosphatdylinositol-4,5-bisphosphate and diacyl glycerol. Finally it may uncouple receptor recognition sites from GTP-binding protein by competing with Mg^{++}.

Lithium is completely absorbed after oral administration reaching peak concentrations after 1–3 hours. Lithium is not metabolized and almost completely excreted unchanged in the urine with a half-life of on average 24 hours, but increasing to 40 hours or longer in the elderly and in patients with compromised renal function. After excretion 70–80% is reabsorbed by proximal renal tubule where it competes with sodium for reabsorption. Therefore low sodium levels decrease lithium excretion with consequent risks for lithium toxicity.

Adverse reactions that are not dose dependent are nausea, vomiting and diarrhoea. Lithium has a low therapeutic index. Some adverse reactions such as thirst and mild polyuria may occur at therapeutic plasma concentrations of 0.4–1.0 mEq/l. At concentrations of 1.0–1.6 mEq/l diarrhea, nausea and incoordination become prominent. At toxic levels ataxia, confusion and stupor occur potentially leading to coma and death.

Extrapyramidal signs such as cogwheel rigidity have been reported with therapeutic doses.

Many interactions with lithium have been described. Thiazide and loop diuretics decrease lithium excretion predisposing to serious lithium toxicity. Also non-steroidal anti-inflammatory agents, especially indomethacin can increase the risks for lithium toxicity due to decreased renal excretion.

Aggravation of the extrapyramidal effects of antipsychotic agents have been described and it has been reported that the use of lithium in combination with haloperidol may result in irreversible neurological toxicity. Lithium can increase the hypothyroid effects of antithyroid agents or iodides.

I.d. Psychostimulants

This group includes the amphetamines, methylphenidate, modafinil and pemoline. In 2005 pemoline was withdrawn from the US market because of hepatotoxicity.

There is no place anymore for the amphetamines in our therapeutic armamentarium. The only indications for the other stimulants, modafinil and methylphenidate, are respectively narcolepsy and the attention deficit disorders (ADHD) and hyperactivity syndromes in children. Their mechanisms of action include enhanced release of dopamine and norepinephrine, re-uptake inhibition of dopamine and norepinephrine and to some extend monoamine oxidase inhibition.

Some of the behavioral effects are a decreased sense of fatigue and an increased alertness and ability to concentrate. In overdose the CNS effects of psychostimulants are agitation, confusion, insomnia, seizures and coma while cardiovascular effects include arrhythmias, palpitations, anginal pain and circulatory collapse.

Methylphenidate is an inhibitor of drug metabolizing enzymes of the cytochrome P450 family and several interactions with drugs like some antiepileptics, antidepressants and oral anticoagulants, have been described.

Atomoxetine is the first non-stimulant drug approved for the treatment of ADHD. It is classified as a norepinephrine reuptake inhibitor and is approved for use in children, adolescents, and adults. However, its efficacy has not been studied in children under six years old.

II. ANTIEPILEPTICS

The various drugs or drug groups that are used for the treatment of epilepsy do not have the same indications and are not interchangeable. For different manifestations of the disease, partial seizures, generalized seizures, either petit mal (absences) or grand mal (tonic–clonic seizures), different agents are considered to be drugs of first choice, dependent on differences in efficacy and tolerance. Although also with anticonvulsant therapy polypharmacy should be avoided, when two different types of seizures coexist each may require a specific agent.

Phenobarbital, primidone, phenytoin and also carbamazepine are inducers of cytochrome P450 enzymes and in combination the effects of substrates

for these enzymes can be diminished. The therapeutic index of these agents is narrow and serum monitoring has to be performed on a regular basis. Antiepileptics are CNS depressants and patients should be warned for sedation.

Although low risks of teratogenesis, including risk of neural tube defects have been reported for several antiepileptics it should be realized that uncontrolled epilepsy poses far more risks for the fetus.

II.a. Barbiturates and Derivatives

Only minimal pharmacological differences exist among the various barbiturates and their major differences are differences in duration of action which are mainly determined by pharmacokinetic factors. Barbiturates are administered orally as anticonvulsant and intravenous administrations are used for anesthetic purposes. Because of their low therapeutic index and their potential for abuse barbiturates are no longer used as sedative–hypnotic agents and have been largely replaced for this indication by the safer benzodiazepines. Barbiturates bind to GABA channels to enhance Cl^- transport and increase conductance at Cl^- channels. Their common pharmacological activity consists of reversible depression of all excitable tissues, i.e. nervous tissue but also, although to a lesser extend, skeletal muscle, smooth muscle and cardiac muscle. In the CNS a concentration dependent continuum of depression occurs, from mild sedation to deep anesthesia. The effects on sleep are not too much different from "normal" sleep patterns. Pain perception is not influenced until unconsciousness is reached and small doses of barbiturates even produce hyperalgesic effects. Phenobarbital is considered to have the most selective anticonvulsant activity.

Pharmacodynamic tolerance, probably on the basis of down-regulation of receptors, develops more rapidly to the effects of barbiturates on mood and sedation than to the anticonvulsant and lethal action. This results in a marked decrease in therapeutic index and the ratio of LD50 and ED50 can approach 1. Furthermore, barbiturates induce P450 enzymes and thus increase their own metabolism resulting in time dependent pharmacokinetic behavior.

The ultra-short acting thiopental, exclusively used in anesthesia, rapidly reaches CNS depressant concentrations due to its high lipid solubility and high blood flow to brain. Redistribution to muscle and other sites is responsible for its short duration of depressant effects. For the short to intermediate acting agents like secobarbital and pentobarbital the duration of action depends on the rate of metabolism. Long acting barbiturates are slowly metabolized, like phenobarbital, or excreted wholly or partially unchanged like respectively barbital and again phenobarbital.

A wide range of drugs can interact with the barbiturates. Additive effects are seen with other sedatives. The metabolism of other drugs can be induced or the metabolism of the barbiturate can be diminished by cytochrome P450 inhibitors.

The most frequent adverse reactions are those that are an extension of the therapeutic effects, i.e. extended CNS depression manifesting itself as distortions in mood and impaired judgment and fine motor skills as well as intellectual performance as long as a day after usage.

Excitement and other paradoxical reactions can occur in the elderly but also in young children.

Barbiturates generally increase the synthesis of porphyrin and intermittent porphyria is therefore an absolute contraindication for their use.

Other serious adverse events are the frequent occurrence of abuse and dependence. At toxic levels sometimes depressed cardiovascular tone will occur. In lethal barbiturate intoxications death is caused by central respiratory depression.

Phenobarbital is still used for the management of partial seizures, generalized tonic–clonic seizures and for the control of status epilepticus. However because of its low therapeutic index and the possibility of dependence, phenobarbital has largely been displaced by other anticonvulsants. For newborns phenobarbital is often the drug of first choice. If given together with sodium valproate the metabolism of phenobarbital may be inhibited while in combination with carbamazepine the serum concentrations of carbamazepine will be reduced due to enzyme induction by phenobarbital.

Primidone is an other second line barbiturate used orally to control tonic–clonic and partial seizures. It is a pro-drug as it is metabolized to phenobarbital and phenylethylmalonamide (PEMA), however both the parent compound as well as the metabolites have anti seizure activity. Its use is more difficult to monitor and adverse effects occur even more frequently than with phenobarbital.

II.b. Hydantoin Derivatives

Phenytoin is the only agent from this group that is frequently used. Its main indications are prophylaxis

of generalized tonic–clonic, and complex and simple partial seizures. It is also used for the control of status epilepticus after initial treatment with diazepam. It prolongs inactivation of Na^+-channels in the CNS and increases the depolarization threshold. Phenytoin is able to diminish the generalization of seizures but does not stop seizure focus activity. It has peculiar pharmacokinetic characteristics. It is slowly and incompletely absorbed and drug formulation can markedly influence absorption. Intramuscular injections should be avoided as they are painful and absorption is unreliable. Phenytoin is highly bound to plasma albumin. Its oxidative hepatic metabolism is saturable and phenytoin therefore shows dose dependent elimination kinetics. Because phenytoin is metabolized in the liver and is also a liver enzyme inducer, many drug interactions have been described. For example the efficacy of oral contraceptives and of oral anticoagulants may be decreased. Enzyme inducers like barbiturates decrease its potency. Also related to induction of enzyme activity is interference with vitamin D metabolism which may cause osteomalacia and rickets.

As phenytoin has a narrow therapeutic index therapeutic drug monitoring to establish therapeutic levels is mandatory. Dose and concentration dependent adverse effects are nausea, vomiting, tremor, confusion, headache and dizziness, nystagmus and ataxia.

Long-term use frequently induces hyperplasia of the gums. Skin rashes are seen in up to 10% of the patients. Serious, most probably pseudo allergic skin eruptions can also occur.

Mephenytoin is N-demethylated to 5,5-phenylethylhydantoin and it is this active metabolite probably mainly accounts for the therapeutic benefit and toxicity. Serious toxicity is common. and mephenytoin is generally used only in patients who fail to respond to or do not tolerate safer agents. Mephenytoin is no longer available in the US or the UK.

Ethotoin has appeared to be of some value in the treatment of partial as well as generalized tonic–clonic seizures and to be relatively free of the typical adverse effects of phenytoin. Because of its low efficacy, it is rarely used and then only in combination with other agents.

II.c. Benzodiazepine Derivatives

This group has been described in some more detail in Section I.a.1 of this chapter. A few benzodiazepines are frequently used as anticonvulsants and clonazepam is exclusively used for its anticonvulsant activity. It has shown efficacy in all forms of epilepsy but it is mainly used for the management of myoclonic and atonic/akinetic seizures in children. It may be also used as an alternative to diazepam in the emergency treatment of status epilepticus. It has a wide therapeutic range in comparison to other anticonvulsants.

Its adverse reactions such as fatigue, drowsiness and ataxia are mainly related to its sedative activity. Some tolerance can occur for these effects.

In the elderly a greater sensitivity to CNS effects can be expected. Bronchial hypersecretion may cause respiratory problems in infants and small children.

Intravenously administered diazepam is first-line therapy for status epilepticus. However there is a serious risk for severe respiratory depression, hypotension, bradycardia and cardiac arrest. Rectal administration as micro-clysma can be an attractive alternative, especially in children.

II.d. Succinimide Derivatives

Ethosuximide and mesuximide are succinimides. Ethosuximide is the agent of first choice for the management of absence (petit mal) seizures. It inhibits low-threshold Ca^{++} currents in the thalamus. As it may precipitate grand mal seizures it is frequently given together with a barbiturate or with phenytoin to prevent that. Its plasma concentrations do not closely correlate with the therapeutic effects.

Enzyme inducers will enhance the metabolism of ethosuximide and reduce its efficacy while its depressant action will be enhanced by other sedatives. Frequently occurring adverse effects include sedation and gastrointestinal disturbances such as nausea and vomiting. Rarely blood dyscrasias including agranulocytosis and pancytopenia are seen as well as serious skin reactions including Stevens–Johnson syndrome.

II.e. Carboxamide Derivatives

Carbamazepine is a tricyclic iminostilbene derivative and structurally related to the tricyclic antidepressants. It is used as a first-line agent for the management of generalized tonic–clonic epilepsy. It is also highly effective for partial seizures but has no efficacy in patients with absence seizures or atonic seizures. In epilepsy it supposedly has the same mechanism of action as phenytoin. An other well

known indication is pain relieve in e.g. trigeminal neuralgia.

Carbamazepine stimulates antidiuretic hormone activity and has been used for the treatment of neurohypophyseal diabetes insipidus. Carbamazepine induces microsomal enzymes and its metabolism is subject to auto-induction. Frequently occurring adverse effects are sedation, dry mouth, dizziness and gastrointestinal disturbances. Photosensitivity reactions, urticaria and Stevens–Johnson syndrome have been described. The elderly are more prone to mental confusion, cardiac abnormalities and problems due to inappropriate ADH secretion.

Oxcarbazepine is a derivative of carbamazepine and although its precise mechanism of action is unknown it has similar properties as carbamazepine and is also used for the treatment of primary generalized tonic–clonic seizures and partial seizures. Also the adverse effects are similar to those of carbamazepine. However the drug interaction profile is different as oxcarbazepine has hardly any enzyme-inducing capacity.

II.f. Miscellaneous Antiepileptics

Valproic acid is a fatty acid derivative which is used for the management of absences and the control of generalized tonic–clonic seizures. Multiple mechanisms of action have been proposed. It prolongs Na^+ inactivation which could explain its effectiveness against grand mal seizures. However also inhibition of T-Type Ca^{++} channels has been postulated.

Sodium valproate is converted to valproic acid in the intestine and the acid is absorbed. Absorption may be delayed by food or by enteric-coated tablets. Valproic acid has a low volume of distribution and high plasma protein binding. In the elderly there is a risk for increased free valproic acid concentrations requiring lower doses and plasma concentrations at the lower therapeutic range. However it should be realized that these plasma concentrations do not correlate very well with the therapeutic or toxic effects and careful observation for symptoms is mandatory.

Valproic acid is metabolized in the liver and excreted in the urine mainly as glucuronide conjugates. Valproic acid is not an hepatic enzyme inducer.

Frequently occurring adverse effects are gastrointestinal complaints and dose related CNS effects including fatigue, sedation, ataxia, dysarthria and other symptoms of incoordination. Rare but potentially dangerous reactions are bone marrow depression and pancreatitis. The risk of serious and potentially fatal hepatotoxicity is greater in children under 2 years.

Trimethadione is an effective agent in the treatment of absence seizures. Trimethadione is N-demethylated to dimethadione and dimethadione inhibits T-type Ca^{++} currents in the thalamus. Because of its potential for serious toxicity trimethadione is only used in patients who do not respond to or do not tolerate other agents. If administered during pregnancy, fetal trimethadione syndrome may result causing Facial Dysmorphism, cardiac defects, Intra Uterine Growth Retardation and mental retardation. The fetal loss rate while using trimethadione has been reported to be as high as 87%.

Lamotrigine is a phenyltriazine derivative and it is used for partial seizures, mostly in combination with other drugs. It is thought to act by blocking voltage-dependent Na^+ channels and by inhibiting the release of the excitatory neurotransmitter, glutamate. The most common adverse effects are dizziness, ataxia, blurred vision and nausea and vomiting.

Gabapentin is a new antiepileptic with efficacy in partial seizures with and without secondary generalization. It is also mainly used in addition to other antiseizure drugs. The use of gabapentin in mixed seizure disorders that include absence seizures is contraindicated as these may be exacerbated. Presently, gabapentin is widely used to relieve pain, especially neuropathic pain. Gabapentin, structurally related to the neurotransmitter GABA, is eliminated solely by renal excretion; it is not bound to plasma proteins, and does not induce hepatic enzymes. No interactions with other antiepileptics have been described. Adverse effects are somnolence, dizziness, ataxia and fatigue but some tolerance to these effects occurs within a few weeks.

Vigabatrin is a new antiepileptic for use in epilepsy unresponsive to other therapy. It is an irreversible inhibitor of GABA-transaminase, the enzyme responsible for inactivation of the neurotransmitter GABA and it has shown efficacy against partial and secondarily generalized seizures. The principal unwanted effects are psychiatric disorders, including depression and psychosis, in a small number of patients.

Felbamate, a new anticonvulsant, has beneficial effects in partial and secondarily generalized seizures. It can reduce symptoms in Lennox–Gastaut syndrome. However an association with aplastic anemia reduces its usefulness and Lennox–Gastaut syndrome is considered to be its only indication.

Topiramate is used to treat epilepsy in both children and adults. In children it is also indicated for

treatment of Lennox–Gastaut syndrome. topiramate is a sulfamate-substituted monosaccharide, related to fructose. Cognitive side effects may be more common with topiramate than with lamotrigine. Another serious side-effect is the development of osteoporosis in adults and children and rickets in children.

Tiagabine is an anti-convulsive medication also used in the treatment for panic disorder as are a few other anticonvulsants. It does appear to operate as a selective GABA reuptake inhibitor. Tiagabine's most common side effects include confusion, difficulty speaking clearly/stuttering and mild sedation.

Zonisamide is a sulfonamide anticonvulsant approved for use as an adjunctive therapy in adults with partial–onset seizures.

III. NEURODEGENERATIVE DISEASES

Parkinson's disease together with Alzheimer's disease, multiple sclerosis, Huntington's disease, and amyotrophic lateral sclerosis belongs to a group of neurodegenerative diseases for which the pharmacological treatments are mostly symptomatic.

There is no treatment to fully arrest the progression of Huntington's disease, but symptoms can be reduced or alleviated through the use of medication and care methods. Emotional symptoms can be alleviated by the use of antidepressants and sedatives, with antipsychotics (in low doses) for psychotic symptoms. Nutrition is an important part of the care for these patients.

Amyotrophic lateral sclerosis (ALS) is a progressive, usually fatal, neurodegenerative disease caused by the degeneration of motor neurons in the central nervous system. No cure has yet been found for ALS. The U.S. Food and Drug Administration (FDA) has approved riluzole as the first drug treatment for the disease. It delays the onset of ventilator-dependence or tracheostomy in selected patients. A Cochrane review states a 9% gain in the probability of surviving one year (see Miller et al., 2007).

Multiple sclerosis is a chronic, inflammatory, demyelinating disease that affects the central nervous system. During symptomatic attacks administration of high doses of intravenous corticosteroids, such as methylprednisolone, is the routine therapy. As of 2007, six disease-modifying treatments have been approved by regulatory agencies of different countries, including two formulations of interferon beta-1a and one of interferon beta-1b. Glatiramer acetate is a random polymer composed of four amino acids that are found in myelin basic protein. It is an immunomodulator, licensed in much of the world for reducing the frequency of relapses in relapsing–remitting multiple sclerosis. The fifth medication, mitoxantrone, is an immunosuppressant also used in cancer chemotherapy. Natalizumab is a humanized monoclonal antibody against integrin-$\alpha 4$ that has proven efficacy in the treatment of multiple sclerosis. In early 2005 natalizumab was voluntarily withdrawn from the market for causing progressive multifocal leukoencephalopathy. In 2006 the FDA re-approved it under certain conditions for patients with relapsing forms of MS.

III.a. Treatments for Alzheimer's Disease

The results with the recently introduced centrally acting inhibitors of acetylcholinesterase like tacrine and rivastigmine for the treatment of Alzheimer's disease are modest at best.

Galantamine is used for the treatment of mild to moderate Alzheimer's disease. However in 2005 the U.S. Food and Drug Administration sent out a warning indicating that the product should not be used in patients with mild cognitive impairment (MCI) because of increased mortality observed in trials for MCI with galantamine. Galantamine is a competitive and reversible cholinesterase inhibitor.

Memantine is the first in a novel class of Alzheimer's disease medications acting a.o. on the NMDA receptor of the glutamatergic system. It also acts as an uncompetitive antagonist at different neuronal nicotinic receptors at potencies possibly similar to the NMDA receptor. Memantine is approved for treatment of moderate to severe Alzheimer's disease and its use is associated with a moderate decrease in clinical deterioration of the disease. Common adverse drug reactions ($\geqslant 1\%$ of patients) include: confusion, dizziness, drowsiness, headache, insomnia, agitation, and/or hallucinations.

III.b. Anti-Parkinson Agents

As dopamine deficiency of the nigrostriatal tract, resulting in an overactivity of cholinergic interneurons, is considered to be the fundamental pathophysiological mechanism for Parkinson's disease two approaches for pharmacological intervention seem rational.

III.b.1. Dopaminergic Agents

Levodopa, the metabolic precursor of dopamine, is the most effective agent in the treatment of Parkinson's disease but not for drug-induced Parkinsonism. Oral levodopa is absorbed by an active transport system for aromatic amino acids. Levodopa has a short elimination half-life of 1–3 hours. Transport over the blood–brain barrier is also mediated by an active process. In the brain levodopa is converted to dopamine by decarboxylation and both its therapeutic and adverse effects are mediated by dopamine. Either re-uptake of dopamine takes place or it is metabolized, mainly by monoamine oxidases. The isoenzyme monoamine oxidase B (MAO-B) is responsible for the majority of oxidative metabolism of dopamine in the striatum. As considerable peripheral conversion of levodopa to dopamine takes place large doses of the drug are needed if given alone. Such doses are associated with a high rate of side effects, especially nausea and vomiting but also cardiovascular adverse reactions. Peripheral dopa decarboxylase inhibitors like carbidopa or benserazide do not cross the blood–brain barrier and therefore only interfere with levodopa decarboxylation in the periphery. The combined treatment with levodopa with a peripheral decarboxylase inhibitor considerably decreases oral levodopa doses. However it should be realized that neuropsychiatric complications are not prevented by decarboxylase inhibitors as even with lower doses relatively more levodopa becomes available in the brain.

With long term levodopa therapy the risk for the occurrence of 'on–off' effects, periodically and paroxysmally occurring periods of the therapy becoming ineffective, increases. Decreasing the peak-trough fluctuations with slow-release levodopa/carbidopa formulations could possibly diminish these 'on–off' effects.

Tolerance occurs and levodopa becomes less effective with long-term use. To some extent this can be counteracted by an increase of dose. An other approach can be to stop levodopa treatment for some time and then resume again later.

Neuropsychiatric adverse reactions that can occur include anxiety, nervousness and depression but also serious psychotic reactions. Involuntary movements, sometimes of a disturbing and complex nature, are frequent in patients on long-term therapy.

Elderly patients display an increased sensitivity and the risks of adverse reactions, especially confusion and postural hypotension, is markedly increased.

The ergot derivatives bromocriptine, pergolide and lisuride are used for treatment of Parkinson's disease as dopamine agonists. They are strong agonists for the D_2 dopamine receptors. Bromocriptine and lisuride are partial antagonists of the D_1 receptors. Pergolide is an agonist at both D_1 and D_2 receptors. However, their actions and spectrum of adverse effects are similar. These agents are well absorbed orally and have plasma half-lives in the range of 3–7 hours. Pergolide is substantially more potent than bromocriptine. Dopamine agonists are mainly used in combination with carbidopa/levodopa in patients with of serious forms of Parkinson's disease. In March 2007, pergolide was withdrawn from the US market due to serious valvular damage.

Pramipexol and ropinirole are dopamine agonists which are not ergot derivatives. They have mainly affinity for the D_2 dopamine receptors. Combined with levodopa the levodopa dose can be considerably reduced. Rotigotine is also a non-ergot dopamine agonist. Rotigotine is intended to be delivered through transdermal patches, so as to ensure a slow and constant dosage in a 24-hour period. This transdermal patch was approved in Europe and in the US respectively in 2006 and 2007 as mono therapy for the treatment of signs and symptoms of the idiopathic form of the disease at an early stage. It could be shown that the drug was able to significantly reduce *off* time and increase *on* time without troublesome dyskinesia.

Apomorphine is a type of dopaminergic agonist, a morphine derivative which does not actually contain morphine, or bind to opioid receptors. Apomorphine is a relatively non-selective dopamine receptor agonist, having possible slightly higher affinity for D_2-like dopamine receptors. It is registered for the treatment of invalidating response fluctuations and for this indication it can be an effective monotherapy.

Amantadine, primarily an antiviral agent, increases dopamine levels in the central nervous system, either by increasing release or by inhibiting dopamine re-uptake, and consequently increases dopaminergic transmission. In mild Parkinsonism amantadine has some antiparkinsonian effects through this mechanism, particularly if it is used at an early stage of the disease. Although it has fewer side-effects than levodopa it is only effective in a small percentage of patients.

Selegiline is a selective and irreversible inhibitor of monoamine oxidase B (MAO-B) as long as it is

used in moderate doses. It does not inhibit peripheral metabolism of catecholamines as nonspecific inhibitors of MAO do. It can therefore safely be used together with levodopa and does not cause the potentially lethal reactions with indirectly acting sympathomimetic amines such as tyramine. In the management of Parkinson's disease selegiline is mostly used in combination with levodopa. The with disease progression frequently occurring 'on–off' effect may also be better controlled.

Amphetamine and methamphetamine are metabolites of selegiline and may cause anxiety and insomnia.

Entacapone and tolcapon are selective and reversible catechol-O-methyltransferase (COMT) inhibitors which also inhibit the break down of levodopa to 3-methoxy-4-hydroxy-L-phenylalanine.

Combined with levodopa and a decarboxylase inhibitor more stable levodopa levels can be obtained. Tolcapon has been withdrawn in many countries because of serious liverfunction disturbances, rhabdomyolysis and neuroleptic malignant syndrome.

III.b.2. Anticholinergic Agents

In Parkinson's disease anticholinergic agents are not as effective as levodopa. They are of use however for the treatment of drug-induced Parkinsonism. They are mostly employed in levodopa resistant patients. Their mechanism of action is by inhibiting the cholinergic interneurons in the nigrostriatum where they have their site of action distal to the dopaminergic neurons that are dysfunctioning.

With respect to both their activity and their spectrum of adverse effects there are no clinically significant differences among the various anticholinergic agents that are used.

Anticholinergic side-effects are dry mouth, urinary retention and constipation. Confusion and drowsiness occur especially in the elderly and because of their poor risk-benefit ratio old age is a relative but serious contraindication for the use of these agents.

Trihexyphenidyl and biperiden have strong central and peripheral anticholinergic activity and both idiopathic as well as drug-induced Parkinsonism can be an indication for their use. Especially the tremor of Parkinsonism is favorably influenced. Large doses of trihexyphenidyl are said to have a mood modifying effect. The existence of a parenteral dosage forms of biperiden extends the applications of this agent. Both have a duration of action of 6–12 hours.

The effectiveness of orphenadrine is less than that of biperiden and trihexyphenidyl. However it can be of use in patients with a mild form of the disease. It can also be of advantage in some elderly patients with intolerance for more potent anticholinergics.

IV. ANESTHETICS

In anesthesia drugs from several groups are used as premedication. Pre-anesthetic medication can decrease the anesthetic doses which otherwise would be required to induce anesthesia and so decrease the risk for adverse effects. Pre-anesthetic medication will increase the rate of induction of anesthesia and can reduce pre-operative pain and anxiety. Drugs include benzodiazepines for sedation and their muscle relaxant properties, opiates for pain relieve and anticholinergics or histamine H_1 receptor antagonists against nausea and vomiting. Neuroleptics are also used as premedication for their antiemetic effects.

General anesthesia is a state of CNS depression in which the patient has a complete absence of sensations and is unconscious. It can be induced by anesthetics administered by intravenous injection or by inhalation.

Several mechanisms of action have been proposed for general anesthetics. The most likely mechanisms are that they all act by potentiating transmitter release at inhibitory synapses or by inhibiting excitatory synapses. Many anesthetic agents, both volatile agents as intravenously administered agents, increase the affinity of the GABA-A receptor for the neurotransmitter GABA.

Usually various anesthetic agents are combined to increase efficacy and at the same time decrease toxicity and shorten the time to recovery. For example induction of anesthesia is obtained with an intravenous agent with a rapid onset of action like thiopentone and then anesthesia is maintained with a nitrous oxide/oxygen mixture in combination with halothane or a comparable volatile anesthetic.

IV.a. Intravenous Anesthetics

Injectable anesthetics act faster and are therefore best suited for induction of anesthesia and for short operative procedures. However recovery from injectable anesthetics is generally slower than with inhalation anesthetics. The high blood flow to the brain leads to rapid delivery of the anesthetics to their site

of action. Thereafter redistribution of drugs to tissues with greater mass and relatively good perfusion such as skeletal muscle and adipose tissue leads to a rapid decline in brain concentrations. So redistribution rather than metabolism is responsible for terminating the action of most injectable anesthetics. Saturation of these tissues with greater mass may lead to a prolongation of the duration of action with repeated dosing and this duration then begins to depend on metabolism and excretion.

Various barbiturates such as the short acting agent pentobarbital and the ultra-short acting agents thiopental and methohexital are used for anesthesia induction. They produce loss of consciousness without analgesia and with little effects on the cardiovascular system. Unconsciousness is combined with respiratory depression as the barbiturates produce non-selective CNS depression.

Opioids play an important role in anesthetic practice. Opioid analgesics potentiate the efficacy of anesthetics. They can be given as part of the premedication as well as during the operation. Examples of short acting agents with high potency are fentanyl, sufentanyl, alfentanil and remifentanil. Because of their hemodynamic stability these agents can be used for patients with compromised myocardial function. Respiration must be maintained artificially and may be depressed into the postoperative period. They are usually supplemented with inhalation anesthetic, benzodiazepines or propofol.

Of the benzodiazepines midazolam is used as an intravenous induction agent. It is also used for sedation during procedures under regional anesthesia. Its potency is 2–3 times higher than that of diazepam. It has therefore the risk of producing serious respiratory depression. However it has less cardiovascular and respiratory depressant effects than barbiturates. Its relatively potent amnesic effect, with its anxiolytic and sedative effects, make lorazepam useful as premedication. It is given before a general anesthetic to reduce the amount of anesthetic agent required.

Ketamine and also tiletamine are structurally and pharmacologically related to phencyclidine. Its mechanism of action is not well understood. It has been suggested that it blocks the membrane effects of the excitatory neurotransmitter glutamic acid. Ketamine produces dissociative anesthesia, which means that the patient seems to be awake but there are no responses to sensory stimuli. Ketamine, which can be administered IV or IM, has strong analgesic activity. It is especially indicated for interventions of short duration without any need for skeletal muscle relaxation as it has poor muscle relaxating properties. It can also be used as an analgesic agent for painful procedures. It is notorious for unpleasant excitatory and hallucinatory phenomena during emergence from anesthesia.

The main indication for etomidate is induction of anesthesia. It has no analgesic properties. It has little respiratory and cardiovascular depressant properties. However it can seriously suppress adrenal function.

Propofol can be used for induction as well as maintenance of anesthesia. It is very lipophilic and induction of anesthesia takes place within 30 seconds. After a single dose the patient awakes in approximately 5 minutes and after anesthesia by continuous intravenous administration of longer duration recovery may take 10–15 minutes. It can be used in combination with the usual range of premedications, analgesics, muscle relaxants and inhalation anesthetic agents.

IV.b. Inhalation Anesthetics

The inhalation anesthetics belong to diverse chemical classes. There main indication is the maintenance of anesthesia after intravenous induction. There are no suggestions that they interact with pharmacologically-defined receptors like some of the injectable anesthetics do and they have no specific site of action. Apparently they cause physical changes in cells such as changes in cell membrane fluidity.

Gas should be differentiated from volatile liquids which are used as inhalation anesthetics. A gas such as nitrous oxide exists in the gaseous form at room temperature and sea-level barometric pressure while vapors are the gaseous states of agents, like halothane, which at room temperature and pressure are liquids.

Although anesthetic biotransformation does not play a role of any significance in terminating the effects of inhalant anesthetics this biotransformation can be of considerable toxicological importance especially for fluorinated anesthetics because of the formation of reactive halide ions which can acutely or chronically harm kidneys, liver and reproductive organs. Inhalation anesthetics produce generalized CNS depression which is responsible for the depth of anesthesia. They may cause some skeletal muscle relaxation and potentiate non-depolarizing neuromuscular blocking drugs. The respiratory depressant effects of these agents are usually additive with

opioids and other classes of respiratory depressant drugs.

Volatile anesthetics have a direct relaxating effect on cardiac and vascular muscle added to indirect effects through reductions in sympathetic tone.

Malignant hyperthermia is a rare but potentially life threatening complication of the use of inhalation anesthetics in combination with succinylcholine.

Inhalation anesthetics still in use include nitrous oxide and the halogenated hydrocarbon inhalation anesthetics such as halothane, isoflurane, methoxyflurane and sevoflurane.

Nitrous oxide is the only inhalation anesthetic that is a gas. It is chemically inert. Nitrous oxide has little effect on overall cardiovascular function. Disadvantages are that it has no muscle relaxing effect and that it cannot be used on its own because of high Minimal Alveolar Concentration values needed for adequate anesthesia. During recovery there is a risk for hypoxia and anesthesia should be slowly tapered off to prevent this event.

Halogenated hydrocarbon inhalation anesthetics may increase intracranial and CSF pressure. Cardiovascular effects include decreased myocardial contractility and stroke volume leading to lower arterial blood pressure. Malignant hyperthermia may occur with all inhalation anesthetics except nitrous oxide but has most commonly been seen with halothane. Especially halothane but probably also the other halogenated hydrocarbons have the potential for acute or chronic hepatic toxicity. Halothane has been almost completely replaced in modern anesthesia practice by newer agents.

Being an ether enflurane is more irritant than halothane. However it has better skeletal muscle relaxant properties and has a lower incidence of cardiac arrhythmias.

Isoflurane, an isomer of enflurane, together with sevoflurane are the most commonly used inhalation anesthetics in humans. Isoflurane does not sensitize the myocardium to catecholamines, has muscle relaxing action so less neuromuscular blocker is required and causes less hepatotoxicity and renal toxicity than halothane.

IV.c. Local Anesthetics

Local anesthetics, when applied at effective concentrations locally to nerve tissue, reversibly block nerve impulse conduction and block somatic sensory, somatic motor and autonomic nerve transmission. Their mechanism of action is based on both frequency and voltage-dependent blockade of neuronal sodium channels. Small fibers are more sensitive than large fibers and myelinated fibers are affected faster than unmyelinated ones.

Local anesthetics are used for topical anesthesia, local infiltration, peripheral nerve block, paravertebral anesthesia, intravenous block also known as regional anesthesia, epidural block, and spinal i.e. subarachnoid blockade. The local anesthetics may be divided into two main groups, the esters and the amide-type agents.

The esters are mainly hydrolyzed by cholinesterases in plasma and to some extent also in the liver. They are generally unstable in solution and fast-acting. With the esters there is, compared to the agents of the amide group, a much higher incidence of hypersensitivity (allergic) reactions. Tetracaine is used for spinal anesthesia. Its surface anesthetic effects are used for topical applications. It is too toxic and its onset of action is too slow for use in other local anesthetic procedures. Other representatives from this group are cocaine, procaine, benzocaine and oxybuprocaine. Procaine has been replaced almost entirely by amide-type agents. Benzocaine and oxybuprocaine have surface anesthetic properties and are respectively used in topical formulations in situations where pain relief for a short period of time is needed like for a sore throat or for hemorrhoids and in ophthalmology.

Amide-type agents include articaine, lidocaine, bupivacaine, prilocaine, mepivacain and ropivacaine. These are metabolized in the liver by microsomal enzymes with amidase activity. The amide group is preferred for parenteral and local use. If by accident rapidly administered intravascularly these agents, especially bupivacaine but also lidocaine, can produce serious and potentially lethal adverse effects including convulsions and cardiac arrest. They can more easily accumulate after multiple administrations. Intravenous lidocaine is sometimes used for regional anesthesia, for infiltration procedures, for the induction of nerve blockade and for epidural anesthesia. However, it is also used as an antiarrhythmic. Bupivacaine is a long-acting local anesthetic used for peripheral nerve blocks and epidural anesthesia.

V. MUSCLE RELAXANTS

The non-depolarizing neuro-muscular blocking agents and depolarizing neuro-muscular blocking

agents which are used in anesthesia were discussed in Chapter 18.

Agents affecting the central nervous system and have muscle relaxant activity together with a unique mechanism of action, i.e. dantrolene, will be briefly discussed here.

Baclofen is a GABA agonist at GABA B receptors and it has a presynaptic inhibitory function by reducing calcium influx. Its indication is increased extensor tone and clonus. Intrathecal administration may control severe spasticity pain. It is used for the treatment of spastic movement, especially in instances of spinal cord injury, spastic diplegia, multiple sclerosis and amyotrophic lateral sclerosis. Its central nervous system effects include drowsiness, somnolence and seizure activity in epileptic patients.

Clonidine and other imidazoline compounds have also been shown to reduce muscle spasms by their central nervous system activity. Tizanidine is perhaps the most thoroughly studied clonidine analog. It is an agonist at α_2-adrenergic receptors, but reduces spasticity at doses that result in significantly less hypotension than clonidine.

Apart from the benzodiazepines which have direct muscle relaxating effects (see Section I.a.1 of this chapter) the other agent that has to be classified as belonging to the directly acting muscle relaxants is dantrolene. Chemically it is a hydantoin derivative, but does not exhibit antiepileptic activity. Dantrolene blocks release of Ca^{++} from the sarcoplasmic reticulum. It is used for the management of malignant hyperthermia and neuroleptic malignant syndrome, although the latter probably is not associated with a defect in Ca^{++} metabolism in skeletal muscle. If the indication is a medical emergency such as malignant hyperthermia, the only significant contraindication is hypersensitivity.

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Chapter 22

Hemopoietic Drugs and Drugs that Affect Coagulation

Chris J. van Boxtel

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I. ANTIANEMIC PREPARATIONS

I.a. Iron Preparations

Iron deficiency anemia develops if iron balance is not maintained. Only 5–10% of elemental iron in the diet is normally absorbed from the GI tract. However, with iron deficiency the amount absorbed can double or even triple. Between 1 and 3 mg/day (pregnant and lactating women) of absorbed iron is needed. The major causes of iron deficiency are excessive blood loss and nutritional deficiencies. In children and people living in developing areas the fact that iron from cereal diets is poorly absorbed can contribute to the occurrence of iron deficiency anemia. Iron is absorbed as ferrous (Fe^{2+}) iron. It is then oxidized to ferric iron (Fe^{3+}) in the gastric and intestines before being transported to the rest of the body. Ferric ions are carried by transferrin to bone marrow, to be incorporated in hemoglobin. About 70% of the total body iron content is in hemoglobin. Body stores of iron as ferritin and hemosiderin are located mainly in the liver, RE system, spleen and bone marrow. Iron is also an essential component of myoglobin and of a number of enzymes such as the cytochromes. Therefore, iron deficiency can affect metabolism independently of the effect on oxygen delivery.

Therapy is followed by an increased rate of production of red cells and up to 50 mg of iron may be utilized daily in the case of iron deficiency.

Orally administered ferrous salts are the preferred treatment for iron deficiency. Ferrous salts are absorbed about three times as well as ferric salts and the bioavailability of the sulfate, fumarate, succinate, gluconate, and other ferrous salts is approximately the same. Ferrous sulfate, being the least expensive, is then the treatment of choice. Ferrous fumarate is available as a syrup and may be useful in small children for the treatment and prophylaxis of iron deficiency.

In most adults with anemia 100 mg elemental iron per day usually produces an adequate response. Iron supplementation in prophylactic doses of 60 mg of elemental iron daily may be justified, e.g. in pregnancy and lactation.

Gastric acid and ascorbic acid facilitate the absorption of iron. Therefore, bioavailability of iron ingested with food is considerably decreased and also enteric-coated iron preparations are absorbed to a lesser extend. Fixed combinations with ascorbic acid increase the absorption of iron by at least 30%. However such increased uptake seems to have little advantage over a modest increase of dose.

Adverse effects consist mainly of gastrointestinal intolerance such as nausea, epigastric pain and diarrhea and, especially in the elderly constipation with continued therapy. All ferrous salts may cause a black coloration of the faeces. Children are particularly susceptible to potentially lethal iron intoxications. Oral iron preparations should not be administered concurrently with tetracyclines as mutual interference with absorption will occur.

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Indications for use of parenteral iron, e.g. as ferrioxidesaccharate or iron dextran, are in patients on hemodialysis and patients with a disease which prevents absorption from the gastrointestinal tract, in patients who are on long term parenteral nutrition and sometimes in patients with inflammatory bowel disease. Parenteral iron does not raise the hemoglobin level significantly faster than oral therapy and carries a risk of severe adverse reactions. Reactions to intravenous iron include headache, malaise, fever, arthralgias, urticaria and in rare cases anaphylactic reactions, which may be fatal.

I.b. Vitamin B_{12} and Folic Acid

Vitamin B_{12} exists as hydroxocobalamin, adenosylcobalamin and cyanocobalamin. Cobalamins are found exclusively in food ingredients of animal origin like meat, liver and to a lesser degree in dairy products. Vitamin B_{12} is absorbed in the distal ileum under the influence of the glycoprotein 'intrinsic factor'. The as hydroxocobalamin absorbed vitamin B_{12} is in the liver in part transformed to desoxyadenosylcobalamin and partly to cobalamine. By the transfer of the methyl group of methyltetrahydrofolate, the primary form in which folate is stored in the body, to cobalamin, methylcobalamine and tetrahydrofolate are formed. Via first the formation of 5,10-methylenetetrahydrofolate and then catalyzed by thymidylate synthetase tetrahydrofolate is further converted to dihydrofolate. In the process 5,10-methylenetetrahydrofolate donates the methylene group to deoxyuridylate for the synthesis of thymidylate needed for DNA synthesis. Thereafter dihydrofolate is reduced by dihydrofolate reductase back again to tetrahydrofolate (Fig. 1). This folate–cobalamin interaction is crucial for the synthesis of purines and pyrimidines and, therefore, of DNA.

With deficiency of either vitamin B_{12} to accept methyl groups from methyltetrahydrofolate, or of

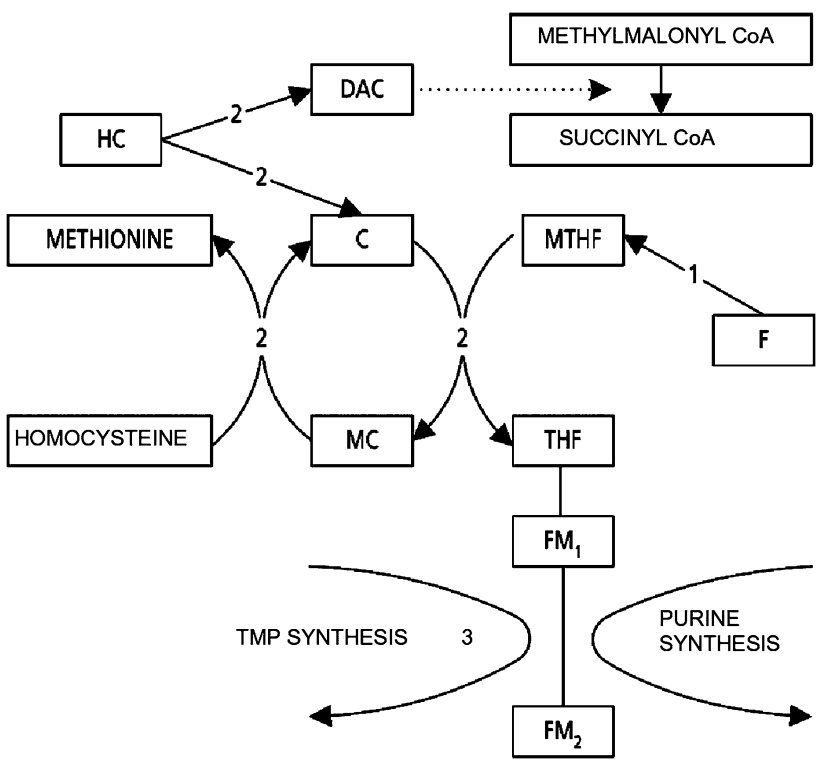


Fig. 1. Folate–cobalamin interaction in the synthesis of purines and pyrimidines and, therefore, of DNA. (1) In gastrointestinal mucosa cells; (2) in the liver; (3) in peripheral tissues. C, cobalamine; DAC, desoxyadenosylcobalamine; HC, hydroxycobalamine; MC, methylcobalamine; F, folic acid; MTHF, methyltetrahydrofolic acid; THF, tetrahydrofolic acid; DHF, dihydrofolic acid; dUMP, deoxyuridinemonophosphate; dTMP, deoxythymidine-monophosphate. (Adapted from *Farmacotherapeutish Kompas*, reproduced with permission.)

folic acid, further steps that require tetrahydrofolate are deprived of substrate, ultimately resulting in megaloblastic anemia.

However, vitamin B_{12} also plays a role in the conversion of methionine to S-adenosylmethionine which could explain the neuropathy that results from vitamin B_{12} deficiency.

About 10–25%, i.e. 50–200 µg, of the daily dietary intake of folic acid in yeasts, liver, and green vegetables is absorbed via active and passive transport in the proximal jejunum. As humans do not have dihydropteroate synthetase, which synthesizes folic acid in bacteria, we require folic acid in the diet. Only small amounts of folate can be stored in the body and dietary deficiency for only a few days can result in symptomatic folate deficiency.

Dietary forms of vitamin B_{12} are converted to active forms in the body. Vitamin B_{12}, mainly from liver, eggs and dairy products, is absorbed in terminal ileum. Intrinsic factor from parietal cells is required for absorption. Vitamin B_{12} is transported in the blood by transcobalamin II and stored in the liver. These stores are such that generally a patient does not become symptomatic until some years after the onset of vitamin B_{12} deficiency.

Folate deficiency can be dietary, especially in the elderly, due to increased demand like in pregnancy, or due to malabsorption syndromes. Agents which can cause folic acid deficiency with long-term use include phenytoin, oral contraceptives, isoniazid and glucocorticosteroids. In rare instances the use of dihydrofolate reductase inhibitors like trimethoprim, methotrexate or pyrimethamine can contribute to the occurrence of folate deficiency. Folinic acid can circumvent the need for the inhibited dihydrofolate reductase.

The main causes for vitamin B_{12} deficiency are impaired absorption due to a lack of gastric intrinsic factor (e.g. pernicious anemia), ileal abnormalities, or it can be the result of a strictly vegetarian diet.

Cyanocobalamin and the derivative hydroxocobalamin, given IM or deep subcutaneously, are indicated for treating vitamin B_{12} deficiency. Only in strict vegetarians oral preparations may be effective. Oral preparations with added intrinsic factor mostly are not reliably in patients with pernicious anemia. More than half the dose of cyanocobalamin injected is excreted in the urine within 48 hours and the therapeutic advantages of doses higher than 100 µg are questionable because of this rapid elimination. As vitamin B_{12} deficiency very rarely results from dietary deficiencies treatment every 2–4 weeks for life is mostly indicated.

Adverse events are rare and mostly allergic reactions such as urticaria and acneiform eruptions that probably can be attributed to impurities and preservatives in the preparations.

Folic acid is used for the treatment of folate deficiency. Oral folic acid is usually the therapy of choice. For megaloblastic anemia doses of 5 mg daily for 4 months should be effective. Folinic acid is available in a parenteral formulation which may be indicated when oral therapy is not feasible and for 'rescue' treatments following certain anti-cancer regimens.

Without a firm diagnosis folic acid should not be given to all patients with megaloblastic anemia as irreversible neurological damage from vitamin B_{12} deficiency may occur.

An important indication for folic acid has become the prevention of neural tube defects when given to women three months before conception and during the first trimester. The Recommended Dietary Allowance (RDA) for folate equivalents for pregnant women is 600–800 µg, twice the normal RDA of 400 µg for women who are not pregnant.

I.c. Hematopoietic Growth Factors

I.c.1. Erythropoietin

Erythropoietin is a protein produced mainly in the cortex of the kidney. Erythropoietin binds to a receptor on the surface of erythroid precursor cells. It stimulates erythropoiesis and is primarily indicated for the treatment of anemia in patients with chronic renal failure. Other indications are the management of anemia in cancer patients and in HIV positive subjects treated with anti-HIV regimens.

Recombinant human erythropoietin for intravenous or subcutaneous injection is available as epoetin alfa, epoetin beta and since 2001 as darbepoeitin alfa. Epoetin alfa and epoetin beta have different carbohydrate moieties. When administered intravenously the elimination half-life of epoetin alfa is approximately 10 hours. Subcutaneous bioavailability is 20–50% of IV and peak concentrations are achieved after some 20 hours. The recommended initial dose is 50–100 units/kg three times a week in patients with chronic renal failure.

No allergic reactions of any importance have been reported and apparently also no antibodies against

this growth factor are formed, even after prolonged administration. Adverse effects that have been associated with its use include hypertension, headache, seizures, and flu-like symptoms. Misuse of erythropoietin for improving achievements in sports caries a serious risk for thrombosis.

I.c.2. Myeloid Growth Factors and Thrombopoietin

The myeloid growth factors are glycoproteins that stimulate the proliferation and differentiation of one or more myeloid cell lines. They are produced mainly by fibroblasts, endothelial cells, macrophages, and T cells. Recombinant forms of several growth factors are now available, including granulocyte-macrophage colony-stimulating factor (GM-CSF), granulocyte colony-stimulating factor (G-CSF), macrophage colony-stimulating factor (M-CSF) and recently also thrombopoietin. G-CSF and GM-CSF are used, for example in bone marrow transplantation programs and with intensive chemotherapy regimens, to prevent infections in patients with severe neutropenia. Recombinant human GM-CSF (sargramostim) is administered by subcutaneous injection or slow intravenous infusion at a dose of 125–500 mg/m^2 per day. Adverse reactions like flushing, hypotension, nausea, vomiting, and dyspnea with a fall in arterial oxygen saturation due to sequestration of granulocytes in the lung can occur as an acute reaction to the first dose.

Recombinant human G-CSF (filgrastim) is administered by subcutaneous injection or rapid intravenous infusion at a dose of 1–20 mg/kg per day. Adverse reactions are mainly mild-to-moderate bone pain after repeated doses and local skin reactions following subcutaneous injections. G-CSF has to be given in the first 24 h after the completion of chemotherapy to produce the most clinical benefit. The cost of G-CSF is justified if there is a considerable risk of febrile neutropenia. Pegfilgrastim is a long-acting form of recombinant-methionyl human granulocyte colony stimulating factor. Pegfilgrastim is composed of filgrastim with a 20-kilodalton (kD) polyethylene glycol (PEG) molecule, covalently bound to the N-terminal methionine residue. It is registered to be used for decreasing the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.

Thrombopoietin is a cytokine that selectively stimulates megakaryocytopoiesis. Thrombopoeitin is not used therapeutically. Theoretical uses include the procurement of platelets for donation and recovery of platelet counts after myelosuppressive chemotherapy. However, a modified recombinant form caused paradoxical reactions, delaying the development of therapeutic thrombopoietin.

Small-molecule, nonpeptide thrombopoietin receptor agonists for oral use are being developed as a treatment for thrombocytopenia of various etiologies.

II. ANTITHROMBOTIC AGENTS

Arterial thrombi (white thrombi) are formed initially from both platelets and fibrin in medium-sized arteries on the basis of atherosclerosis. These thrombi can lead to symptoms of, among others, myocardial ischemia and myocardial infarction. The treatment is primarily aimed at prevention of thrombus formation with platelet aggregation inhibitors. For the treatment of myocardial infarction thrombolytic agents are used and for secondary prevention both oral anticoagulants and anti-platelet drugs are employed.

Venous thrombi (red thrombi) are formed mainly from fibrin in situations where vascular stasis exists or in hypercoagulability states. Here the symptoms consist of deep vein thrombosis with the risks of pulmonary embolism and the mainstay of therapy is anti-coagulation with heparin and oral anticoagulants.

The extrinsic coagulation pathway where Tissue Factor activates Factor VII leading to activated Factor X, contains many vitamin K-dependent factors and is thus effectively inhibited by oral anticoagulants. This pathway can best be monitored with the Prothrombin Time (PT). This is reported as an INR value when used for the dosing of oral anticoagulants. On the other hand, the intrinsic pathway contains many intrinsic proteases and therefore heparin can be an effective inhibitor. It is monitored with the activated Partial Thromboplastin Time (aPTT). Anti-proteases such as alpha1-antitrypsin, alpha2-macroglobulin, alpha2-antiplasmin and antithrombin III prevent the intravascular activation of the intrinsic pathway.

Antithrombin III is used in the management of acute thrombotic episodes and for prophylaxis during surgery and pregnancy in patients with antithrombin III deficiency. Several mediators of the

clotting process, such as tissue plasminogen activator (tPA), part of the extrinsic pathway, and Factor XII, part of the intrinsic pathway, also promote fibrinolysis.

II.a. Heparins

Unfractionated heparin is an animal product, a mixture of sulfated mucopolysaccharides with a molecular weight varying from 3000–30,000. It potentiates the effects of antithrombin III, making this antiprotease 1000 fold more effective. Its effects are immediate and last for several hours and it is therefore especially useful when rapid and short-lasting effects are needed. Heparin is administered intravenously or as subcutaneous injections as it is not available orally. Intramuscular injections can cause serious intramuscular hematoma. Indications for using intravenous dosages are treatment of deep-vein thrombosis and pulmonary embolism and of acute myocardial infarction before oral anticoagulants become effective. Heparin is also used for anticoagulation during open-heart surgery or hemodialysis. For prophylaxis of thrombosis in bed-ridden patients low doses of subcutaneously administered heparin are used.

Heparin is highly bound to plasma proteins and has a short elimination half-life of 1–5 hours depending on the dose. It is distributed to the reticuloendothelial system and metabolized in the liver to inactive metabolites. It does not cross the placental barrier, however there is a risk of heparin-induced maternal osteopenia if it is used throughout pregnancy.

Hypersensitivity and thrombocytopenia are adverse effects not related to the mechanism of the wanted effect and also not strongly dose related. Heparin in high doses inhibits platelet aggregation and prolongs the bleeding time. A serious side-effect of heparin is heparin-induced thrombocytopenia (HIT syndrome). HITS is caused by an immunological reaction that makes platelets aggregate within the blood vessels, thereby using up coagulation factors. Formation of platelet clots can lead to thrombosis, while the loss of coagulation factors and platelets may result in bleeding. Overdoses with heparin, which have an incidence of up to 10%, carry a serious risk for hemorrhage. They can be treated with protamine sulfate. However as protamine sulfate itself has anticoagulant properties this antidote should be used with caution.

Low molecular weight heparins such as dalteparin, enoxaparin, nadroparin and tinzaparin are isolated from standard heparin e.g. by gel filtration. They can also be produced by partial depolymerization with nitrous acid and other chemical reactions. They have average molecular weights between 4000 and 6000. They have less antithrombin activity but can be used as effectively as heparin with improved safety. Administered subcutaneously they have a longer duration of action than unfractionated heparin and the use of low molecular weight heparins has allowed once daily dosing, thus not requiring a continuous infusion. Low molecular weight heparins have replaced heparin for most indications.

Danaparoid although sometimes considered as a low molecular weight heparin is chemically distinct from heparin and thus has little cross-reactivity in heparin-intolerant patients.

Fondaparinux is a synthetic pentasaccharide. It is used for the prevention of deep vein thrombosis in patients who have had orthopedic surgery as well as for the treatment of deep vein thrombosis and pulmonary embolism.

Another type of anticoagulant are the direct thrombin inhibitors. Current members of this class include argatroban, lepirudin, and bivalirudin.

II.b. Oral Anticoagulants

Bishydroxycoumarin (dicoumarol) is a natural occurring anticoagulant found in sweet clover. A number of coumarin derivatives have been synthesized as anticoagulants, warfarin, phenprocoumon and acenocoumarol being most frequently used. The nonpolar carbon substituent at the 3 position required for activity is asymmetrical. The enantiomers differ in both pharmacokinetic and pharmacodynamic properties. The coumarins are marketed as racemic mixtures.

Coumarins are antagonists of vitamin K. For the production of the active forms of the coagulation factors II, VII, IX and X reduced vitamin K is needed. Oral anticoagulants inhibit vitamin K epoxide reductase involved in recycling reduced vitamin K from its oxidized form, vitamin K epoxide, and thus the formation of vitamin K-dependent coagulation factors. Because of the long half-life of some of the coagulation factors the full antithrombotic effect is not achieved for several days after starting coumarin administration. In rare cases extremely high doses are needed because of coumarin-resistance, which is inherited as an autosomal dominant trait. In Table 1 some characteristics of heparin and coumarins are compared.

Table 1. Comparison of some of the characteristics of heparin and coumarins

	Anticoagulants	
	Heparin	Coumarin
Mechanism of action	Potentiates anti-protease activity of antithrombin III	Inhibits vitamin K epoxide reductase
Pathways affected	Intrinsic pathway and common pathway	Extrinsic pathway and common pathway
Route of administration	Intravenously or subcutaneously	Orally
Onset of action	Immediate effect	Effect 8–12 hours after dosing (time needed to deplete existing clotting factors)
Duration of action	Hours	Days (time needed to synthesize new clotting factors)
Laboratory monitoring	Partial Thromboplastin Time (PTT)	Prothrombin Time (PT)
Antidote	Protamine sulfate	Vitamin K–prothrombin complex concentrate

Adapted from Lutty and Harrison (1977), *Basic and Clinical Pharmacology Made Memorable*, reproduced by permission of Harcourt Publishers.

Coumarins are metabolized into inactive metabolites in the liver by cytochrome P450 enzymes, leading to numerous potential drug interactions.

Phenprocoumon has a long plasma half-life of 5 days and thus a duration of action that can last 7–10 days. On the other hand acenocoumarol has a half-life of 10–24 hours and therefore a shorter duration of action. The half-life of warfarin ranges from 25–60 hours and its the duration of action is 2–5 days. Both warfarin and phenprocoumon are highly protein bound and interactions may occur with other drugs that bind to albumin.

Doses are determined by the individual responses as reflected by the prothrombin time and quantified by the INR, the International Normalized Ratio which is based on the WHO recommendations for standardization of thromboplastins.

Bleeding is the major toxicity of oral anticoagulant drugs and especially the risk of intracerebral or subdural hematoma in patients over 50 years of age on long-term oral anticoagulant therapy is increased considerably. Vitamin K_1 (phytonadione) is an effective antidote in overdosed patients. However, since the synthesis of clotting factors is required, 24 hours or longer may be needed for significant improvement in hemostasis by vitamin K_1.

Coumarin-induced skin necrosis is a rare complication of oral anticoagulant therapy. Especially patients suffering from a rare and life-threatening blood disorder known as protein C deficiency are at risk. In these cases Protein C Concentrate (human), Ceprotin, can be given. Ceprotin is of course also indicated for patients with severe congenital Protein C deficiency for the prevention and treatment of venous thrombosis and purpura fulminans.

Oral anticoagulants should not be used during pregnancy as they can be the cause of birth defects and abortion.

II.c. Platelet Aggregation Inhibitors

II.c.1. Cyclooxygenase Inhibitors

Far out the most important agent in this group is aspirin, a cyclooxygenase inhibitor which is discussed in more detail in Chapter 26. Its unique properties as a platelet aggregation inhibitor are brought forward by the fact that while platelet cyclooxygenase is irreversibly inhibited at low doses of aspirin the synthesis in endothelium of prostacyclin, a platelet aggregation inhibitor itself, recovers more quickly.

The main indications for aspirin as a platelet aggregation inhibitor are prevention of stroke in patients with cerebrovascular disease, prevention of myocardial infarct in patients with unstable angina or after myocardial infarction. For the prevention of myocardial infarction in someone with documented or suspected coronary artery disease, doses as low as 75 mg daily (or possibly even lower) are sufficient.

II.c.2. Adenosine Reuptake Inhibitors

Dipyridamole is a vasodilator and interferes with platelet function via intracellular cyclic AMP. Adenosine interacts with the adenosine receptors to cause

increased cAMP via adenylate cyclase and cAMP impairs platelet aggregation. However its beneficial effects are disputed. Oral bioavailability is between 30% and 70% and it has an elimination half-life varying from 1–12 hours. It is metabolized in the liver and excreted in bile with some enterohepatic recirculation. Adverse effects include gastrointestinal complaints such as nausea and abdominal cramps and also dizziness and headache. Orthostatic hypotension can occur at high doses.

II.c.3. Adenosine Diphosphate (ADP) Receptor Inhibitors

The blockade of the adenosine diphosphate (ADP) receptor (P2Y12) inhibits platelet aggregation by blocking activation of the glycoprotein IIb/IIIa pathway and inhibits the binding of fibrinogen to activated platelets. Ticlopidine inhibits platelet aggregation and clot retraction in this way. Abnormal platelet function persists for several days after discontinuation of treatment. Ticlopidine is recommended for patients unable to tolerate aspirin. Apart from risks of bleeding its side effects include diarrhea in 10% of patients and severe neutropenia in approximately 1% of patients. Because it has been reported to increase the risk of thrombotic thrombocytopenic purpura (TTP) its use has largely been replaced by the newer drug, clopidogrel.

Clopidogrel is indicated for prevention of vascular ischaemic events in patients with symptomatic atherosclerosis. It is also used, along with aspirin, for the prevention of thromboembolism after placement of an intracoronary stent. Platelet inhibition can be demonstrated two hours after a single dose of oral clopidogrel, but the onset of action is slow, so that a loading-dose is usually administered. Although rare, severe neutropenia and also thrombotic thrombocytopenic purpura may occur.

II.c.4. Phosphodiesterase Inhibitors

Cilostazol is a selective cAMP phosphodiesterase inhibitor. It inhibits platelet aggregation and is a direct arterial vasodilator. It is used for the symptoms of intermittent claudication in individuals with peripheral vascular disease. Side-effects of cilostazol include headache, diarrhea, increased heart rate, and palpitations. Drugs similar to cilostazol have increased the risk of death in patients with congestive heart failure.

II.c.5. Glycoprotein IIb/IIIa Inhibitors

A relatively new group of platelet aggregation inhibitors are the GPIIb/IIIa receptor antagonists. They bind to the GPIIb/IIIa receptor on the platelet membrane and thus prevent binding of among others ADP, fibrinogen and von Willebrand factor on activated platelets.

Abciximab is the Fab-fragment of a monoclonal antibody against the receptor. It is used in combination with heparin or aspirin during percutaneous coronary interventions.

Tirofiban is a synthetic, nonpeptide inhibitor of glycoprotein-(GP)-receptors. Tirofiban has a rapid onset and short duration of action after intravenous administration. Coagulation parameters turn to normal 4–8 hours after the drug is withdrawn. Tirofiban in combination with heparin and aspirin is indicated in the management of patients with unstable angina or non-Q-wave myocardial infarction.

Eptifibatide is a cyclic heptapeptide derived from a protein found in the venom of certain snakes. It selectively blocks the platelet glycoprotein IIb/IIIa receptor. It is used to reduce the risk of acute cardiac ischemic events (death and/or myocardial infarction) in patients with unstable angina or non-ST-segment-elevation (e.g., non-Q-wave) myocardial infarction. It is always used in combination with aspirin or clopidogrel and (low molecular weight or unfractionated) heparin. Eptifibatide undergoes renal elimination. In such patients with renal insufficiency where a glycoprotein IIb/IIIa inhibitor is likely to provide benefit, abciximab is to be preferred. The major adverse event is severe bleeding.

II.c.6. Other Platelet Aggregation Inhibitors

Sulfinpyrazone is a uricosuric and also inhibits platelet functions, probably mainly as a result of some inhibition of prostaglandin synthesis. However clinical efficacy in secondary prevention of myocardial infarction is inconsistent at the most.

Epoprostenol is the natural occurring prostacyclin which is formed in vascular endothelial cells. It increases cyclic AMP in the thrombocyte and is a strong platelet aggregation inhibitor. It is used to prevent thrombotic complications during hemodialysis when heparin is contraindicated. As its duration of action is no longer than 30 minutes it has to be given as an intravenous infusion.

The synthetic analogues of prostacyclin, beraprost, treprostinil and iloprost, although also platelet aggregation inhibitors, are used to treat pulmonary arterial hypertension.

II.d. Thrombolytic Agents

Plasminogen, an inactive precursor, is activated to plasmin which as a protease is able to break down fibrin clots. The thrombolytic agents in use promote the conversion of plasminogen to plasmin at the site of a thrombus. Indications include post-myocardial infarction treatment. The thrombolytic must be administered within 6 hours for an optimal effect. Other indications are treatment of acute pulmonary thromboembolism, deep-vein thrombosis, acute arterial thrombosis and thromboembolism, as well as in the clearance of arteriovenous catheters and cannulae. Agents are streptokinase, anistreplase, urokinase, alteplase, reteplase and tenecteplase.

Streptokinase has no intrinsic enzymatic activity, but forms a complex with plasminogen. As it is a protein produced by β-hemolytic streptococci in the patient inactivating antibodies can be present as a result of prior streptococcal infections. Starting with a loading dose is aimed at depletion of the amount of these antibodies. As streptokinase lacks fibrin specificity it can readily induces a systemic fibrinolysis. Anistreplase is a streptokinase–plasminogen complex used for the same indications as streptokinase. Urokinase is a protease with even shorter elimination half-life than streptokinase, without specific advantages and with the same risk of systemic fibrinolysis. Alteplase, reteplase and tenecteplase are tissue plasminogen activators (tPA) produced by recombinant DNA technology. Tissue plasminogen activator, t-PA, is a poor plasminogen activator in the absence of fibrin. It activates bound plasminogen several hundredfold more rapidly than it activates plasminogen in the circulation and this specificity of t-PA for fibrin limits induction of a systemic lytic state. Its half-life is 5–10 minutes.

The major toxicity of all thrombolytic agents is hemorrhage. Streptokinase can cause allergic reactions with fever, rash and, although rarely, anaphylaxis.

III. ANTIFIBRINOLYTICS

III.a. Amino Acids

Aminocaproic acid and tranexamic acid inhibit fibrinolysis by inhibiting plasminogen binding to fibrin or fibrinogen and the conversion of plasminogen to plasmin.

Aminocaproic acid is a potent inhibitor of fibrinolysis. Its main indication is therefore bleeding complications from fibrinolytic therapy, e.g. with streptokinase. Although it has been used in a variety of bleeding conditions, including bleeding after tooth extractions in hemophiliacs, the clinical significance of reduced bleeding in these settings is disputed. The main risk associated with aminocaproic acid is the increased risk for thrombosis because of the inhibition of fibrinolysis.

Tranexamic acid (Cyklokapron, Transamin) is a synthetic derivative of the amino acid lysine. It exerts its antifibrinolytic effect through the reversible blockade of lysine binding sites on plasminogen molecules.

III.b. Proteinase Inhibitors

Aprotinin is a polypeptide extracted from animal tissue. It inhibits proteolytic enzymes like trypsin, kallikrein, chymotrypsin and also plasmin. It has been used as an antifibrinolytic agent in a number of clinical situations. It was mainly recommended for use in fibrinolytic states during cardiac surgery. It is eliminated, almost completely by break down in smaller peptides and amino acids with an elimination half-life of 5–10 hours. Adverse effects include hypersensitivity reactions including occasional cases of anaphylaxis, bronchospasm, skin rashes, gastrointestinal effects, muscle pains and blood pressure changes. In November 2007 aprotinin was withdrawn from the market because of increased risk of death when used to prevent bleeding during heart surgery.

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Chapter 23

Drugs Affecting Gastrointestinal Function

Chris J. van Boxtel

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I. DRUGS FOR TREATMENT OF PEPTIC ULCER DISEASE

I.a. Introduction

Gastric acid secretion occurs in three different phases. In the cephalic phase it is the anticipation of food which gives vagal stimulation and thus an increased acid secretion. In the gastric phase the main stimulus is stomach distension. However gastric-acid secretion is also stimulated by exogenous products like alcohol, coffee and other xanthines and calcium. Some amino acids, e.g. phenylalanine and tryptophan also have stimulatory activity. In the intestinal phase stimulating factors are proteins, protein digestion-products and small intestine distension. Formation of gastric acid takes place inside the parietal cells where carbonic anhydrase forms H^+ and HCO_3^- from CO_2 and H_2O. Via activation of H^+/K^+-ATPase the H^+ ions are then excreted into the lumen, exchanging it for K^+. HCO_3^- is exchanged for Cl^- with as net result the excretion of HCl. This process is stimulated by gastric histamine H_2 receptors, muscarinic receptors and gastrin receptors and inhibited by somatostatin receptors.

The goals of medical treatment of peptic ulcer disease are to relieve symptoms, heal the ulcer and to prevent recurrence. For the first two the therapeutic tactics are aimed at reducing aggressive factors, in the first place gastric acid, and to promote or introduce defensive or cytoprotective factors. For neutralizing gastric acid antacids are effective and H_2 histamine receptor antagonists and proton pump inhibitors reduce gastric acid secretion. The use of cytoprotective agents compares often favorably with other treatment modalities. In patients who test positive for *Helicobacter pylori*, eradication of this bacterium with antimicrobial agents promotes healing and reduces the likelihood of relapse. There are various treatment regimens for eradication of *H. pylori*, and treatment of all ulcers found to be *H. pylori*-positive ($\pm$60% of ulcers). These regimens are mostly combinations of amoxicillin, metronidazole together with bismuth subsalicylate. Often a gastric acid secretion inhibitor such as omeprazole is added.

For prevention of peptic ulcer disease avoiding ulcerogenic medication such as NSAIDs, including aspirin, is probably the most important strategy. Reducing gastric acidity is also the main approach for the treatment of reflux esophagitis.

I.b. Antacids

Antacids are weak bases which react with gastric hydrochloric acid raising gastric pH by forming salt and water. From bicarbonate and carbonate-containing antacids also CO_2 is released. Elevation of the pH of the antrum will increase gastrin secretion, resulting in a compensatory secretion of acid and pepsin. Pepsin is reversibly inactivated at pH 5.0, and irreversibly inactivated at higher pH

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values. However partial neutralization actually increases peptic activity. Antacids differ considerably in their neutralizing efficacy and capacity and their risks for adverse events like electrolyte disturbances. Antacids affect bowel motility. Magnesium salts increase intestinal motility, whereas aluminum decreases it with respectively risks for diarrhea and constipation. By raising gastric and urinary pH and influencing gastric motility antacids can interact with a number of drugs by altering their kinetics.

I.b.1. Magnesium Compounds

The trisilicate, hydroxide, carbonate and oxide salts of magnesium are components of many antacid preparations indicated for the relief of dyspepsia and the treatment of reflux esophagitis and peptic ulcers. Magnesium hydroxide, $Mg(OH)_2$, also binds phosphate. $Mg(OH)_2$ reacts relatively rapidly with H^+. The related carbonate, $MgCO_3$, reacts more slowly. $Mg(OH)_2$ can slow stomach emptying which prolongs its neutralizing effect. Up to 5% may be absorbed with large doses. Magnesium is eliminated renally and may accumulate in patients with renal impairment. Hypermagnesaemia may cause nausea, vomiting, ECG changes, respiratory and mental depression, and coma. Poor absorption of magnesium salts results in diarrhea. Magnesium hydroxide interferes with the absorption of folic acid and iron.

I.b.2. Aluminum Compounds

Apart from increasing gastric pH aluminum-containing antacids adsorb bile acids, various proteins, fluoride and phosphorus. In patients with renal impairment they can be used as phosphate-binders. The binding of bile salts is a useful property in situations were reflux is a problem. Aluminium hydroxide, $Al(OH)_3$, particles may also reduce pepsin activity by adsorption above pH 3. $Al(OH)_3$ acts relatively slowly. It has sustained neutralizing capacity by forming complex conglomerates. Combinations of Mg^{2+} and Al^{3+} hydroxides act rapidly and have sustained neutralizing capacity. Magaldrate is a hydroxy-magnesium aluminate complex that is directly converted by gastric acid to Mg^{2+} and $Al(OH)_3$. When used alone aluminum compounds tend to cause constipation. Many preparations contain also therefore a mixture of aluminum and magnesium compounds which do not affect normal bowel function as much as would their single components.

Only a small amount of aluminum is absorbed, and is usually readily eliminated in the urine, unless renal function is impaired. Then absorbed Al^{3+} can contribute to osteoporosis, encephalopathy, and proximal myopathy. There is some concern that excess of aluminium may contribute to the development of Alzheimer's disease and other neurodegenerative disorders.

I.b.3. Calcium Compounds

$NaHCO_3$ and $CaCO_3$ can neutralize HCl rapidly, depending on particle size and crystal structure, and effectively. $NaHCO_3$ acts rapidly but absorption of unneutralized $NaHCO_3$ produces risks for alkalosis and sodium retention which may lead to edema, hypertension or heart failure. Also neutralized antacids may cause alkalosis by permitting the absorption of endogenous $NaHCO_3$. Ca^{2+} may stimulate the secretion of gastrin and HCl and calcium-containing antacids have been associated with rebound acid hypersecretion.

About 15% of orally administered Ca^{2+} is absorbed which can cause problems in patients with uremia. $NaHCO_3$ and $CaCO_3$ can then lead to hypercalcemia and further deteriorate renal function.

When large doses of $NaHCO_3$ or $CaCO_3$ are given the *milk-alkali syndrome* can occur as a result from the absorption of too much Ca^{2+} and alkali.

Combinations of $NaHCO_3$ and $Al(OH)_3$ have both the rapid effect of the carbonate and the longer lasting effect of $Al(OH)_3$.

I.c. Gastric Acid Secretion Inhibitors

I.c.1. H_2 Histamine Receptor Antagonists

H_2 receptor antagonists competitively inhibit the interaction of histamine with H_2 receptors. They are highly selective and have no clinically relevant effect on other receptors including H_1 receptors. As histamine mediates the effects of various other stimuli H_2 receptor antagonists also inhibit acid secretion stimulated by gastrin and by muscarinic agonists. Clinically their most important action is the inhibition of basal (fasting) and nocturnal acid secretion. After cimetidine, the first agent of this class, many competitors were marketed such as ranitidine, famotidine, nizatidine and roxatidine.

H_2 receptor antagonists are rapidly and almost completely absorbed, however some first pass metabolism may occur reducing the bioavailability. Although subject to hepatic metabolism, these drugs

are excreted in large part in the urine without being metabolized. Therefore their dosage, especially those of cimetidine, should be reduced in patients with impaired renal function.

They have a low incidence of adverse reactions and the reactions that occur are generally mild. Rapid intravenous infusion of H_2 antagonists may cause bradycardia. Cimetidine is more inclined to cross the blood–brain barrier and CNS effects such as somnolence and confusion have been described, especially in the elderly and in patients with impaired renal function. Cimetidine in high doses, as the only one of its class, has antiandrogenic effects which could be explained by an increase of prolactin secretion, binding to androgen receptors and inhibition the cytochrome P450 mediated hydroxylation of estradiol.

As it inhibits microsomal cytochrome P450 cimetidine has a high potential for drug interactions not shared by the other H_2 receptor antagonists. The oxidative metabolism of agents such as anticoagulants, most antiepileptics, some beta-blockers, warfarin, theophylline and many hypnotics, neuroleptics and antidepressants may be reduced, leading to increased effects.

I.c.2. Proton Pump Inhibitors

At neutral pH proton pump inhibitors are chemically stable, lipid-soluble, weak bases that have no inhibitory activity. In an acid environment they become protonated and a sulfenamide is formed. This sulfenamide binds covalently to the K^+H^+-ATPase proton pump in the gastric parietal cells, inhibiting this enzyme irreversibly and thus the entry of H^+ ions into lumen. Omeprazole metabolizes at a pH of about 3.9–4.1, whereas rabeprazole metabolizes at a pH of about 4.9. Secretion of acid only becomes possible again after new molecules of K^+H^+-ATPase are formed.

Agents in this class are omeprazole, lansoprazole, pantoprazole and rabeprazole. Esomeprazole is the S-enantiomer of omeprazole. After ingestion of gastric acid resistant formulations they are rapidly and more or less completely absorbed. Bioavailability may be reduced if administered with food or antacids. Elimination is via metabolism in the liver and the renal excretion of inactive metabolites. The elimination half-live is very variable, however, as explained above, not related to the duration of action.

No significant adverse effects were reported thus far. Carcinoid tumors were found in rats, probably due to the effects of hypergastrinemia. Gynecomastia and impotence can occur. Proton pump inhibitors are associated with fractures. There is a risk for drug interactions because of the elevated gastric pH and because omeprazole as well as lansoprazole inhibit hepatic microsomal cytochrome P450 activity.

I.d. Cytoprotective Agents

Sucralfate, the basic aluminum salt of sucrose octasulfate, is a sucrose hydrogen sulphate aluminum complex. Its free SO_4^{2-} groups bind to proteins in the stomach thus increasing production of mucus, HCO_3^-, and probably also prostaglandins. It has its mucoprotective effect by forming, in reaction with hydrochloride acid, a paste-like gel which adheres to the base of ulcer craters for up to 6 hours. Antacids prevent this protective gel formation. Furthermore, sucrose octasulfate is believed to inhibit peptic hydrolysis, also *in vivo*. Sucralfate is a safe agent with constipation as its most frequent side effect. Although only minimal absorption of sucralfate takes place aluminum toxicity can occur in people with renal insufficiently.

Colloidal bismuth subcitrate and bismuth subsalicylate chelate at acid pH with proteins, protecting the ulcer from gastric acid, pepsin and bile. These agents have a high affinity for damaged tissue and form a visible coating in the bases of ulcer craters. The efficacy of bismuth preparations in the treatment of duodenal and gastric ulcers compares favorably with the H_2 antagonists and other ulcer healing agents with a lower relapse rate than the other drugs. The observed benefits of bismuth also reflect its antibacterial action against *Helicobacter pyloris*, which is strongly associated epidemiologically with peptic ulcer disease.

By reacting with bacterial H_2S the oral cavity and feces will be colored black. Bismuth and also salicylate when bismuth subsalicylate is used, are to a minor degree absorbed. Children should not take bismuth subsalicylate while recovering from the flu or chicken pox, as epidemiologic evidence points to an association between the use of salicylate containing medications during certain viral infections and the onset of Reye's syndrome.

I.e. Other Drugs for Treatment of Peptic Ulcer Disease

Misoprostol is a stable analog of prostaglandin E_1. It reduces acid secretion by inhibiting histamine-stimulated adenyl cyclase activity in the parietal cell.

However the dosages that are needed to inhibit gastric acid secretion are higher than those for achieving cytoprotective effects, i.e. enhanced secretion of mucus and HCO_3^-. Its indication is mainly protection against NSAID-associated gastric ulceration. Only misoprostol 800 μg/day has been directly shown to reduce the risk of ulcer complications.

Adverse effects are uncommon although diarrhea and abdominal cramping in up to 30% of patients may limit its use. Misoprostol should be avoided in pregnant subjects and women of childbearing potential should be advised of adequate contraception as misoprostol may cause miscarriage. Effects on the developing human fetus are not known.

Pirenzepine is a tricyclic drug with a structure comparable to that of imipramine. It has selectivity for M_1-, relative to M_2-, and M_3-muscarinic receptors. Probably by an interaction with postganglionic muscarinic M_1-cholinergic receptors it is able to inhibit the relaxation of the lower esophageal sphincter. Pirenzepine, and also its analog telenzepine, interferes with gastric acid as well as gastrin secretion. However, due to its relatively poor efficacy and its high incidence of anticholinergic adverse effects the benefit–risk ratio of this drug compares unfavorably with other anti ulcer agents.

Carbenoxolone is a derivative of glycyrrhizic acid and both carbenoxolone and liquorice have ulcer healing properties. However, carbenoxolone has considerable mineralocorticoid activity, frequently producing Na^+ and fluid retention, hypertension and hypokalemia. It is therefore not generally recommended for routine use.

Alginates are extracted from algae and may decrease acidic reflux and increases esophageal clearance of acid. Preparations include alginic acid combinations and Gaviscon®. The mechanism of action could be that the alginate component forms a viscous layer on the mucosa and on the surface of the gastric contents, thus impairing reflux. However, the efficacy of these products in managing gastroesophageal reflux is controversial.

II. INTESTINAL ANTI-INFLAMMATORY AGENTS

Sulfasalazine was the first of the 5-aminosalicylic acid (5-ASA) congeners that was shown to be effective in the treatment of active Crohn's disease with involvement of the colon and of ulcerative colitis. Maintenance therapy with sulfasalazine reduces relapse rate. However a considerable number of patients experience adverse effects which are by the sulfa component of sulfasalazine. Then preparations of 5-aminosalicylic acid can be used.

Sulfasalazine is absorbed in the proximal intestine and is then excreted unchanged in the bile. In consequence most of orally administred sulfasalzine reaches the colon as such. It is then split by the intestinal flora into its components sulfapyridine, a sulfonamide antimicrobial agent, and 5-aminosalicylic acid (5-ASA). It has been proven that in inflammatory bowel disease 5-ASA is responsible for the beneficial effects while the sulpha component only contributes to the adverse reaction profile. Although some 5-ASA is absorbed and excreted in urine with a half-life of 0.5–1.5 hours, most is eliminated unchanged in the faeces. Sulfapyridine is to a major extend reabsorbed, metabolized in the liver and excreted in the urine with a half-life, depending on the acetylator phenotype, between 5 and 15 hours.

Adverse reactions occur more frequently in slow acetylators. They include acute hemolysis in patients with glucose-6-phosphate dehydrogenase deficiency, and agranulocytosis. Fever, arthralgias, and rashes occur in up to 20% of patients. Gastrointestinal complaints are common. Hypersensitivity reactions including photosensitivity are also seen. Less frequent are hepatic function disturbances.

5-Amino-salicyclic acid itself is not effective orally because it is poorly absorbed and is decomposed before reaching the lower intestine. However it can be used as suppositories and in rectal enemas.

There are oral formulations that deliver drug to the lower intestine. In mesalazine 5-amino-salicylic acid is formulated in a polymer-coated oral preparation. Olsalazine is a dimer of 5-aminosalicylate linked by an azo bond. Balsalazide is delivered to the colon where it is cleaved by bacterial azoreduction to release equimolar quantities of mesalazine and 4-aminobenzoyl-β-alanine. The newer 5-ASA preparations were shown to be superior to placebo and tended towards therapeutic benefit over sulfasalazine. However, considering their relative costs, a clinical advantage to using the newer 5-ASA preparations in place of sulfasalazine appears unlikely.

Glucocorticoid therapy is indicated in selected patients with inflammatory bowel disease, chronic ulcerative colitis as well as Crohn's disease. Agents include prednisolone, hydrocortisone and budesonide, the latter having a predominantly local effect

as it is rapidly metabolized in the liver. For colitis, formulations of prednisolone as the sodium phosphate are used as enema's.

Corticosteroids are the mainstay of therapy in Crohn's disease.

Also the immunosuppressives cyclosporine, azathioprine and methotrexate have been shown to be effective treatment modalities in active Crohn's disease.

A new approach for the management of Crohn's disease is the employment of tumor necrosis factor (TNF) antagonists. The chimeric monoclonal antibody directed against tumor necrosis factor, infliximab, is highly effective in repeated treatments for Crohn's disease. Etanercept is an artificially engineered dimeric fusion protein that mimics the inhibitory effects of naturally occurring soluble TNF receptors. Adalimumab and golimumab are fully human monoclonal antibodies directed against TNF. Both are effective TNF antagonists like infliximab.

Anti-TNF therapy can give rise to serious reactions, including anaphylaxis, sometimes fatal blood disorders, tuberculosis and other infections, rare reports of lymphoma and solid tissue cancers, rare reports of serious liver injury, rare reports of drug induced lupus and rare reports of demyelinating central nervous system disorders, which prompted the FDA to change the respective labeling of these drugs.

III. ANTISPASMODIC AGENTS

III.a. Muscarinic Receptor Antagonists

Muscarinic receptor antagonists can be divided into naturally occurring agents and their derivatives and the synthetic antimuscarinics. The naturally occurring muscarinic receptor antagonists are the alkaloids of the belladonna plants. The most important of these are atropine and scopolamine. The H_2-selective histamine receptor antagonists and proton pump inhibitors have replaced atropine and other nonselective muscarinic receptor antagonists as inhibitors of acid secretion. Antimuscarinics used in the relief of muscle spasm have marked effects on smooth muscle and on motility of the gastrointestinal tract. Salivary secretion is sensitive to inhibition by muscarinic receptor antagonists.

In the treatment of irritable bowel syndrome, often a therapeutic dilemma, there is some evidence that a high fibre maintenance diet combined with short-term antispasmodics may be beneficial.

III.a.1. Belladonna Alkaloids and Derivatives

Atropine, a tertiary amine, competitively antagonizes acetylcholine activity. Full therapeutic doses of atropine produce definite and prolonged inhibitory effects on the motor activity of the stomach, duodenum, jejunum, ileum, and colon, characterized by a decrease in tone and in amplitude and frequency of peristaltic contractions.

Atropine has a mild antispasmodic action on the gallbladder and bile ducts. It has been superseded in gastroenterology by agents with fewer adverse effects.

Belladonna acts in the same way as atropine; it is available as a tincture and in certain polycomponent preparations used for their biliary and intestinal antispasmodic action. Belladonna alkaloids show rapid absorption from the gastrointestinal tract.

Butylscopolamine and methscopolamine bromide, quaternary ammonium derivatives of scopolamine without its central actions and homatropine methylbromide, a quaternary derivative of homatropine, are less potent than atropine in antimuscarinic activity. They are used for their antispasmodic action in gastroenterology. The usual oral doses act for 6–8 hours. However, the quaternary ammonium derivatives are poorly absorbed after an oral dose and their eficacy is therefore very variable. Only parenteral administrations are recommended.

Hyoscyamine is a tertiary amine. It is the levoisomer to atropine. Tetertiary amines have the potential to cross the bloodbrain barrier and their oral absorption is also considerably better. Other synthetic tertiary amines used for their antispasmodic properties are dicyclomine and phencyclimine.

III.a.2. Synthetic Anticholinergics

Propantheline, a quaternary ammonium compound, is one of the more widely used of the synthetic muscarinic receptor antagonists. Propantheline is indicated as adjunctive therapy in GI disorders involving smooth muscle spasm. The clinical impression is that the quaternary ammonium compounds have a relatively greater effect on gastrointestinal activity. Being less lipophilic they are less likely to cross the blood–brain barrier. Other drugs in this category include anisotropine, clidinium, glycopyrrolate, sopropamide iodide and mepenzolate bromide.

III.b. Non-anticholinergic Antispasmodics

These compounds do not have any appreciable affinity for muscarinic receptors. Their mechanism of action is based on interference with sodium channels, thus blocking calcium influx in the smooth muscle cell. Agents in this group are papaverine, mebeverine, pinaverine and also dicycloverine. Although dicycloverine is a tertiary amine structurally related to the antimuscarinics, it has little antimuscarinic activity at low doses. It appears to act directly as a non-selective smooth muscle relaxant. Mebeverine has papaverine-like properties and is claimed to be selectively spasmolytic on smooth muscle of the gastrointestinal tract. Its spasmolytic action on the sphincter of Oddi is approximately ten fold greater than that of papaverine. These drugs are indicated for the relief of intestinal, biliary and genitourinary spasm, especially for patients in whom anticholinergics are contraindicated, e.g. patients with glaucoma or prostate hypertrophy.

IV. ANTIEMETICS AND PROKINETIC AGENTS

IV.a. Antiemetics

The vomiting centre in the hypothalamus receives impulses from the chemo-effector trigger zone (CETZ) and from cortical centres such as emotional, visual and olfactory areas, and from peripheral sources, including the inner ear and gastrointestinal tract. While mainly muscarinic mechanisms operate at the vomiting centre, dopaminergic mechanisms predominate at the CETZ. The CETZ can be stimulated by a multitude of xenobiotics, including medicines.

Centrally acting agents include dopamine antagonists, anticholinergics, histamine H_1 receptor antagonists with high affinity for muscarinic receptors, serotonin 5-HT3 antagonists, supposedly acting on receptors located on gastric vagal afferent fibers leading to the vomiting center and cannabinoids acting on central cannabinoid receptors. Benzodiazepines may be useful adjuncts in the control of nausea and vomiting induced by chemotherapeutic agents.

The anticholinergic agent scopolamine is available as a patch formulation. Its slow release causes a duration of action of 3 days. It is highly effective for motion sickness.

Locally-acting are all agents that decrease stimulation of receptors in the GI tract. A viscous formulation of local anesthetics such as lidocaine increases the threshold of receptor-activity to vomiting. Adsorbents and mucosa protective agents like kaolin and pectin, activated charcoal, bismuth subsalicylate, attapulgite and cholestyramine have similar effects. Cola Syrup and phosphorylated carbohydrate can decrease GI muscle spasm with consequently less input into the vomiting center.

Glucocorticosteroids are effective, especially in combination with other antiemetics, in controlling nausea and vomiting provoked by chemotherapeutic agents. The efficacy in this respect of dexamethasone and methylprednisolone are best documented. However their mechanism of action is not well understood.

Domperidone is a dopamine antagonist with high selectivity for the CETZ. However, as it does not penetrate so well into the CNS, its main effects are confined to the periphery, and its antiemetic effects are less than those of metoclopramide. Less selective dopamine blockers are metoclopramide, promethazine and neuroleptics such as prochlorperazine. The antiemetic effect of metoclopramide, a derivative of procainamide, results from blocking dopamine receptors in the brain. Its prokinetc action is brought forward by peripheral antidopaminergc effects. Metoclopramide has antiemetic efficacy in the post-operative period, in infection, uraemia, radiation sickness and during cancer chemotherapy. However, it is ineffective for Meniere's disease or motion sickness or nausea and vomiting from other labyrinthine disturbances. Prochlorperazine, a phenothiazine derivative of the piperazine type, is a neuroleptic with potent antiemetic activity, weak anticholinergic activity and a relatively low potential to cause sedation.

Histamine H_1 receptor antagonists with prominent anticholinergic properties are the mainstays of therapy for the prevention of motion sickness. Some H_1 antagonists are useful in suppressing vertigo. Alone, these agents are of little use against chemotherapy-induced emesis. More recently introduced agents are the serotonin 5HT3 antagonists like ondansetron, dolasetron, granisetron and tropisetron. In 2007 palonosetron was added to these. Although effective in the management of chemotherapy- and radiotherapy-induced emesis there is no proof that they are better than the steroid–antiemetic–benzodiazepine combinations.

IV.b. Prokinetic Agents

Gastric motility is influenced to a major extend by stimulation of cholinergic and dopaminergic receptors. Furthermore, the gastrointestinal peptide motilin is also a prokinetic agent. It stimulates gastric emptying by interacting with specific receptors. The antibiotic erythromycin also acts as an agonist at these receptors.

The prokinetic agents metoclopramide, cisapride, and domperidone, some of which are used as antiemetic agents, play a major role in the management of patients with gastric hypomotility. However, the usefulness of these agents for irritable bowel syndrome is controversial. Metoclopramide increases gastrointestinal motility and gastro-oesophageal sphincter tone by its dopaminergic antagonist activity and further by increasing acetylcholine release from myenteric neurons and probably by sensitizing muscarinic receptors for acetylcholine. The gastrointestinal actions of metoclopramide are blocked by atropine. Metoclopramide thus reduces oesophageal reflux and enhances gastric emptying. It is rapidly absorbed following oral administration however a significant hepatic first-pass metabolism reduces its bioavailability. Up to 30% is excreted unchanged in the urine and its half-life is considerably prolonged in renal failure. Metoclopramide can produce serious extrapyramidal reactions like torticollis, especially in children and the elderly.

The effects of domperidone on gastrointestinal motility resemble those of metoclopramide but are not reduced by muscarinic antagonists. The beneficial effects of domperidone are ascribed to dopamine D2 receptor antagonism. Gastric emptying is enhanced by an increase in gastric peristalsis and relaxation of the pylorus. Domperidone is rapidly absorbed but has a low bioavailability and most of the drug and its metabolites are excreted in the feces. Although it has difficulties crossing the blood brain barrier, extrapyramidal reactions have been reported.

Cisapride is a selective cholinomimetic agent with no antidopaminergic activity. It increases acetylcholine release from the myenteric neurons. It has the same indications as metoclopramide but is also useful for dysmotility problems of the lower GI tract. In many countries it has been either withdrawn or has had its indications limited due to reports about long QT syndrome due to cisapride.

Muscarinic receptor agonists, such as carbachol and bethanechol, can improve intestinal motility, e.g. in the post operative state. Both drugs act with some selectivity on gastrointestinal tract. However cardiac arrhythmias can occur.

V. ANTIDIARRHOEALS

V.a. Intestinal Adsorbents

Nonspecific antidiarrheal agents may be useful in treating self-limiting diarrhea. Kaolin and pectin or chalk may adsorb noxious compounds but evidence that such adsorbents are effective is unconvincing. Disadvantages can be prolongation of the course of infection and interference with absorption of desired drugs.

Colestyramine bind bile acids in the large bowel and is an effective antidiarrheal agent when high concentrations of bile acids are the cause of the diarrhea.

There is some evidence that bismuth subsalicylate can be effective in travelers' diarrhea due to *Escherichia coli* and for nonspecific diarrhea by such mechanisms as binding bacterial toxins, bactericidal action and local anti-inflammatory effects.

Some bulk forming preparations like methylcellulose can under certain circumstances thicken the consistency of the bowel contents and so decrease diarrhea.

V.b. Antipropulsives

Decreasing intestinal motility will favor the intestinal absorption of water. For this purpose the activity of opioids can be employed. Also combinations of opioid agonists with muscarinic receptor antagonists are used for this purpose.

Diphenoxylate is a synthetic meperidine analog with little or no analgesic activity. However in high doses it shows opioid activity such as euphoria and a morphine-like physical dependence after chronic administration. Its insolubility however, in aqueous solution prevents parenteral abuse. Nevertheless, diphenoxylate has in most countries been replaced by loperamide.

Loperamide is also structurally related to meperidine and its mechanism of action is like diphenoxylate. Gastointestinal motility is decreased by inhibition of the contractions of the longitudinal as well as the circular musculature, and the activity of this agent is at least in part mediated by its affinity for opiate receptors. As it hardly crosses the blood–

brain barrier only a small abuse potential exists. Loperamide is conjugated in the liver. In children under two years of age loperamide conjugation may be insufficient. Loperamide-oxide is a pro-drug of loperamide. In the large bowel loperamide is formed which acts locally. Less than 20% is absorbed.

Codeine phosphate is still used for diarrhea predominantly based on hypermotility but the longer-acting loperamide is more convenient and has less central nervous system effects. Codeine has an exceptionally low affinity for opioid receptors and its effects are due to the fact that it is converted for approximately 10% to morphine. The active metabolite of morphine, morphine-6-glucuronide, may also accumulate during repeated administration of codeine to patients with impaired renal function.

VI. LAXATIVES

The mechanisms of action of many laxatives are not well understood due to the complex factors that affect colonic function. However three general mechanisms can be recognized: (1) fluid retention in colonic contents thereby increasing bulk, (2) direct or indirect effects on the colonic mucosa to decrease net absorption of water and NaCl and (3) increase of intestinal motility.

VI.a. Bulk-Forming Laxatives

These laxatives act by softening and increasing faecal mass thus promoting normal peristalsis. The outer layers of cereal grains, especially wheat, form an important source of natural fibre in the diet and by increasing faecal mass natural fibre has laxative effects.

Among the bulk-forming agents are both natural and semisynthetic polysaccharides and celluloses derived from grains, seed husks, or kelp, psyllium, methylcellulose, and carboxy-methylcellulose, as well as the synthetic resin polycarbophil. There is often a delay of several days before the effects of a bulk-forming laxative become apparent. Bulk-forming laxatives have few side effects and minimal systemic effects. Allergic reactions may occur, especially with use of plant gums. It is obvious that dextrose-containing preparations are contraindicated for diabetics and in some patients sodium or calcium loads should be avoided.

Bulk-forming laxatives may interfere with drug absorption.

VI.b. Osmotic Laxatives

Saline laxatives like $MgSO_4$, $Mg(OH)_2$, $Mg_2{}^+$ Citrate and Na^+ Phosphates act via their osmotic pressure to retain water in the colon. Other osmotic laxatives are carbohydrates such as lactulose, glycerin, sorbitol, and mannitol. They are not absorbed and are resistant to digestion in the small intestine. Most agents are orally administered. It should be noted however that glycerin, sodium phosphates and sorbitol are formulated for rectal use. From lactulose lactic and acetic acids are formed by intestinal bacteria and apart from its osmotic effects it thus acidifies the content of the colon. The reduction of the pH stimulates motility and secretion.

Macrogol is also an osmotic laxative. Macrogol 4000 is a long linear polymer, also known as polyethylene glycol. It is not absorbed from the gut into the bloodstream, but remains in the gut where it causes water to be drawn into the lower bowel. Anaphylaxis to macrogol has been described.

Adverse effects include abdominal pain, diarrhoea and nausea. Electrolyte disturbances, can result from absorption. From the various inorganic salts both anions and cations can be absorbed. Magnesium levels can be raised in patients with renal impairment.

Use of lactulose can cause cramps and abdominal discomfort. High doses may produce excessive loss of fluid and K^+. Lactulose is contraindicated in patients on a galactose-free diet and in patients with diabetes.

VI.c. Stimulant Laxatives

Stimulant laxatives increase intestinal motility thereby decreasing absorption of water and electrolytes. Included in this group are diphenylmethane derivatives and anthraquinones.

The two most important diphenylmethanes are phenolphthalein and bisacodyl. Senna and cascara are the sources of anthraquinone laxatives. However, although still available in some countries phenolphthalein is now removed from most markets because of concerns over carcinogenicity. As recent as 2006 the United States Food and Drug Administration (FDA) has categorized castor oil as “generally recognized as safe and effective” (GRASE) for over-the-counter use as a laxative. On the other hand, in 2002 cascara was banned by the FDA.

Bisacodyl is desacetylated by intestinal and bacterial enzymes to its active metabolite. As much as

5% of an orally administered dose is absorbed and excreted in the urine as the glucuronide. Some enterohepatic circulation also occurs. Suppositories of bisacodyl may produce local irritation and with prolonged use even erosions may develop.

Long-term use of stimulant laxatives can cause a reduction of colonic innervation with a consequent loss off their efficacy. Atony and dilatation of the colon will then lead to a further deterioration of normal bowel function and to laxative dependence.

VII. BILE ACIDS

In the bile cholesterol is kept soluble by fats, phospholipids like lecithin and by bile acids. The important bile acids in human bile are cholic acid, chenodeoxycholic acid or chenodiol and ursodeoxycholic acid or ursodiol. Bile acids increase bile production. Dehydrocholic acid, a semisynthetic cholate is especially active in this respect. It stimulates the production of bile of low specific gravity and is therefore called a hydrocholeretic drug. Chenodiol and ursodiol but not cholic acid decrease the cholesterol content of bile by reducing cholesterol production and cholesterol secretion. Ursodiol also decreases cholesterol reabsorption. By these actions chenodiol and ursodiol are able to decrease the formation of cholesterolic gallstones and they can promote their dissolution.

Dehydrocholic acid is sometimes used to facilitate T-tube drainage after gallbladder surgery. Chenodiol and ursodiol are indicated for the dissolution of gallstones. All three drugs are administered orally. In general ursodiol is better tolerated than chenodiol. Chenodiol can produce diarrhea and it is hepatotoxic in a minority of patients due to the formation of the hepatotoxin lithocholic acid by intestinal microorganisms. Both drugs are contraindicated in women who are or may become pregnant.

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Chapter 24

Hormones and Hormone Antagonists

Chris J. van Boxtel

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I. HYPOTHALAMIC AND PITUITARY HORMONES

I.a. Hypothalamic Hormones

I.a.1. Gonadotropin-Releasing Hormone Agonists and Antagonists

Gonadotropin-releasing hormone (GnRH) is a decapeptide made in the arcuate nucleus of the hypothalamus. It binds to receptors in the pituitary gland. Pulsatile administration stimulates luteinizing hormone (LH) and follicle-stimulating hormone (FSH) secretion while continuously administration inhibits gonadotropin release. Gonadorelin is a synthetic decapeptide which is identical and has the same action as the natural occurring gonadotrophin-releasing hormone. Initially it produces increases in the plasma concentrations of both LH and FSH and is used in the diagnosis of hypothalamic-pituitary-gonadal dysfunction and in the treatment of hypogonadism and infertility. Synthetic analogues are leuprolide, histrelin, goserelin, triptorelin, nafarelin and buserelin. The latter are much more potent than gonadorelin. Prolonged use of these analogues also produces pituitary desensitization and hypogonadotrophic hypogonadism with as a consequence, a pseudocastrate state with decreased levels of gonadal hormones. Indications include prostatic carcinoma and in gynecology leiomyoma uteri, menorrhagia, endometriosis. They are also used as part of ovulation induction programs. The side-effects are those of hypo-oestrogenism and menopausal symptoms. Allergic reactions and anaphylaxis may occur.

In contrast to the above mentioned agonists, the therapeutic effect of GnRH antagonists is immediately apparent. However, there action is short-lived and daily injections are necessary to maintain their effect. Therefore they are not used in the long-term therapy of patients with cancer. Agents are cetrorelix and ganirelix. The main application of GnRH antagonists is currently short term use in the prevention of endogenous ovulation in patients who undergo exogenous stimulation with FSH in the preparation for IVF.

I.a.2. Somatotropin Inhibitors

Somatostatin or growth hormone inhibiting hormone, is a synthetic peptide hormone which is identical to the natural occurring hormone that is found in the hypothalamus but also in the gastrointestinal tract and the pancreas. Somatostatin binds to four structurally related membrane glycoproteins which are high affinity receptors for the hormone. It inhibits the release of growth hormone from the pituitary. In also inhibits the release of insulin, glucagon and gastrin. The precursor of somatostatin, prosomatostatin, has a much higher potency for inhibiting insulin release than somatostatin. Somatostatin has a very short half-life of only a few minutes. Octreotide is the longer-acting octapeptide analogue of somatostatin. Indications include acromegaly, endocrine tumors of the gastrointestinal tract and as adjunct treatment with pancreas surgery. Lanreotride is

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a long-acting analogue of somatostatin. These hormones are used for the management of upper gastrointestinal hemorrhage. Octreotide and lanreotride have been approved for the treatment of acromegaly.

Adverse effect of octreotide include nausea, vomiting, abdominal cramps and steatorrhea.

I.a.3. Growth Hormone-Releasing Hormone

Growth hormone-releasing hormone (GHRH), or sermorelin, is the hypothalamic hormone which stimulates growth hormone production in the anterior pituitary lobe. Different peptides have been isolated with such activity and it appeared that the first 29 amino acids were indispensable for their effects. GHRH analogues are used for diagnostic purposes. They can be administered intravenously, subcutaneously as well as intranasally. A therapeutic application is the substitution for somatotropin, i.e. growth hormone, in those patients with growth hormone deficiency that can still respond to GHRH. Its very short half-life then necessitates multiple daily doses. The advantage would be that feedback on the pituitary is preserved and that eventually normal pituitary function could be restored.

I.b. Anterior Pituitary Lobe Hormones

I.b.1. Thyroid-Stimulating Hormone

Thyroid-stimulating hormone (TSH), or thyrotropin, stimulates thyroid cell adenyl cyclase activity thus increasing c-AMP production with consequent increased iodine uptake and increased production of thyroid hormones. Thyrotropin which consists of two peptides, TSH-alpha and TSH-beta, is prepared from bovine pituitaries. TSH is mainly used as a diagnostic agent. Together with ^{131}I it is used in the management of thyroid carcinoma as it enhances radioiodine uptake. TSH is administered intramuscularly or subcutaneously. It undergoes degradation in the kidneys with an elimination half-life of about 1 hour.

Apart from possible symptoms of hyperthyroidism adverse effects include nausea and allergic reactions.

I.b.2. Gonadotropins

Follicle-stimulating hormone (FSH) and luteinizing hormone (LH) are the two gonadotropins made in the anterior pituitary lobe. FSH stimulates gametogenesis and follicular development in women and it stimulates spermatogenesis in men. FSH promotes androgen conversion into estrogens by the granulosa cells and stimulates the production of an androgen-binding protein in the Sertoli cells. LH stimulates androgen production and enhances maturing of the corpus luteum.

The menotropins, human menopausal gonadotropin (HMG) and urofollitropin are prepared from the urine of postmenopausal women. HMG has approximately equal amounts of FSH an LH. Urofollitropin has only FSH activity. Follitropin alpha and follitropin beta are two FSH products which are made with recombinant DNA technology. Lutropin alpha is recombinant human LH. Human chorionic gonadotropin (HCG) is produced in the placenta and excreted in the urine. It has mainly LH activity. Choriogonadotropin alpha is the world's first recombinant chorionic gonadotropin (r-hCG) for the treatment of anovulation, the most common cause of infertility in women.

The indications for the use of gonadotropins are for boys and men respectively undescended testes and secondary hypogonadism. For women gonadotropins are used for ovulation induction.

Adverse effects include headache, oedema, gynecomastia and depression.

I.b.3. Adrenocorticotropin

Adrenocorticotropin (ACTH) stimulates the adrenal cortex and the production of glucocorticoids, mineralocorticoids and adrenal androgens. Release of ACTH itself is regulated by the hypothalamic hormone corticotropin-releasing hormone, a potent mediator of endocrine, autonomic, behavioral and immune responses to stress. Cosyntropin and tetracosactide are synthetic analogues of the naturally-occurring ACTH. Corticotropins are mainly used for diagnostic purposes in adrenocortical insufficiency. They have almost no role in therapeutics as for adrenocortical insufficiency glucocorticoids are the drugs of choice.

I.b.4. Somatropin and Analogues

The anabolic effects of somatropin are mediated by somatomedins or insulin-like growth factors. Somatropin is a synthetic polypeptide identical to the natural occurring growth hormone which stimulates longitudinal growth. Only preparations made with recombinant DNA technology are used nowadays. They can consist of 191 amino acids as growth hormone itself or 192 amino acids with one extra methionine. Somatropin is employed in the treatment

of short stature, but only in the presence of open epiphyses, to stimulate normal growth development. A 12-week course of recombinant human growth hormone (rhGH) improved the abnormal fat distribution that can develop in HIV patients taking antiretroviral medication.

Fluid retention is a frequently occurring adverse reaction. Hypersensitivity reactions and lipodystrophy at injection sites can occur.

Mecasermin was recently approved to replace natural insulin-like growth factor-1 (IGF-1) in pediatric patients who are deficient, promoting normalized statural growth. It contains recombinant-DNA-engineered human insulin-like growth factor-1 (rhIGF-1). Hypoglycemia, mostly mild and thought to be related to the drug's insulin-like activities, occurred in a significant portion of patients (42%) during their course of therapy.

Pegvisomant is a growth hormone receptor antagonist registered for the treatment of patients with acromegaly who had insufficient benefit from surgery or radiation.

I.c. Posterior Pituitary Lobe Hormones

I.c.1. Vasopressin and Analogues

Vasopressin (synonym antidiuretic hormone, ADH) is released by among others a decrease of blood pressure. Deficiency of vasopressin results in diabetes insipidus. By stimulating V1 receptors on vascular smooth muscle cells it produces vasoconstriction. Activation by vasopressin of V2 receptors on renal tubule cells causes antidiuresis through increased water permeability and water resorption. Extra renal V2-like receptors are associated with the release of coagulation factor VIII. Desmopressin and terlipressin, a derivative of lypressin, are synthetic analogues of vasopressin. Desmopressin differs from terlipressin and vasopressin in being longer-acting and in having only minimal vasoconstrictor effects. Vasopressin and analogues are used in the treatment of pituitary diabetes insipidus. Vasopressin has documented efficacy in the short-term management of bleeding oesophageal varices and colonic diverticular bleeding.

Desmopressin is sometimes used in mild Hemophilia A and Von Willebrand's disease. In December 2007, US drug regulators banned using desmopressin nasal sprays for treating bedwetting after two children died from hyponatremia.

Ornipressin has almost no antidiuretic activity but it is a potent vasoconstrictor and has been used to limit bleeding during surgery.

I.c.2. Oxytocin

Oxytocin is a nonapeptide which in physiologic doses gives contraction of myoepithelial cells surrounding mammary alveoli causing milk ejection in lactating women. In pharmacological doses it induces uterine contractions and maintains labor. The sensitivity of the uterus increases during pregnancy. The myometrial contractions can be inhibited by beta-adrenoceptor agonists and magnesium sulphate (see Chapter 20).

Oxytocin is used for the induction of labor, or augmentation of labor in selected patients with uterine dysfunction, and to prevent or control bleeding after birth or abortion. Demoxytocin, a synthetic oxytocin has similar activities as oxytocin.

It should be said here that for the induction of myometrial contractions also use is made of prostaglandin E2 and prostaglandin F2alpha analogues like dinoprostone, sulproston and carboprost. Dinoprostone is the naturally occurring prostaglandin E2, sulproston is a synthetic prostaglandin E2 derivative and carboprost is a synthetic analogue of naturally occurring prostaglandin F2alpha.

II. CORTICOSTEROIDS FOR SYSTEMIC USE

Among the corticosteroids mineralocorticosteroids and glucocorticosteroids should be distinguished on the basis of their pharmacological activities. Some examples of corticosteroids for systemic use are given in Table 1. Mineralocorticoids have effects mainly on electrolyte and water homeostasis, while glucocorticoids are associated with anti-inflammatory, immunosuppressant and metabolic activity in connection with protein and lipid synthesis, calcium metabolism, gluconeogenesis and glycogen storage.

II.a. Mineralocorticosteroids

The naturally occurring mineralocorticosteroid is aldosterone. Its release is not ACTH dependent but is stimulated under control of the renin–angiotensin system. Aldosteron is not in clinical use because of its short halflife (20 min). Fludrocortisone is a synthetic analogue with considerably more potent mineralocorticoid than glucocorticoid activity. It is used as substitution therapy in adrenocorticoid insufficiency and in low-renin hypoaldosteronism. It is well absorbed orally and its effects last 1–2 days.

Table 1. Comparative corticosteroid characteristics

Corticosteroid	Relative sodium-retaining potency*	Relative anti-inflammatory potency*	Approximately equivalent IV or oral doses (mg)	Approximate plasma half-life (hours)	Biological half-life (hours)
Short-acting					
Hydrocortisone	1	1	20	1–2	8–12
Cortisone	0.8	0.8	25	0.5–1.5	8–12
Intermediate-acting					
Prednisolone	0.8	4	5	2.1–3.5	18–36
Prednisone	0.8	4	5	3.4–3.8	18–36
Methylprednisolone	0.5	5	4	3.5	18–36
Triamcinolone	0	5	4	2–5	18–36
Fludrocortisone	125	10		3.5	18–36
Long-acting					
Dexamethasone	0	25	0.75	3–4.5	36–54
Betamethasone	0	25	0.75	3–5	36–54

*Relative comparison, setting the mineralcorticoid and glucocorticoid properties of hydrocortisone as 1.

Plasma potassium should be monitored carefully. The retention of sodium together with water will consequently be followed by weight gain and oedema.

II.b. Glucocorticosteroids

Glucocorticosteroids diffuse or are transported through cell membranes and bind to the cytoplasmic glucocorticosteroid receptor complex and is then transported into the nucleus. An interaction takes place with glucocorticosteroid response elements on various genes. The expression of various regulatory proteins is then activated or inhibited. Thus incorporation of aminoacids in proteins can be inhibited and enzyme systems active in glucose metabolism are stimulated. However also non-genomic effects of glucocorticosteroids can result from their action on cellular and subcellular membranes with a prompt onset of stabilization or sometimes labilization. Other effects of glucocorticosteroids, apart from their effects on glucose metabolism, include increase in neutrophils due to an increased efflux from the bone marrow and a decreased migration from the blood vessels. Glucocorticosteroids administration causes an immediate reduction in circulating lymphocytes as a result of their movement from the vascular bed to lymphoid tissue. Part of their immunosuppressant effects is probably based on lymphocyte redistribution. Long-term use decreases the size and cellularity of the lymph nodes, spleen, and thymus. They suppress both humoral and cellular immunity although they are less effective against plasma cells. Corticosteroids are more effective against the primary immune response than they are against previously sensitized immune responses. They inhibit the ability of the leukocytes and tissue macrophages to respond to antigens and mitogens.

Glucocorticosteroids are the most potent anti-inflammatory agents available. They stabilize lysosomal membranes and reduce the concentration of proteolytic enzymes at the site of inflammation. They promote the synthesis of proteins called lipocortins which inhibit phospholipase-A2 and thus inhibit production of arachidonic acid, leukotrienes and prostaglandins. Furthermore, the expression of COX-II and through that the inflammatory effects of the licosanoids is inhibited. Glucocorticosteroids reduce the release of histamine from basophils, decrease capillary permeability and cause vasoconstriction. Glucocorticosteroids stimulate the loss of calcium with the urine and inhibit the resorption of calcium from the gut.

Unwanted effects of supraphysiologic amounts of glucocorticosteroids include muscle weakness and decreased muscle mass and reduction of growth in children. Patients who are on glucocorticosteroids are at risk for infections, especially pulmonary infections and systemic fungal infections. Monitoring of blood pressure, blood glucose and lipids is indicated in patients who receive long-term corticosteroid therapy.

Glucocorticosteroids are notorious for a multitude of adverse metabolic reactions. With pharmacological doses iatrogenic Cushing's syndrome with fat redistribution from the extremities to the trunk and face, increase in the growth of fine hair over the thighs and trunk and in some cases also the face, weight gain, thinning of the skin and striae, is almost inevitable. Hyperglycemia can occur especially in diabetics. Long-term use brings the risks of osteoporosis and aseptic necrosis of the hip. Ophthalmologic control is sometimes indicated for the occurrence of cataracts and increased intraocular pressure. Psychic effects vary from mild euphoria to alarming psychotic reactions.

Cortisol (synonym hydrocortisone) is the naturally occurring glucocorticosteroid. It is in equilibrium with the inactive metabolite cortisone. Under normal circumstances the daily production of hydrocortisone is about 20 mg. Release follows a circadian rhythm and is under control of corticotrophin-releasing hormone (CRH) made in the hypothalamus and the pituitary hormone ACTH, with a negative feedback by the circulating steroids. Circulating cortisol has a high affinity binding to corticosteroid-binding globulin (transcortin) and is for 75% bound to this protein. The remainder is free (5%) or is bound to plasma albumin. The binding to albumin has a large capacity for binding but a low affinity. The corticosteroid-binding globulin is increased in pregnancy and also in patients treated with estrogens. Hydrocortisone is metabolized to 17-hydroxycorticosteroids which are excreted in the urine. The half-life of cortisol is 60–90 min.

As a result of saturation of protein binding glucocorticosteroids may exhibit a dose-dependent kinetic behavior with increases of both distribution volume and half-life with increased doses.

Most glucocorticosteroid are metabolized in the liver to hydroxy- and ketosteroid metabolites which are excreted by the kidneys as glucuronides, sulfates and unconjugated products. Enzyme-inducing agents will diminish the efficacy of glucocorticosteroids.

Indications for glucocorticosteroids include adrenal insufficiency and inflammatory, non-infectious processes of all sorts such as various types of arthritis, auto-immune diseases, asthma, inflammatory bowel diseases, especially Crohn's disease but also ulcerative colitis and further many skin diseases and some diseases of the eye. Their antimitotic activity is used in various anti-cancer chemotherapeutic regimens. They still have an important place as immunosuppressants in various transplant programs.

Giving exogenous corticosteroids suppresses ACTH secretion which results in adrenal gland atrophy. Therefore glucocorticosteroid doses should be tapered off to allow the patient to adjust and prevent symptoms of adrenal insufficiency. For the short acting glucocorticosteroids an alternate day regimen should be considered to lower the risks for adrenal suppression.

A large variety of glucocorticosteroids have been marketed for the treatment of steroid-responsive diseases (see Table 1). They show differences from hydrocortisone with respect to their lipophilicity, and their glucocorticosteroid and mineralocorticosteroid potency and sometimes their duration of action.

Hydrocortisone is a relatively short-acting agent. For replacement therapy in adrenal insufficiency it is administered orally and in combination with fludrocortisone. Hydrocortisone sodium succinate is a water-soluble derivative which can be used parenterally in emergencies such as acute bronchospasm and hypersensitivity reactions like anaphylactic shock.

Prednisone, which in the body is converted to the active form prednisolone, is the most widely used corticosteroid. Maximal activity occurs mostly within 1–2 hours after oral administration, and the effects last up to 36 hours. For patients with colitis localized in the lower part of the colon prednisolone sodium phosphate is formulated for rectal administration as an enema.

The mineralocorticosteroid activity of methylprednisolone is even less than that of prednisone/prednisolone. It has a comparable duration of action. It is less suitable for substitution therapy in patients with adrenal hypofunctional states. Methylprednisolone sodium succinate is formulated for parental administration while methylprednisolone acetate is used for intra-articularly or peri-articularly injections. It can also be administered IM and then has prolonged systemic effects, lasting 1–4 weeks as the acetate is absorbed slowly from the site of injection. Oral absorption is rapid with peak effects within 1–2 hours. The duration of action is then about 1.5 days.

Dexamethasone has a high potency and has minimal mineralocorticoid activity. It is rapidly absorbed after oral administration with peak effects within 1–2 hours. The duration of action is about 3 days after oral administration and up to weeks after injections of the sodium phosphate derivative. This long

duration of action makes it unsuitable for alternate-day therapy. Parenteral administration is suitable for acute disorders including anaphylaxis and cerebral oedema. An other indication is the prevention of respiratory distress syndrome (RDS) in situations were there is a special risk for the fetus. It is then given prior to delivery. The sodium phosphate of dexamethasone can be used for parenteral administrations and for intra-articular injections and injections in soft tissue lesions.

Betamethasone is hardly ever used orally. It has a long duration of activity and can therefore also be used for alternate-day therapy. The parenteral formulation is also the sodium phosphate salt which when given IV or IM has a rapid onset of action. There are many similarities with dexamethasone such as their metabolic pathways and the indications for which both steroids are used, like the prevention of neonatal RDS and reduction of raised intracranial pressure. Combinations of betamethasone acetate and sodium phosphate have, when used for intra-articular and intra-lesional injections, the dual advantage of a rapid onset of action together with the long duration of action of a depot preparation.

Triamcinolone acetonide and hexacetonide are mainly used for intra-articular, intra-bursal and intra-synovial injection for rheumatological indications. Triamcinolone acetate has a prolonged systemic effect when given intramuscularly.

Budesonide is used for inflammatory bowel disease. It has a high first pass metabolism. It has efficacy in the terminal ileum and the right colon. Budesonide in comparison with prednisolone has been associated with fewer bone density losses and unlike other corticosteroids has little influence on the hypothalamic–pituitary–adrenal axis.

There are a number of corticosteroids that are used in pulmonology as inhalation medications. For rhinitis sprays may be used which also contain corticosteroids. Coricosteroids in these topical medications include beclometasone, fluticasone, mometasone and also budesonide.

III. THYROID HORMONES AND RELATED AGENTS

III.a. Thyroid Hormone

The thyroid gland produces thyroxine (T4) and triiodothyronine (T3) and this production is under control of the hypothalamus and the pituitary gland. TRH (thyrotropin releasing hormone) from the hypothalamus stimulates the secretion of TSH (thyroid stimulating hormone = thyrotropin) from the anterior pituitary lobe, while somatostatin is an inhibitor of this secretion. Thyroglobulin is synthesized in the thyroid follicular cells and secreted into the lumen of the follicles. Iodide is taken into the thyroid follicular cells by an active Na^+-cotransport. Peroxidase catalyzes the oxidation of iodide and its attachment to thyroglobulin resulting in the formation of mono-iodotyrosine and di-iodotyrosine. Mono-iodotyrosine and di-iodotyrosine then join to form tri-iodothyronine. Little tri-iodothyronine is released from the thyroid gland and thyroxine is also deiodinated in peripheral tissues to form tri-iodothyronine, the major active hormone, and inactive reverse T3. T3 is carried, in part, by thyroxine-binding globulin (TBG) in the blood. However, T4 binds more tightly to this transport protein than does T3. Thyroxine is formed by coupling two molecules of di-iodotyrosine. It has little biological effect in itself and is more of a 'pro-hormone'. Large quantities are released from the thyroid gland. It strongly binds to TBG in the blood and is slowly converted to T3 in the periphery. It has a longer half-life than T3. Thyroid hormones bind to receptor proteins on cell membranes. Inside the cell they bind to cytoplasmic binding proteins and to receptors on chromatin and on mitochondria. Large numbers of thyroid hormone receptors are found in pituitary, skeletal muscle, liver, lung, kidney, intestine and heart while few receptor sites exist in spleen and testes. The affinity of these receptors for T4 is ten times lower than for T3. Thyroid hormones increase transcription in target cells and exhibit negative feedback on TSH release from the pituitary. Available preparations may be synthetic or of animal origin.

Synthetic levothyroxine sodium is used most commonly and is the drug of choice. Oral doses are incompletely absorbed. In plasma levothyroxine is for more than 99% bound to proteins, mainly to TBG. Maximal effects are reached in 3–4 weeks and the activity persists for 1–3 weeks after withdrawal of chronic therapy. It has a half-life of 7 days which permits once-daily administration. Its adverse effects mainly consist of signs and symptoms of hyperthyroidism.

Tri-iodothyronine (synonym liothyronine) is rarely used orally for maintenance therapy. Its half-life is only 24 hours and multiple daily doses are required. Its high potency carries a greater risk for cardiotoxicity. It is mainly used for diagnostic purposes.

Parenterally it is indicated in the management of myxedema coma or when thyroxine cannot be given orally. Onset of action occurs within a few hours and its activity lasts for some days after withdrawal of therapy.

III.b. Antithyroid Preparations

As the symptoms of hyperthyroidism mimic in many aspects those of sympathic stimulation propranolol, and probably also other non-selective beta blockers (see Chapter 20), give rapid relieve in thyrotoxicosis while having no effect on the underlying disease.

The available agents with antithyroid activity are the thioamides propylthiouracil, carbimazole and methimazole also known as thiamazole. Their thiocarbamide group is indispensable for antithyroid activity. The mechanism of action is complex. The most important action is the prevention of hormone synthesis by an inhibition of the thyroid peroxidase-catalyzed reactions involved in iodine organification. These agents also block the coupling of the iodotyrosines.

Propylthiouracil also inhibits the peripheral deiodination of T4 and T3. The onset of clinical effects is slow as the synthesis of the thyroid hormones is more affected than their release and it can take several weeks before the stores of T4 are depleted.

Antithyroid agents are used for the management of hyperthyroidism. The different agents are equally effective and have the same toxic potential. Their commonest adverse effects are skin rashes, while the most serious reaction is the occurrence in about 0.5% of the patients of a potentially fatal agranulocytosis.

Propylthiouracil is rapidly but incompletely absorbed after oral administration. It is metabolized in the liver with an elimination half-life of 1–2 hours. Carbimazole is absorbed rapidly and converted to methimazole, the active metabolite. Methimazole is metabolized in the liver and excreted in urine, less than 10% as unmetabolized methimazole. The elimination half-life of methimazole varies from 5 to 15 hours. Clinical responses are seen in 10–20 days but 2–10 weeks are needed for maximal inhibition.

Methimazole is excreted in breast milk and can cause hypothyroidism and goiter in the newborn child.

III.c. Iodine

Iodine is used pre-operatively and in the management of thyrotoxic crisis. It temporarily inhibits proteolysis of thyroglobulin and prevents the release of thyroxine. Iodine also makes the thyroid gland shrink and makes it less vascular and therefore simplifies surgical procedures. Clinical effects become apparent within 24 hours. Various aqueous solutions exist for oral administration. Iodine is contraindicated in the last two trimesters of pregnancy as it can cause goiter and hypothyroidism in the newborn. Also breast-feeding is not advised. The most common adverse effects are gastrointestinal irritation and hypersensitivity reactions.

Radio-iodine, ^{131}I, diffusely kills thyroid cells resulting in eventual and inevitable hypothyroidism which often makes substitution with thyroxine necessary. Administered as capsules it is an effective oral treatment for hyperthyroidism. Patient should not be pregnant or become pregnant in the month following treatment. Breast-feeding is contraindicated. Painful radiation thyroiditis may occur.

IV. DRUGS USED IN DIABETES

IV.a. Insulins

Insulin is a protein with a molecular weight of 5808. It consists two chains, the A chain and the B chain, linked by disulfide bridges and it has in total 51 amino acids. In the synthesis of insulin proinsulin is hydrolyzed to insulin and C-peptide. Insulin secretion is stimulated by glucose, vagal stimulation and by some amino acids. Both a K^+ channel and Ca^{2+} channel on the pancreatic beta-cell are involved in the mechanism of insulin secretion. In the fasting state with low glucose levels ATP is depleted and the K^+ channels are open. The cell is in the resting, hyperpolarized state. Hyperglycemia increases intracellular ATP which closes the ATP dependent potassium channels. The cell depolarizes, Ca^{2+}-channels are opened and with the influx of Ca^{2+} insulin is secreted into the blood. Insulin is bound with high specificity and high affinity by insulin receptors which are found on the membranes of most tissues. These receptors consist of an alpha subunit which is the binding site and a beta subunit that spans the membrane and contains a tyrosine kinase. Binding to the alpha subunit stimulates tyrosine kinase activity and phosphorylation of proteins in the cell is the major effect. This is followed by up-regulation of various glucose transporters, of which GLUT 4 is the most important one, in the membranes of target cells. Binding of insulin causes aggregation of receptor-subunits and repeated binding can cause internalization and destruction of the receptor. Insulin promotes

glycogenesis and antagonizes glucogenic effects of glycogenolysis, ketogenesis and gluconeogenesis in the liver. In muscle it promotes protein synthesis and glycogenesis. Insulin promotes fat uptake and storage in adipocytes. It stimulates lipoprotein lipase and hydrolysis of triglycerides from circulating lipoproteins, it promotes glucose transport and glycolysis, generating glycerophosphate which permits esterification of fatty acids generated by lipoprotein hydrolysis and it inhibits intracellular lipase, preventing lipolysis in adipose tissue.

Insulin is removed from the circulation by the liver and the kidney. The disulfide connections between the A and B chains are hydrolyzed through the action of glutathione insulin trans-hydrogenase. After this cleavage further degradation occurs by proteolysis. In patients treated with subcutaneous insulin injections the clearance by the liver is 40% and by the kidney 60%. The half-life of circulating insulin is 3–5 min.

Human insulin is synthesized using recombinant DNA technology and is identical to the naturally occurring hormone. Also from porcine insulin human insulin can be produced by a semisynthetic procedure in which enzymatically one amino-acid is replaced. Although the highly purified porcine and bovine insulins that are now produced do not have significant disadvantages with respect to their antigenicity compared to human insulins in many countries insulins from animal origin are replaced altogether by human insulins.

Insulin lispro, insulin aspart, insulin detemir, insulin glargine and insuline glulisine are human insullin analogues with the same mechanism of action. It should be noted however that the potency of insulin detemir was decreased four fold compared to human insulin. By changing amino acids on some locations absorption rates and the duration of action may be changed compared to human insulin.

Insulins differ in their onset and their duration of action. A longer duration of action is realized by making formulations which, at physiologic pH, are more slowly absorbed from subcutaneous depots. This can be achieved by adding the protein protamine or zinc. Thus a differentiation can be made between short-acting, intermediate-acting and long-acting insulins (see Table 2).

However, it should be noted that these groups have considerable overlap and that the differences between these groups show large interindividual variabilities as the absorption rate and thus the duration of action does not only depend on formulation differences but also on the site of administration, tissue blood flow, pH and other variables. It is also important to realize that the number of products and brand names is enormous.

Short-acting and also fast-acting insulins are clear colourless solutions of neutral human insulin. They are mostly administered subcutaneously but can also be given intramuscularly or intravenously and by infusion pumps in diabetic ketoacidosis and during surgery. Examples are Actrapid, a soluble biosynthetic human insulin of monocomponent purity and Humulin Regular a biosynthetic human insulin of rDNA origin, i.e. made with recombinant DNA technology.

Intermediate- to long-acting insulins are turbid suspensions at neutral pH with either protamine in phosphate buffer in the NPH (neutral protamine Hagedorn or isophane) insulins or mixtures of amorphous and crystalline zinc insulin with varying concentrations of zinc in acetate buffer in the lente and ultralente insulins. As their long duration of action is solely based on their slow absorption these insulins should only be administered subcutaneously. They are usually combined with short-acting preparations. Examples are Humulin NPH, an isophane biosynthetic human insulin (rDNA origin) suspension and Insuman Basal, also an isophane biosynthetic human insulin. The human insulin in Insuman Basal is produced by recombinant DNA technology.

Biphasic insulins are fixed dose combinations of a short-acting and intermediate-acting insulin in various proportions. Examples are Humulin, a biosynthetic human insulin (rDNA origin) suspension with respectively 20%, 30% and 40% regular and 80%, 70% and 60% isophane insulin and Mixtard, a biphasic biosynthetic human insulin suspension with respectively 10%, 20% and 40% soluble and 90%, 80% and 60% isophane insulin.

Detemir needs some special attention here. Insulin detemir differs from human insulin in that one amino acid has been omitted from the end of the B chain, and a fatty acid has been attached. Detemir's action is extended because its altered form makes that it is slowly released from the subcutaneous depot. More than 98% of detemir in the bloodstream is bound to albumin. Because it slowly dissociates from the albumin, it is available to the body over an extended period.

Insulins are mostly administered subcutaneously using conventional disposable needles and syringes. To facilitate multiple subcutaneous injections

Table 2. Time-action profiles of various insulins

Brand name	Onset of action (h)	Duration of action (h)	Insulin type
Short acting insulins			
Actrapid	0.5–1 (s.c.)	7–8	Human insulin
Apidra	10–20 min	2–5	Insulin glulisine
Humaject Regular	0.5–1 (s.c.)	7–8	Human insulin
Humalog	0.25 (s.c.)	2–5	Insulin lispro
Humulin Regular	0.5–1 (s.c.)	7–8	Human insulin
Insuman Infusat	0.5–1 (s.c.)	7–8	Human insulin
Insuman Rapid	0.5–1 (s.c.)	7–8	Human insulin
Novorapid	0.25 (s.c.)	2–5	Insulin 'aspart'
Intermediate-acting insulins			
Humulin NPH	1–2 (s.c.)	14–24	Human insulin, isophane
Insulatard	1–2 (s.c.)	14–24	Human insulin, isophane
Insuman Basal	1–2 (s.c.)	14–24	Human insulin, isophane
Long-acting insulins			
Levemir		max 24 h	Insulin detemir
Lantus	1 (s.c.)	24	Insulin glargine
Mixtures of short- and long-acting insulins			
Humalog Mix	0.25 (s.c.)	12–24	Insulin lispro/insulin lispro protamine
Humulin	0.5–1 (s.c.)	12–24	Human insulin + isophane
Insuman Comb	0.5–1 (s.c.)	12–24	Human insulin + isophane
Mixtard	0.5–1 (s.c.)	12–24	Human insulin + isophane
Novomix	0.25 (s.c.)	up to 24 h	Insulin 'aspart'/insulin 'aspart' protamine

portable pen-sized injectors have been developed. Inhalable insulin**,** a powdered form of recombinant human insulin, became available in 2006 but the production was stopped in 2007 due to insufficient cost-effectiveness.

Apart from possible symptoms of hypoglycemia adverse effects include lipohypertrophy from repeated injections in the same subcutaneous area and localized allergic skin reactions as well as generalized allergic reactions.

The administration of non-selective beta-adrenergic antagonists may change insulin requirements. An other consequence of the use of beta-blockers is their ability to mask the early symptoms of hypoglycemia.

IV.b. Oral Hypoglycemic Agents

Oral antidiabetic agents might be indicated in non-insulin dependent diabetes mellitus (NIDDM), i.e. diabetes Type II where insulin resistance caused by down-regulation of insulin receptors or a failure of the pancreas to release insulin even though it is formed, play a role. However, oral antidiabetic agents alone are not always capable of normalizing blood glucose concentrations and should than be combined with or replaced by insulin. They should also not be used without proper dietary regulation.

IV.b.1. Alpha-Glucosidase Inhibitors

By competitively inhibiting the alpha-glucosidase enzymes in the mucosa cells of the small intestine these agents suppress the breakdown of di-, oligo- and polysaccharides into monosaccharides and thus decrease carbohydrate absorption. In this way postprandial elevations of blood glucose levels can be prevented or diminished.

Agents include acarbose, miglitol and voglibose. Only bacterial breakdown products of acarbose are absorbed which are then rapidly eliminated by the kidneys. Adverse events mainly consist of gastrointestinal complaints which in rare cases can be confused with ileus. Some hepatotoxicity has been reported.

Miglitol is for 60–90% absorbed. It is eliminated by renal excretion with an elimination half-life of 2–3 hours. Some mild gastrointestinal discomfort may occur.

Voglibose is considered to be an improvement over the other two alpha-glucosidase inhibitors both in terms of potenty and side effect profile.

IV.b.2. Biguanides

The activity of the biguanides is based, at least in part, on the promotion of cellular uptake of glucose and glucose utilization in tissues. Metformin also inhibits gluconeogenesis in the liver.

Other mechanisms that have been proposed are a decreased glucose absorption in the gastrointestinal tract, a decrease of plasma glucagon levels and an increased binding of insulin to its receptors. The blood glucose lowering action does not, or only to a minor degree, depend on the presence of functioning pancreatic beta cells. During biguanide therapy hypoglycemia is essentially unknown. Therefore the biguanides are considered to be more euglycemia than hypoglycemic agents.

Biguanides can be agents of first choice only in Type II diabetic patients with serious overweight as in these patients insulin resistance has a high prevalence.

Agents include phenformin, buformin and metformin. Phenformin is no longer recommended because of considerable risks for potentially lethal lactic acidosis. And buformin was withdrawn from the market in most countries also due to a high risk of causing lactic acidosis. However also with metformin there is some risk of lactic acidosis. Biguanides should therefore only be used with caution and as second choice agents. Impaired renal or hepatic function and also the presence of infections and excessive alcohol intake increase their risks. Metformin is for about 50% absorbed after oral administration and is mainly eliminated in the urine as unchanged drug with an elimination half-life of 1.5–3 hours. The most frequent adverse effects of metformin are gastrointestinal and taste disturbances. Metformin is contraindicated in patients with heart failure.

IV.b.3. Sulfonylureas

The sulfonylureas promote insulin secretion. They block the K^+ channels of the pancreatic beta cell membrane causing the beta cell to remain depolarized which promotes insulin secretion. They also antagonize the effects of glucagon and potentiate the action of insulin in target tissues. However, some pancreatic beta cell responsiveness must exist for these agents to be effective and they cannot be of use in insulin dependent diabetes.

In patients with Type II diabetes the sulfonylureas can provide good control of blood glucose. but it remains controversial to what extend they are of benefit for the long-term prognosis and if they protect against tissue damage, e.g. microvasculopathy. Sometimes the combination of a sulfonylureas with a biguanide is indicated for adequate control.

Agents include chlorpropamide, tolbutamide, tolazamide, acetohexamide and the second generation sulfonylureas glibenclamide, gliclazide, glyburide, glimepiride, glipizide and others. Most sulfonylureas are mainly eliminated by hepatic metabolism and interactions with enzyme inducers such as phenytoin, carbamazepine and rifampicin or enzyme inhibiting agents like cimetidine, fluconazole, ketoconazole, or miconazole can occur. Some of the metabolic products of the sulfonylureas have hypoglycemic activity. Several sulfonylureas have a protein binding of over 90% and displacement interactions then should be anticipated.

Chlorpropamide with its half-life of over 30 hours is long acting and has been associated with serious and prolonged hypoglycemia. It has been largely displaced by tolbutamide.

Tolbutamide is a short-acting agent. It is rapidly metabolized in the liver with an elimination half-life of 6–10 hours. Protein binding is more than 90%. It has the advantages of causing less frequently and less serious hypoglycemia than the more potent sulphonylureas.

Tolazamide is slowly absorbed and its hypoglycemic action only becomes manifest after several hours. Its is metabolized in the liver with an elimination half-life of about 7 hours. However several of its metabolites retain hypoglycemic activity. Its duration of action is shorter than that of chlorpropamide.

Acetohexamide has a duration of action of 10–16 hours. It is metabolized in the liver to an active metabolite. Acetohexamide is not used often anymore and it is considered only to be indicated in a minority of patients with maturity-onset diabetes.

Glibenclamide has an intermediate duration of action. It is well absorbed with peak levels $\pm$ 4 hours after oral dosing. Its protein binding is about 90%. Glibenclamide is metabolized in the liver with an elimination half-life of $\pm$10 hours. However some of the metabolites which are excreted in the urine have hypoglycemic activity which makes glibenclamide

contraindicated in severe renal impairment. It can be given once daily as its duration of action is about 24 hours.

Glyburide has high potency and its duration of action extends at least over 24 hours. It is metabolized in the liver. It can cause serious hypoglycemia. As is the case with chlorpropamide, a minority of patients can react with flushes after ethanol intake when on glyburide medication.

Gliclazide is slowly absorbed. It is metabolized and excreted in the urine, in part as unchanged drug with an elimination half-life of 6–14 hours. Its duration of action is about 12 hours. Glicazide reduces platelet adhesiveness and increases fibrinolytic activity. This could be of importance as both factors have been implicated in the pathogenesis of the long-term organ failure in diabetes.

Glimepiride is more rapidly absorbed than glicazide with peak plasma concentrations after 2–3 hours. It has very high protein binding of over 99%. Glimepiride is metabolized in the liver with and elimination half-life of 3–6 hours. Its active hydroxy metabolite has an elimination half-life of 5–8 hours and is responsible for part of the hypoglycemic activity of glimepiride.

Glipizide has its maximal effect after 1 hour but its duration of action can extend over 24 hours. It is metabolized in the liver to inactive metabolites.

IV.b.4. Thiazolidinediones

Thiazolidinediones act by binding to peroxisome proliferator-activated receptors inside the cell nucleus. When activated, the receptor migrates to the DNA, activating transcription of a number of specific genes resulting in among others, a decrease of insulin resistance, modified adipocyte differentiation, a decrease of leptin levels leading to an increased appetite and a fall of the levels of certain interleukins (e.g. IL-6). The only approved use of the thiazolidinediones is in combination therapy for diabetes mellitus type 2 where a sulfonylurea derivative or metformin alone were not effective enough.

The members of this class are derivatives of the parent compound thiazolidinedione, and include: rosiglitazone, pioglitazone and troglitazone which was withdrawn from the market due to an increased incidence of drug-induced hepatitis.

Thiazolidinediones cause fluid retention and are thus contraindicated for patients with heart failure.

IV.b.5. Other oral hypoglycemic agents

Repaglinide en nateglinide are not sulfonylurea agents but their mechanism of action is very alike. Repaglinide is the first carbamoylmethyl-benzoic acid derivative that has been registred for the treatment of diabetes mellitus. It closes ATP-dependent potassium channels in the beta cell membrane with consequent depolarization, opening of calcium channels and increased insulin release. It is rapidly absorbed with peak plasma levels after 1 hour. It has a protein binding of over 98%.

Repaglinide is metabolized in the liver with an elimination half-life of 1 hour. Also its adverse reaction profile is very similar to that of the sulfonylureas, i.e. apart from hypoglycemia, gastrointestinal complaints and skin reactions.

Sitagliptin is a selective dipeptidylpeptidase 4 (DPP-4) inhibitor which increases the active form of GLP-1 (glucagon-like-peptide-1) and GIP (glucose-dependent insulinotropic peptide). This enzyme-inhibiting drug is to be used either alone or in combination with metformin or a thiazolidinedione for control of type 2 diabetes mellitus. Adverse effects were as common with sitagliptin (whether used alone or with metformin or pioglitazone) as they were with placebo, except for nausea and common cold-like symptoms.

IV.c. Glucagon

Glucagon is a polypeptide consisting of a single chain of 29 amino acids. It is synthesized by the alpha cells of the pancreatic islets of Langerhans. One of its precursor peptides is glicentin, a 69 amino acid polypeptide which, together with other glucagon-like peptides is also secreted by intestinal cells. Glucagon binds to specific receptors on hepatic cells, increasing adenyl cyclase activity and the production of cAMP. This stimulates glycogenolysis and gluconeogenesis and raises plasma glucose. Glucagon has, apart from these metabolic effects but also mediated by an increase of cAMP, potent positive inotropic and chronotropic cardiac effects very similar to those of beta-adrenergic agonist but bypassing the beta-adrenoceptors.

Its major indication is the treatment of hypoglycemia in diabetics when oral glucose administration is not possible. It should be noted however that it is only effective for that indication if sufficient glycogen stores are present. Glucagon is also used for the diagnosis of endocrine tumors and to

establish beta cell function. It can be effective in producing positive cardiac inotropism in beta blockade overdose.

Glucagon is rapidly absorbed from subcutaneous and intramuscular injection sites. It is extensively degraded in the liver and kidneys and also in plasma and at its receptor sites. Its plasma half-life is a few minutes.

Adverse effects are generally mild; some nausea may occur. Its positive inotropic action can result in myocardial ischaemia in patients with coronary artery disease.

V. CALCIUM HOMEOSTASIS

Calcium metabolism is primarily regulated by parathyroid hormone (PTH), vitamin D and calcitonin. However glucocorticosteroids also alter calcium homeostasis by stimulating renal calcium excretion, by antagonizing vitamin D stimulated intestinal calcium transport, by inhibiting bone collagen synthesis and by potentiating PTH stimulated bone resorption. Estrogens prevent accelerated bone loss during the postmenopausal period by antagonizing the bone resorbing action of PTH.

Parathyroid hormone is a single-chain polypeptide of 84 amino acids which is produced in the parathyroid glands. It increases serum calcium and decreases serum phosphate. In bone it promotes resorption of calcium. It indirectly increases osteoclastic activity by promoting the action of osteoblasts. It has been shown that in low doses PTH may even increase bone formation without stimulating bone resorption. In the kidney PTH increases resorption of calcium and it increases excretion of phosphate. An other important activity in the kidney is the enhanced synthesis of 1,25-dihydroxyvitamin D. An increased serum calcium level inhibits PTH secretion and increased serum phosphate decreases free serum calcium and thus stimulates PTH secretion.

Teriparatide is a recombinant form of parathyroid hormone, used in the treatment of advanced osteoporosis.

V.a. Vitamin D

Vitamin D is a secosteroid present in the diet but is mainly produced non-enzymatically in the skin from cholesterol under the influence of ultraviolet light. Vitamin D synthesis is promoted by PTH. This is vitamin D_3 or cholecalciferol. Vitamin D_2, ergocalciferol is found in vegetables. Both forms of vitamin D have the same activity. Vitamin D is a precursor of a number of active molecules. In the liver it is hydroxylated to 25-hydroxyvitamin D which is further converted in the kidney to 1,25-dihydroxyvitamin D and 24,25-dihydroxyvitamin D. Vitamin D_2, vitamin D_3, 25-hydroxyvitamin D as calcifediol and 1,25-dihydroxyvitamin D as calcitriol are all available for clinical use. Vitamin D increases calcium and phosphate absorption in the intestinal tract. In bone 1,25-dihydroxyvitamin D increases resorption of calcium thus raising plasma calcium. There are indications that 24,25-dihydroxyvitamin D may increase deposition of calcium in bones by increasing osteoblastic activity. In the kidney vitamin D increases reabsorption of calcium and phosphate.

The pharmacotherapeutic uses of vitamin D include vitamin D deficiencies, rickets in children and osteomalacia in adults, and renal osteodystrophy in patients with chronic renal failure. For metabolic rickets in patients with a deficiency of 1,25-dihydroxyvitamin D synthesis in the kidney calcitriol or dihydrotachysterol, an analogue of calcitriol, should be chosen. Under most circumstances hypoparathyroidism can be managed with vitamin D_3 and dietary calcium supplements.

Paricalcitol is a synthetically manufactured analogue of calcitriol. It is indicated for the prevention and treatment of secondary hyperparathyroidism in chronic kidney disease. Cinacalcet, a drug that acts as a calcimimetic, can be added if the effects on PTH levels are isufficient.

Calcipotriol, a vitamin D derivative without vitamin D activity is used to treat psoriasis.

Vitamin D and its metabolites are bound in plasma to a carrier protein. These molecules are cleared by the liver, 25-hydroxyvitamin D and 24,25-dihydroxyvitamin D with an elimination half-life of several weeks and 1,25-dihydroxyvitamin D with an elimination half-life measured in hours.

Excess vitamin D can result in hypervitaminosis D with serious vitamin D toxicity characterized by hypercalcemia and nephrocalcinosis.

V.b. Calcitonin

Calcitonin is a single chain polypeptide of 32 amino-acids. It is secreted by the parafollicular cells of the thyroid gland. However in the circulation various forms of calcitonin are present, probably including several precursors. Calcitonin inhibits osteoclastic resorption of bone and it increases calcium and

phosphate excretion in the urine. Its indications are Paget's disease, hypercalcemia and osteoporosis.

Three forms of calcitonin are available, salmon, porcine and human calcitonin. Long-term use of porcine calcitonin, being the most antigenic product, can lead to the production of neutralizing antibodies. Synthetic salmon preparations are therefore preferable. Human calcitonin is less immunogenic but it is also less active. Human calcitonin monomer has a half-life of about 10 minutes while the half-life of salmon calcitonin is considerably longer. However these half-lives are not directly related to the duration of action which varies from 30 min to 12 hours after intravenous administration and from 8 hours to 24 hours when administered subcutaneously or intramuscularly. Calcitonin is metabolized in the blood and in tissues like for example the kidneys.

Adverse effects that are encountered frequently include transient nausea, flushing and allergic skin reactions.

V.c. Bisphosphonates

The bisphosphonates are all analogues of pyrophosphate. They inhibit osteoclast resorption of bone and they are able to inhibit the formation and dissolution of hydroxyapatite crystals. however their exact mechanism is not well understood. Other effects which have relevance for bone homeostasis include inhibition of the activities of PTH, prostaglandins and 1,25-dihydroxyvitamin D. Bisphosphonates bind to bone with high affinity. They have therefore a duration of action that continues long after their use has been stopped.

Agents include etidronic acid, pamidronic acid, clodronic acid, alendronic acid, ibandronic acid, risedronic acid, zoledronic acid and tiludronic acid. Formulations of clodronic acid and pamidronic acid are available for intravenous administration. The indications for the use of bisphosphonates include treatment of postmenopausal osteoporosis, hypercalcaemia of malignancy and Paget's disease.

Oral formulations are very poorly absorbed with bioavailability ranging from less than 1–6%. Doses should be taken on an empty stomach to improve absorption. Increasing the dose will lead to gastrointestinal complaints. Of the absorbed dose 20–50% is adsorbed to bone and only very slowly released. Free bisphosphonates are eliminated in the urine with an apparent half-live of about 20 hours. However, the elimination half-life of risedronic acid is more than 400 hours and it can be given with an interval of only once per three months.

Adverse effects include gastrointestinal disturbances after oral use, flu-like symptoms and skin reactions, mild hypocalcaemia and after intravenous administration transient proteinuria and rarely deterioration of renal function.

VI. GONADAL HORMONES AND INHIBITORS

The so-called sex hormones are primarily produced in the gonads; estrogens, progesterone and small amounts of testosterone in the ovaries and in the testis mainly testosterone but also small amounts of estrogen. In both sexes small amounts of androgens are also produced in the adrenal gland. The female sex hormones are normally secreted by the ovaries from puberty until menopause. During pregnancy when pituitary and ovarian activity are suppressed a large amount of estrogen is produced by the placenta. The pathways of synthesis of testosterone, estrone and estradiol in the gonads are similar to those in the adrenal cortex. Cholesterol is converted to pregnenolone which, via the precursor 17alpha-hydroxypregnenolone forms the quantitatively major androgen dehydroepiandrosterone (DHEA). Pregnenolone is also the direct precursor of progesterone. DHEA, which has very weak androgen activity, is converted via androstenedione to testosterone and estrone. The most important estrogen is estradiol. Testosterone is actually the precursor of estradiol which is also further oxidized in the liver, the circulation and in target cells to the weaker estrogen estrone. Metabolic products of estrone are estrogen and estriol. In the post-menopause estrone, derived via androstenedione, is the predominant estrogen.

The gonadal hormones regulate the biochemistry of reproduction. They have a feed-back coupling to FSH and LH secretion by the anterior lobe of the pituitary gland (see Section Ia.1). Their indications are mainly in endocrinology. However gonadal hormone analogues are also used in oncology (see Chapters 27 and 40).

In some countries dietary supplements containing dehydroepiandrosterone (DHEA) or dehydroepiandrosterone sulfate (DHEAS) have been advertised with claims that they may be beneficial for a wide variety of ailments. However, there is a lack of any proven benefit from DHEA supplementation.

VI.a. Androgens and Anabolic Steroids

Testosterone is the major androgen produced by the Leydig cells of the testis, amounting to about 8 mg/day (range 2.5–10 mg) in adult males. It is metabolized primarily in the liver and excreted in urine as 17-ketosteroids. In the circulation testosterone is for about 60% bound to a alpha$_2$-globulin, sex hormone-binding globulin. Most of the remaining testosterone is bound to albumin. It is converted to the more potent 5-alpha-dihydrotestosterone by the enzyme 5-alpha-reductase in a variety of tissues including skin, prostate, seminal vesicles, epididymis and kidney. The androgens act intracellularly in target cells where testosterone and dihydrotestosterone bind to the cytosol androgen receptor and subsequently induce the synthesis of functional proteins. Androgens promote growth and they are needed for the development of the male sex organs and the development and maintenance of secondary male characteristics. In the male large doses of androgens induce suppression of the secretion of gonadotropin with consequent atrophy of the interstitial tissue and tubulus of the testes.

Pharmacologic doses in women stimulate growth of facial and body hair and produce deepening of the voice, enlargement of clitoris, frontal baldness and prominent musculature. Natural androgens stimulate erythrocyte production.

In men testosterone administration is indicated for primary hypogonadism, e.g. in Klinefelter syndrome or after orchidectomy, and for hypopituitarism.

To stimulate spermatogenesis both testosterone and gonadotropic hormones need to be administered.

Testosterone and its derivatives can be administered in several ways. Fluoxymesterone and methyltestosterone are 17-alpha-alkylated derivatives which are active when administered orally.

Mesterolone is a non-17-alkylated derivative which is also has weak activity orally. Testosterone itself has little activity when taken orally and is used sublingually or as an implant. By esterification of testosterone formulations of long-acting testosterone derivatives in oily solutions for intramuscular injection were developed.

Adverse effects include changes in libido and the occurrence of oedema, weight gain and gynecomastia, may occur. Androgens are potentially hepatotoxic, testosterone less than methyltestosterone and fluoxymesterone. Androgens can potentiate anticoagulant action.

The growth promoting or anabolic effects, expressed as among others trophic effects on muscle and a reduction of nitrogen excretion, are in some androgen analogues to variable degree dissociated from the other androgenic effects on male sex organs and on the maintenance of secondary male characteristics. Examples are oxymetholone, oxandrolone, nandrolone and stanozol. These anabolic steroids which are derivatives of testosterone, can be of some value in the management of bone marrow aplasia in carefully selected patients. Indications are the management of chronic aplastic anemias and the anemia in renal failure if recombinant erythropoietin is not available. They have also been used for osteoporosis in postmenopausal women and in metastatic breast cancer although for these conditions respectively bisphosphonates and anti-hormones are to be preferred. Stanozol has favorable effects in hereditary angioedema.

The anabolic steroids can cause serious adverse reactions including tumorigenesis, testicular atrophy with decreased spermatogenesis and in women virilization. Anabolic steroid abuse in sports where excessive doses are used, is associated with among others hepatotoxicity.

VI.b. Estrogens

The most important natural occurring estrogen is estradiol. It is produced in the granulosa cells of the ripening follicle. Estradiol is in the circulation for about 40% bound to sex hormone-binding globulin. It is also bound to albumin. After passage through the membrane of target cells it binds to the cytosol estrogen receptor and initiates the production of specific enzymes and regulating proteins. Estrogens stimulate the development of female primary and secondary sex characteristics. Estrogens cause proliferation of the endometrium and contribute to the regulation of the menstrual cycle. They stimulate the synthesis in the liver of proteins like transcortin, thyroxine binding globulin and also sex hormone-binding globulin. Also the formation of plasma renin substrate is enhanced. Furthermore they have favorable effects on bone and lipid metabolism by increasing bone mineralization and decreasing LDL-cholesterol with at the same time an increase of HDL-cholesterol. They augment the coagulability of blood by increasing circulating levels of coagulation factors and decreasing antithrombin III. Estrogen analogues are used, both alone and in combination with progestogen and its derivatives, to

suppress ovulation as in oral contraceptives, as replacement therapy in primary hypogonadism and after e.g. ovariectomy, to correct menstrual disturbances and infertility, for the management of perimenopauzal complaints and to treat menopausal symptoms and prevent the long-term consequences of the menopause such as osteoporosis. They are also used for hormonal therapy in oncology. Several regimens of oral estrogen administration, so-called "morning after" pills, are known for effective contraception following unprotected intercourse.

Estrogens can be divided into three groups: the natural occurring estrogens estradiol, estriol and estrone, the equine estrogens equilenin, quilin and their congeners and the synthetic steroidal estrogens like ethinylestradiol, mestranol or quinestrol and nonsteroidal estrogens such as diethylstilbestrol (DES) which was banned in the late seventies due to first and second generation risks of health problems, especially various forms of cancer. Tibolon is a synthetic steroid with progestogen, weak estrogen and some androgen activity. It is indicated for menopausal symptoms when combinations of an estrogen and a cyclic administered progestogen are not well tolerated.

Estrogens are given, alone or in combination with progestogens, to postmenopausal women in order to prevent osteoporosis as well as treat the symptoms of menopause. Estrogen is also used in the therapy of vaginal atrophy, hypoestrogenism (as a result of hypogonadism, castration, or primary ovarian failure), amenorrhea, dysmenorrhea and oligomenorrhea. Estrogens can also be used to suppress lactation after child birth. Estrogens may also be used in males for treatment of prostate cancer.

Estrogens are administered orally, parenterally by injection or as subcutaneous implants, transdermally and topically. After oral administration a considerable first pass effect, both in the intestinal mucosa and in the liver, takes place with large interindividual variability. Estrogens are hydroxylated and conjugated in the liver and excreted mainly in the bile. The conjugates can be hydrolyzed in the intestine to active compounds that are reabsorbed again. Their hepatic oxidative metabolism is increased by enzyme inducers and the enterohepatic circulation may be decreased by some antibiotics which disturb the intestinal bacterial flora.

The main contraindications to oestrogen treatment are estrogen dependent tumors and previous deep vein thrombosis or embolus.

Adverse effects include nausea and vomiting, painful swelling of the breasts, fluid retention and hypertension. Liver function disturbances may occur. Estrogens can cause endometrial hyperplasia which is considered to be a premalignant abnormality. This can be prevented by the addition of progestogens. Estrogens increase cholesterol excretion in the bile and predispose for gallstones. In many countries the labeling of all estrogen and estrogen with progestin products for use by postmenopausal women include a warning about cardiovascular and other risks. With estrogen-plus-progestin products there is an increased risk of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli and deep venous thrombosis in postmenopausal women 50 years of age or older. The use of tibolon by postmenopausal women is associated with a small increase of the risk on stroke.

VI.c. Progestogens

Progesterone, apart from being a hormone itself, is the precursor of androgens, estrogens and of corticosteroids. It is mainly produced in the corpus luteum and in pregnancy by the placenta. After entering the cell it binds to cytosol progesterone receptors where after the ligand–receptor complex binds to a response element on DNA to activate gene transcription. The progestogen activity of progesterone consists of bringing the endometrium in the secretory phase after priming with estrogens. It decreases the endometrial proliferation caused by estrogens. Its gestagenic effects are the maintenance of an existing pregnancy and it further acts systemically to produce the anatomical and physiological changes of pregnancy including growth of breast alveoli, relaxation of smooth muscle and metabolic changes. Other effects of progesterone outside pregnancy are a stimulation of lipoprotein lipase activity. It favors fat deposition and in the liver it promotes glycogen storage. It competes with aldosterone at the level of the renal tubule causing increase aldosterone secretion. Progesterone is the only natural occurring progestagen. All other progestogens are synthetic.

Progestogens inhibit GnRH secretion and suppress LH release. They have anti-oestrogenic effects by reducing the number of oestrogen receptors and increasing oestradiol dehydrogenase.

Progestogens have a high affinity for sex hormone-binding globulin. Natural progesterone is rapidly metabolized in liver and can therefore not be given orally. In oral contraceptives synthetic

progestogens are used. These also undergo extensive metabolism in the intestinal mucosa and on first pass through the liver. Their efficacy can be hampered by enzyme inducing agents. But unlike for example with ethinylestradiol enterohepatic circulation does not play a significant role and interactions with antibiotics are not to be expected. Synthetic progestogens all share the progestagenic effects but only some also display gestagenic activity. They may have androgenic and oestrogenic effects.

Progestogens may be divided into four main groups: the 19-nortestosterone and 18-homosteroid derivatives, including ethynodiol, lynestrenol, norethisterone, norethynodrel, gestodene, norgestrel, norgestimate and desogestrel, the 17-alpha acetoprogesterone derivatives including medrogestone and medroxyprogesterone, the halogenated progesterone derivatives like cyproterone and finally the retro-progesterones and hydroxyprogesterones such as dydrogesterone and hydroxyprogesterone acetate. It should be noted that Cyproterone actually is an antiandrogen. However it has weak progestational activity and can be used to treat flushes. As part of some combined oral contraceptive pills it decreases acne and hirsutism. Drospirenone is a newer synthetic progestogen that is an analogue to spironolactone.

The major uses of progestogens are for hormone replacement therapy and for hormonal contraception where they suppress ovulation and make the cervical mucus impenetrable to spermatozoa. Other indications include secondary amenorrhea, dysmenorrhea, infertility and habitual abortion and endometrium suppression in endometriosis. Progestogens are also used for palliation in metastasized endometrial and breast carcinoma. Medrogestone has been used in the treatment of fibroid uterine tumors.

Adverse effects include flushes, weight gain, mood changes, vaginal dryness, decreased libido, breast enlargement and tenderness and in some patients the prolonged time required for the return of normal ovulatory function. Androgen side-effects like acne and hirsutismus can occur with the 19-nortestosterone derivatives.

VI.d. Hormonal Contraceptives for Systemic Use

VI.d.1. Progestogens and Estrogens

Combined oral contraceptives contain one of the synthetic estrogens ethinylestradiol or mestranol, and a progestogen. The progestogens are 19-nortestosterone derivatives and include lynestrenol, desogestrel, gestodene, norethisterone, norethynodrel, norethindrone, norgestimate, ethynodiol, levonorgestrel and norgestrel. The main reason the progestogens are added is to ensure prompt withdrawal bleeding.

Combined oral contraceptives can be divided into monophasic (fixed) and phased regimens with a subdivision of the monophasic pills in preparations containing 50 µg ethinylestradiol or 50–100 µg mestranol and preparations with 20–35 µg ethinylestradiol. The low-dose pills are recommended for general use. Among these low-dose formulations are the so called third generation pills which contain, together with the estrogen ethinylestradiol, as progestogen desogestrel, norgestimate or gestodene. Epidemiological studies have shown that these third generation pills are associated with a slightly higher risk for thrombo-embolic complications than the second generation pills in which ethinylestradiol is combined with levonorgestrel, lynestrenol, norethisterone or norgestimate. Since 2000 low-dose monophasic pills containing 20–30 µg ethinylestradiol and 3 mg drospirenone have become available. It should be noted that drospirenone, being an analogue to spironolactone, has anti-mineralocorticoid effects. With respect to thrombo-embolic complications it is a third generation pill and is also contraindicated in women with a history of deep venous thrombosis.

High-dose monophasic preparations are indicated for the management of dysfunctional uterine bleedings and when persistent breakthrough bleedings occur with low-dose oral contraceptives. The monophasic combinations are taken in a fixed dose combination once daily over 21 or 22 days, followed by an interval of 7 or 6 days.

In phased combinations the oestrogen/progestogen content varies in such a way that it imitates the cyclic pattern of endogenous hormone secretion. Phased combinations always contain as estrogen ethinylestradiol. The combination of ethinylestradiol with the progestogen gestodene as found in the majority of the third generation monophasic pills is also present in some triphasic combination pills. In biphasic combinations the estrogen concentrations are constant with a progestogen concentration of 500 µg for the first 10 days and of 1000 µg the second 11 days. In triphasic combinations both the estrogen concentrations and the progestogen concentrations

are different for the first 6–7 days, the second 5–7 days and the last 4–6 days.

The disadvantages of these phased combinations are fluid retention, poor relief of dysmenorrhoea and the premenstrual syndrome and a relatively high medication error rate.

The efficacy of oral contraceptives can be reduced by enzyme inducers and by antibiotics which change the intestinal bacterial flora and so decrease the enterohepatic circulation of oral contraceptives.

Contraindications for oral contraceptives form episodes of thrombosis or embolism and cardiovascular disease. Estrogen containing pills should not be used immediately postpartum since they can interfere with lactation.

The adverse effects include those described for the estrogens and progestogens in general such as nausea, vomiting and fluid retention, painful swelling of the breasts, liver function disturbances and changes in mood and libido. Most of the adverse reactions are transient. The incidence of venous thromboembolic complications is slightly increased. Although a rare benign tumor, the majority of hepatic adenoma cases are associated with oral contraceptive use.

VI.d.2. Progestogens

Small doses of progestogens administered orally, intramuscularly or by implantation can be used for contraception. Agents available as oral progestogen-only contraceptives are norethisterone, levonorgestrel, lynestrenol and etynodiol. These pills are taken daily with no medication-free interval. They can be indicated when combination pills are not tolerated or in the post partum period. However they are less reliable than combination pills. There is a high incidence of abnormal bleeding. As so-called "morning after" pill high oral doses of levonorgestrel are used as an effective contraception following unprotected intercourse.

Used as long-acting depot preparations intramuscularly administered medroxyprogesterone acetate provides contraception for up to 3 months and norethisterone enanthate up to 2 months. These preparations can be indicated when compliance can pose problems. They are not associated with thromboembolism or cardiovascular disease. Adverse reactions are abnormal and prolonged bleeding and amenorrhoea.

Capsules for subcutaneous implantation, containing levonorgestrel for contraception and levonorgestrel containing intra-uterine devices are available in some countries. They are highly effective and their efficacy lasts for several years.

VI.e. Gonadal Hormone Inhibitors

Cyproterone and cyproterone acetate are antiandrogens with a steroidal structure that inhibit the action of androgens at the target organs. The acetate has also progestogen activity suppressing the feedback enhancement of LH and FSH and thus increasing the antiandrogenic effect. They are indicated for severe acne and hirsutism in women and in men to decrease aberrant sexual behavior. Adverse effects in women include weight gain and decreased libido.

Bicalutamide, flutamide and nilutamide are nonsteroidal antiandrogens that are used for the treatment of prostatic carcinoma. They act as competitive antagonists at the androgen receptor. Flutamide also inhibits the formation of dihydrotestosterone from testosterone.

Tamoxifen and torimefene competitively bind to estrogen receptors. They can act both as estrogen agonists and antagonists. The balance between agonism and antagonism varies within different species and different organ systems. The anti-tumor effect in women with breast cancer has been ascribed to estrogen antagonism. This is in agreement with the increased risk of breast carcinoma described after long-term treatment with estrogen replacement therapy. Fulvestrant is an estrogen receptor antagonist with no agonist effects, which works both by down-regulating and by degrading the estrogen receptor. It is used for treatment of hormone receptor-positive metastatic breast cancer in postmenopausal women with disease progression following anti-estrogen therapy.

Clomiphene is a nonsteroidal agent with oestrogenic and anti-oestrogenic properties. The mechanism of action is not precisely clear, but it ultimately leads to the release of the pituitary gonadotropins FSH and LH. It stimulates ovulation in anovulatory or oligo-ovulatory women with adequate endogenous oestrogen activity and an intact hypothalamic–pituitary–ovarian axis.

It is readily absorbed orally. It is metabolized in the liver and undergoes enterohepatic recirculation. It is eliminated in faeces with a half-life of 5–7 days. Its most common adverse effects are hot flushes.

Danazol is an isoxazole derivative of 17alpha-ethinyl testosterone. It has weak androgenic activity. It inhibits gonadotrophin secretion and is used to suppress ovarian function. It induces endometrial atrophy and has found its major use in the management of endometriosis. Gestrinon has the same indication and acts via a similar mechanism. Danazol has also been used in the management of benign breast disorders such as fibrocystic disease.

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Chapter 25

Antimicrobial Agents

Chris J. van Boxtel

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I. INTRODUCTION

Selective toxicity is often one of the attributes of antimicrobial agents. This selectivity is characterized by the chemotherapeutic index. This is the ratio of the doses, c.q. concentrations of the agent which show activity against the pathogen and the doses, c.q. concentrations that are toxic to the patient. The higher this chemotherapeutic index the more selective the antimicrobial agent is. Most of the antimicrobials have a large therapeutic index by action on metabolic pathways that are essential for the microorganism but not for the host. Some important mechanisms are inhibition of cell wall synthesis (e.g. penicillins, cephalosporins, vancomycin), inhibition of cell membrane function (e.g. amphotericin, azoles), inhibition of protein synthesis (e.g. aminoglycosides, tetracyclines, macrolides) and inhibition of nucleic acid synthesis (e.g. quinolones, sulfonamides, trimethoprim). However one has to bear in mind that for many of the antimicrobial drugs the exact mechanism of action is not known.

Antimicrobial agents can be subdivided according to their mechanism of action, by their general structure or by their indications. For a systematic presentation of the various agents mostly some compromise between the three is found. In this text the structural relationships are the principal guidelines for their classification.

Various mechanisms can be responsible for the development of resistance. Chromosomal resistance and plasmid-mediated resistance must be differentiated. Chromosomal mutations generally act by decreasing the ability of the drug to reach its target and chromosomal resistance generally develops against only one drug. Mutations associated with plasmid-mediated resistance generally act by way of inactivation of the drug. For plasmid mediated resistance active cell-division is not needed and this type of resistance can spread quickly. Furthermore, multi-resistance against several agents can reside on the same plasmid.

For some indications combination chemotherapy is indicated however then bacteriostatic or bactericidal agents should not be mixed. Synergism between the actions of different drugs is one of the aims of combination therapy. Other indications are delay of development of resistance or the treatment of 'mixed' infections.

II. ANTIBACTERIALS

II.a. Beta-Lactam Antibiotics

The penicillins and cephalosporins share their mechanism of action, pharmacological effects, clinical effects and also immunologic characteristics. They are called beta-lactam drugs because of their unique lactam ring. This ring is present in the penicillins, the cephalosporins, monobactams and carbapenems. The biological activity depends on the presence and

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the structural integrity of the 6-aminopenicillanic acid nucleus. It is clear that enzymatic destruction of this nucleus ends the biological activity of the beta-lactam drug. However this biological inactive metabolite still carries the antigenic determinant of the penicillins. This antigenic determinant can be attached to peptide chains and then used as skin-testing material in allergy tests.

II.a.1. Penicillins

The penicillins are derived from 6-aminopenicillanic acid with the beta-lactam ring as its active principle. They are irreversible transpeptidase inhibitors and thus inhibit peptidoglycan synthesis. They bind to a penicillin-binding protein in the bacterial cell wall and activate cell wall hydrolases, in this way further stimulating the breakdown of the peptidoglycan layer. Penicillins are bactericidal. However, for penicillin susceptibility the microorganisms must be actively dividing and it must be protected by a cell wall. Bacterial formation of beta-lactamase can induce break down of the beta-lactam ring, thus conferring resistance to the microorganism.

Some penicillins cannot be given orally as their beta-lactam ring is hydrolyzed and inactivated in the stomach by gastric acid. In general intramuscular injections are painful and therefore not advised. The pharmacokinetic behavior of penicillins is further characterized by short elimination half-lives. Renal elimination is prominent.

Being polar molecules the penicillins are water soluble and have rather small volumes of distribution. Most penicillins have only moderate protein binding except the members of the isoxazole family, cloxacillin, dicloxacillin and flucoxacillin which are highly protein bound. Penicillins are only able to cross the blood–brain barrier if the meninges are inflamed. In general penicillins have a large therapeutic index and there are hardly any dose limitations. The most prominent adverse effects are related to penicillin-hypersensitivity which mostly appears as skin rashes but can manifest itself as life threatening anaphylactic shock. The incidence is in the range of 5–10% of patients. Cross-reactivity exists between the various penicillins. In 5–15% of the patients also hypersensitivity against cephalosporins can be expected. At high doses penicillins can show CNS toxicity presenting itself as seizures, especially in patients with a history of brain trauma or with renal insufficiency.

II.a.1.1. Beta-lactamase-sensitive penicillins. The penicillins with a narrow spectrum and which are sensitive to beta-lactamase include benzylpenicillin (penicillin G), phenoxymethylpenicillin (penicillin V), phenethicillin and the longer-acting depot preparations, benzathine benzylpenicillin and procaine penicillin (see Table 1).

Penicillin remains the agent of choice for many infections caused by gram-positive cocci and anaerobes.

Benzylpenicillin is inactivated by gastric acid. Phenoxymethylpenicillin is 2–4 times less active than benzylpenicillin against most benzylpenicillin-susceptible organisms.

Benzathine benzylpenicillin is a depot form of benzylpenicillin, mainly indicated for prophylaxis against rheumatic fever.

Procaine penicillin modestly extends the duration of action of benzylpenicillin. The dose is limited by the volume that can be administered intramuscularly. If the insoluble penicillins are by accident injected intravenously potentially life-threatening reactions can result.

II.a.1.2. Beta-lactamase-resistant penicillins. Staphylococcal strains which are able to produce beta-lactamase remain sensitive to the beta-lactamase-resistant penicillins such as cloxacillin and flucloxacillin. However the beta-lactamase-resistant penicillins appeared, at least in vitro, to be less active against those bacterial strains that are still penicillin-sensitive.

II.a.1.3. Broad spectrum penicillins. To the aminopenicillins belong ampicillin and amoxicillin. Ampicillin is a semisynthetic penicillin with a much broader spectrum. It has activity against many gram-positive and gram-negative bacteria. It is inactivated by beta-lactamase.

Amoxicillin is a hydroxylated derivative of ampicillin with similar antibacterial activity. Its oral bioavailability is improved over that of ampicillin because it has higher acid stability.

In combination with beta-lactamase inhibitors, like e.g. clavulanic acid, the aminopenicillins can be effective also against beta-lactamase-producing organisms.

Pivampicillin, talampicillin, epicillin and ciclacillin are pro-drugs and analogues of ampicillin with no significant advantages over ampicillin and amoxicillin.

Piperacillin, a ureidopenicillin, has high activity against *Pseudomonas aeruginosa*.

Table 1. Classification of penicillins according to their most important characteristics

Drug name	Acid stability	Administration	Beta-lactamase resistance	Spectrum
Benzylpenicillin (penicillin G)	No	IV	No	Narrow
Benzathine penicillin G	No	IM	No	Narrow
Phenethicillin	Yes	PO	No	Narrow
Phenoxymethylpenicillin	Yes	PO	No	Narrow
Methicillin	No	IV, IM	Yes	Narrow
Nafcillin	Yes	PO, IM, IV	Yes	Narrow
Oxacillin	Yes	PO, IM, IV	Yes	Narrow
Cloxacillin	Yes	PO	Yes	Narrow
Dicloxacillin	Yes	PO	Yes	Narrow
Flucloxacillin	Yes	PO, IM, IV	Yes	Narrow
Ampicillin	Yes	PO, IM, IV	No	Broad
Amoxicillin	Yes	PO, IM, IV	No	Broad
Carbenicillin indanyl	Yes	PO	No	Broad
Carbenicillin	No	IV	No	Broad
Ticarcillin	No	IV, IM	No	Broad
Piperacillin	No	IV, IM	No	Broad
Azlocillin	No	IV	No	Broad
Mezlocillin	No	IV, IM	No	Broad

II.a.2. Cephalosporins

Cephalosporins are broad-spectrum semi-synthetic beta-lactam antibiotics. Their mechanism of action is the same as that of the penicillins. Most cephalosporins are given intravenously and only a few can be orally administered. They are mainly eliminated by urinary excretion although for some biliary excretion plays a significant role. Probenecid inhibits the tubular secretion of those beta-lactam antibiotics that are excreted by this mechanism. Cephalosporinase is a similar bacterial enzyme as beta-lactamase and can inactivate cephalosporins. In general the cephalosporins have a broader spectrum than the penicillins. With the orally administered agents nausea, vomiting and diarrhea are frequent. Hypersensitivity reactions can be dangerous and 10–15% of penicillin allergic patients also react to cephalosporins. Renal toxicity can be manifest as interstitial nephritis or tubular necrosis. Acute tubular necrosis has been reported most frequently with cephaloridine. Nephrotoxic reactions are synergistic with those of the aminoglycosides. There is a risk of thrombophlebitis after intravenous administration and intramuscular injection are painful. Cephalosporins which contain a methylthiotetrazole group can cause hypoproteinemia, bleeding disorders and in combination with alcohol disulfiram-like reactions.

Although manifest hemolytic anaemia is rare a positive Coomb's test may develop in about 3% of patients. As with the penicillins neurotoxicity manifested by hallucinations, confusion and convulsions may occur with high doses or in patients with renal impairment.

The first-generation cephalosporins include cephradine, cephalothin, cefazolin, cefadroxil and cefalexin. They are effective against gram-positive organisms, including some penicillinase-producing staphylococci, as well as against some gram-negative bacteria.

Cefadroxil and cefalexin are available in oral formulations, cephradine can be given parenterally or orally while cephalothin and cefazolin are administered parenterally.

The second-generation cephalosporins like cefamandole, cefoxitin, cefuroxime and cefaclor, have less activity against gram-positive organisms however they are more active against gram-negative organisms. Cefuroxime axetil is an orally-administered form and also cefaclor is an orally-administered second-generation cephalosporin.

Third-generation cephalosporins have a much broader spectrum of activity. They are effective against *E. coli*, *Klebsiella*, *Enterobacter*, *Serratia* and indole-positive *Proteus* species and they are also very effective against *H. influenzae*. However, their activity against *S. aureus* is somewhat less.

Cefotaxime can be used in infections due to beta-lactamase producing strains of *H. influenzae* and *N. gonorrhoeae*. Ceftriaxone has an antibacterial spectrum similar to that of cefotaxime but its longer half-life allows for less frequent dosing. Ceftazidime is especially effective against *Pseudomonas aeruginosa*. Cefixime and cefpodoxime are third-generation cephalosporins that can be administered orally.

Fourth-generation cephalosporins were developed such as cefpirome and cefepime with additional activity against gram negative pathogens and greater stability against beta-lactamases.

II.a.3. Other Beta-Lactam Antibacterials

Monobactams like aztreonam are monocyclic, as opposed to bicyclic, beta-lactam antibiotics. They are beta-lactamase-resistant. The monobactams are active against gram negative rods but lack activity against gram positive bacteria or against anaerobes. They are administered intravenously and they are rapidly excreted in the urine.

Side-effects of monobactams include occasional skin rashes and elevation of serum transaminases but major toxicity has not been reported. Penicillin-allergic patients can apparently tolerate these drugs.

Carbapenems are a class of antibiotics structurally related to beta-lactam antibiotics. Imipenem is its first representative. It has a wide spectrum with activity against gram negative rods, gram positive organisms and against anaerobes. Imipenem has good ability to cross the blood–brain barrier. Imepenem is resistant to beta-lactamases. It is inactivated by dihydropeptidases in renal tubules and is therefore administrated together with cilastatin, an inhibitor of renal dihydropeptidase. Adverse effects include gastrointestinal disturbances, skin rashes, seizures in patients with excessive levels and possible allergic cross-reactivity in penicillin-sensitive patients. Other carbapenems are meropenem and ertapenem which could be preferred in patients with CNS pathology as risks to induce seizures are supposed to be minimal. In 2006, ertapenem was approved for pediatric use in certain infections.

Beta-lactamase inhibitors include clavulanic acid, sulbactam and tazobactam. They are structurally related to the beta-lactam antibiotics however the antibacterial activity of these compounds is very weak or negligible. They are strong inhibitors of bacterial beta-lactamases and can protect beta-lactam antibiotics from hydrolysis by these enzymes.

II.b. Tetracyclines

The tetracyclines include among others tetracycline, doxycycline, minocycline and oxytetracycline. They have a broad spectrum of activity but because of increasing problems of resistance, to a large extend their use has been taken over by other agents for many indications. These antibiotics enter microorganisms partly by passive diffusion and also partly by an energy dependent process of active transport. Inside the cell tetracyclines bind reversibly to the 30s ribosomal subunit thereby blocking the binding of aminoacyl tRNA to the mRNA-ribosome complex, required for peptide elongation and protein synthesis. A deficient active transport mechanism in bacteria results in the impossibility for these bacteria to concentrate tetracyclines in their cells. Resistant bacteria may also be deficient in passive permeability. The degree of resistance is variable. The resistance to tetracyclines is transmitted by plasmids and the genes for this resistance are closely associated with the resistance to aminoglycosides, sulfonamides and chloramphenicol.

Tetracyclines remain the agents of choice in rickettsial infections, and are also used in chlamydial, vibrio, mycoplasmal and spirochaetal infections, brucellosis and the management of chronic bronchitis and acne. They are used in combination with other agents in the treatment of malaria and amoebiasis, and doxycycline is used for prophylaxis of malaria.

Tetracyclines block ADH in the kidney and especially demeclocycline is used to treat the syndrome of inappropriate ADH secretion.

Differences in clinical effectiveness are partly due to differences in absorption, distribution and excretion of the individual drugs. In general tetracyclines are absorbed irregularly from the gastrointestinal tract and part of the dose remains in the gut and is excreted in the faeces. However this part is able to modify the intestinal flora. Absorption of the more lipophilic tetracyclines, doxycycline and minocycline is higher and can reach 90–100%. The absorption is located in the upper small intestine and is better in the absence of food. Absorption is impaired by chelation with divalent cations. In blood 40–80% of tetracyclines is protein bound. Minocycline reaches very high concentrations in tears and saliva. Tetracyclines are excreted unchanged, in both the urine by passive filtration and in the feces. Tetracyclines are concentrated in the bile via an active

enterohepatic circulation. Doxycycline and minocycline are reabsorbed from the gut and thus slowly excreted causing persistent high plasma levels. In renal failure doxycycline does not accumulate as other elimination passways take over.

Tetracyclines have a wide variety of adverse effects. They can cause nausea, vomiting and diarrhoea by direct irritation to the gastrointestinal tract and if it is going to occur these gastrointestinal complaints will be evident already after the first dose. Calcium as well as magnesium and aluminum are chelated by tetracyclines. Calcium chelation also takes place in teeth and bones, leading to teeth discoloration, deformity and growth inhibition. Tetracyclines cross the placenta and reach the foetus. They are also excreted in milk. So administration to children and to pregnant or lactating women is contraindicated.

With the exception of doxycycline and minocycline, tetracyclines inhibit to some extend protein synthesis from amino acids also in mammalian cells. This antianabolic effect is reflected by raised blood urea levels in the patient.

Vestibular reactions like dizziness, vertigo, nausea and vomiting are particular for minocycline. Especially in pregnant women and when given in high doses hepatotoxicity has been described. Also patients with preexisting liver disease are susceptible. In patients with kidney disease renal function can further deteriorate.

Demeclocycline has a spectrum of activity comparable to tetracycline but it may cause nephrogenic diabetes insipidus. It is also associated with a high incidence of photosensitivity.

Tigecycline is the first clinically-available drug in a new class of antibiotics called the glycylcyclines. It is structurally similar to the tetracyclines in that it contains a central four-ring carbocyclic skeleton and is actually a derivative of minocycline. It was given a U.S. FDA fast-track approval and was approved in 2005. Tigecycline is active against many gram-positive bacteria, gram-negative bacteria and anaerobes – including activity against methicillin-resistant *Staphylococcus aureus* (MRSA).

II.c. Aminoglycosides

The aminoglycosides include streptomycin, gentamicin, tobramycin, netilmicin, kanamycin, amikacin, sisomicin, neomycin, paromomycin and others. Those are bactericidal antibiotics. This bactericidal activity is concentration dependent in contrast to the bactericidal effects of beta-lactams which are primarily time dependent. Protein-synthesis is inhibited by aminoglycosides at the 30s ribosomal subunit. They block the binding of messenger RNA to the ribosome, causing misreading of the messenger RNA. They also cause cell membrane damage. The aminoglycosides lose their activity at low pH and they are also not active in abscesses. They are active against many gram-negative bacteria, including *Pseudomonas* and certain strains of Staphylococcus species, but ineffective against streptococci and anaerobes.

Tobramycin may be more active than gentamicin against *Pseudomonas* but is less active against other problematic gram-negative organisms. For the treatment of chronic pulmonary *Pseudomonas aeruginosa* in patients with cystic fibrosis an inhalational form of tobramycin is available. Netilmicin has similar activity to gentamicin, but may be less active against *Pseudomonas*. Streptomycin is active against *Mycobacterium tuberculosis* and is only used in the treatment of tuberculosis. Paromomycin was granted orphan drug status in 2005 and was approved by the Drug Controller General of India in September 2006 for treatment of visceral leishmaniasis. Aminoglycosides only work on aerobes as drug-uptake requires active transport and this transport is most active under aerobic conditions. Aminoglycosides are almost always employed in combination with either broad-spectrum penicillins like carbenicillin or piperacillin, third generation cephalosporins, e.g. ceftazidime or cefoperazone or with aztreonam. Penicillins increase bacterial permeability and improve aminoglycoside transport into the cells resulting in a synergistic effect.

The occurrence of resistance is common. The most important form of resistance is bacterial metabolism by adenylation, acetylation or phosphorylation of the aminoglycoside which renders it inactive. This form of resistance is plasmid controlled. Amikacin shows a remarkable lack of resistance problems, partly due to its resistance to these inactivating enzymes to which other aminoglycosides are more susceptible. Also altered uptake of drug may play a role. Active transport is required for drug uptake and resistance can occur by alterations in transport channels or cell-wall permeability. Finally an alteration of the 30s ribosomal target can make the microorganism resistant to the aminoglycoside.

The pharmacokinetic behavior of the aminoglycosides is characterized by poor oral absorption.

Parenteral, mostly intravenous, drug administration is necessary. The aminoglycosides do not distribute to the central nervous system or the eyes. In the bile concentrations are 25–30% of the blood levels. Aminoglycosides cross the placenta and may have toxic effects on the fetus, particularly ototoxicity. They are not subject to any significant metabolism and these drugs are excreted by passive glomerular filtration with elimination half-lives of approximately 2–3 hours. Notwithstanding these rather short half-lives aminoglycosides can be administered on a once daily basis. If this phenomenon can be attributed *in vivo* to the *in vitro* observed post-antibiotic effects is under debate. The daily dose is determined by the blood levels as most adverse effects are dose-dependent and there is a strong need for drug levels to be monitored. Ideally a post-dose sample for peak levels and a pre-dose sample, obtained just prior to the next dose should be determined. In once-daily regimens a post-dose sample and a sample taken 3 times the estimated half-live after the dose will provide useful information.

Ototoxicity with both auditory and vestibulatory effects is the most serious of the adverse reactions of aminogycosides as it is mostly irreversible. Vestibular involvement manifests itself by dizziness, nystagmus, vertigo and ataxia. Cochlear toxicity results initially in high-frequency hearing loss. Amikacin more often causes cochlear damage than vestibular problems, while gentamicin and tobramycin are associated more frequently with vestibular symptoms.

Nephrotoxicity results from high drug levels in proximal tubular cells. It is usually reversible. The risks for nephrotoxicity is increased by the antimicrobials vancomycin and amphotericin-B but also by cyclosporin, cis-platin and other nephrotoxic agents. Neuromuscular blockade can occur at high doses and is especially seen in combination with neuromuscular blocking agents or in patients with myasthenia gravis. To limit the risks for serious ototoxicity and nephrotoxicity aminoglycoside therapy should be restricted to preferably one dose or to a maximum of three days.

Neomycin is too toxic for parenteral use. Its only use is via the oral route for pre-operative sterilization of the bowel or for selective decontamination in hematologic patients. However absorption may be increased significantly if there is inflammation of the bowel wall and such absorption can pose problems for the patient.

II.d. Macrolides and lincosamides

II.d.1. Macrolides

Macrolides and lincosamides have the same receptor site. They bind to the bacterial 50s ribosomal subunit, inhibiting protein synthesis and hence cell growth. Macrolides are usually bacteriostatic at low concentrations, but can become bactericidal for sensitive strains at high concentrations.

Erythromycin has a similar antibacterial spectrum as penicillin G and is therefore often used as an alternative in penicillin-allergic patients. It is active against *Legionella pneumophila*, *Bordetella pertussis*, *Mycoplasma pneumonia*, *Chlamydia trachomatis* as well as against anaerobes especially oral organisms. It has high activity against *Corynebacterium diphtheria*. The gram-negative spectrum is limited to *Campylobacter*, *Moraxella catarrhalis* and *N. gonorrhoeae*.

Resistance can occur via plasmid-mediated methylation of the receptor site which reduces the binding of the macrolide. Also plasmid-mediated esterase activity, especially in coliform bacteria, can inactivate the macrolides.

The macrolides are orally absorbed but they are acid-labile. They therefore need to be administered in acid-resistant capsules or as acid-resistant esters. The macrolides are widely distributed into all fluids except the CNS. Protein binding is about 90%. They are eliminated via biliary excretion with extensive enterohepatic circulation. Elimination half-lives vary from 1.4 h for erythromycin to 40–60 h for azithromycin.

Adverse effects include dyspepsia, nausea and vomiting. Interaction with motilin receptors can increase gastrointestinal motility resulting in diarrhea. Prolongation of the QT interval in the electrocardiogram can result in the torsades de pointes variant of ventricular tachycardia which can be fatal. Cholestatic hepatitis, although first reported for erythromycin estolate apparently can occur with all erythromycin formulations. Some members of the family of cytochrome P450 drug metabolizing enzymes, mainly CYP3A4, can be inhibited with the potential of clinically significant drug–drug interactions.

Roxithromycin, clarithromycin, azithromycin and dirithromycin are more recently developed macrolides with similar antimicrobial activity to erythromycin. However they are better absorbed, have longer elimination half-lives and lower incidence of gastrointestinal side-effects. Azithromycin and

clarithromycin were approved for the treatment of disseminated mycobacterial infections due to Mycobacterium avium complex (MAC).

II.d.2. Lincosamides

Clindamycin is a chlorine-substituted derivative of lincomycin. However it is more potent and is better absorbed from the gastrointestinal tract and has therefore replaced lincomycin in most situations. Clindamycin is in principle a bacteriostatic agent. Its indications are mainly limited to mixed anaerobic infections. As mentioned above it has a similar mechanism of action as erythromycin. It selectively inhibits bacterial protein synthesis by binding to the same 50s ribosomal subunits. Erythromycin and clindamycin can interfere with each other by competing for this receptor. Also cross-resistance with erythromycin frequently occurs. Resistance is rather chromosomal rather than plasmid mediated and is especially found in cocci and *Clostridium difficile*.

Clindamycin can be administered orally with a high bioavailability. Also formulations for intravenous administration exist. Protein binding is about 90%. It is distributed throughout the body except the CNS. It shows excellent penetration in bone and in empyema and abscesses. It is metabolized in the liver and excreted in the bile. The elimination half-life is about 3 h. Adverse effects include gastrointestinal distress, skin rashes and decreased liver function. Pseudomembranous colitis is relatively frequently seen due to resistance of *Clostridium difficile*.

II.e. Sulfonamides and Trimethoprim

Both the sulfonamides and trimethoprim interfere with bacterial folate metabolism. For purine synthesis tetrahydrofolate is required. It is also a cofactor for the methylation of various amino acids. The formation of dihydrofolate from para-aminobenzoic acid (PABA) is catalyzed by dihydropteroate synthetase. Dihydrofolate is further reduced to tetrahydrofolate by dihydrofolate reductase. Micro organisms require extracellular PABA to form folic acid. Sulfonamides are analogues of PABA. They can enter into the synthesis of folic acid and take the place of PABA. They then competitively inhibit dihydrofolate synthetase resulting in an accumulation of PABA and deficient tetrahydrofolate formation. On the other hand trimethoprim inhibits dihydrofolate reductase, also inhibiting formation of tetrahydrofolate. Thus synergism exists between sulfonamides and trimethoprim.

II.e.1. Sulfonamides

The action of sulfonamides is bacteriostatic and is reversible in the presence of an excess of PABA, e.g. in necrotic tissue and abscesses. Again, microorganisms require extracellular PABA to form folic acid. They are effective against sensitive strains of gram-negative and gram-positive bacteria, Actinomyces, Nocardia and Plasmodia. However, high levels of resistance currently limit their use. They are generally indicated for treatment of uncomplicated urinary tract infections. Sulfapyridine is a component of sulfasalazine which is an important agent for the management of inflammatory bowel disease and is sometimes used in rheumatoid arthritis. Resistance to sulfonamides often results from a mutation causing overproduction of PABA. Other mechanisms are changes in the bacterial permeability to the agents and structural changes of the target enzyme, dihydropteroate synthetase.

Sulfonamides are rather slowly absorbed with peak blood levels 2–6 h after oral intake. Intravenous preparations are sometimes used with comatose patients. Sulfonamides are distributed throughout the body, including the CNS. Binding to serum proteins varies from 20% to 90%. Several sulfonamides are acetylated in the liver followed by excretion in the urine. Soluble sulfonamides are eliminated by glomerular filtration.

Mild adverse effects include general malaise and some fever. More serious reactions are erythema multiforme and ulceration of the skin and mucous membranes. Hypersensitivity reactions which are common. Rashes are seen in 5% of patients. Severe hypersensitivity can ultimately result in Stevens–Johnson syndrome. Hepatitis has been reported. There is a serious risk for hemolytic anemia in patients with glucose-6-phosphate dehydrogenase deficiency. However also other blood dyscrasia's like aplastic anaemia, granulocytopenia and thrombocytopenia can occur. In acid urine sulfonamides may precipitate resulting in crystalluria. Adequate hydration will prevent this adverse event. Sulfonamides should not be taken in the last month and the long acting sulfonamides even not in the last trimester of pregnancy because of an increased risk of kernicterus in the new-borns.

The short-acting sulfonamides include sulfadimidine, sulfamerazine and sulfathiazole. Sulfadimidine, as the most important representative of this group, is relatively soluble and has therefore a lower risk of causing crystalluria while sulfamerazine and sulfathiazole are less soluble sulfonamides. Sulfadimidine has good oral absorption. It has an elimination half-life between 1.5 and 5 hours, depending on acetylator phenotype.

Intermediate-acting sulfonamides include sulfadiazine and sulfamethoxazole. Sulfamethoxazole is combined with trimethoprim in co-trimoxazole. Sulfadiazine shows good penetration into the cerebrospinal fluid and is effective for cerebral Toxoplasmosis. It has an elimination half-life 10–17 hours which prolonged in renal impairment.

The use of the long-acting sulfonamides such as sulfadimethoxine and sulfadoxine is limited because of a high rate of hypersensitivity reactions. Sulfadoxine in combination with pyrimethamine is indicated for chloroquine-resistant falciparum malaria.

II.e.2. Trimethoprim

Trimethoprim is a competitive inhibitor of the enzyme dihydrofolate reductase and can thus prevent the formation of tetrahydrofolate thereby blocking the synthesis of purines. The affinity of trimethoprim for the enzyme in microorganisms is 10,000 times higher than for the human enzyme which explains the selective toxicity. Used alone its main indication is acute uncomplicated urinary tract infections. It is then as effective as co-trimoxazole but has the advantage of fewer adverse reactions.

It has a favorable pharmacokinetic profile with 90–100% oral absorption. Effective concentrations are reached in the CSF and also in prostatic tissue. Protein binding is about 45%.

Only 10–20% is metabolized in the liver and trimethoprim is mainly excreted in urine as unchanged drug with a elimination half-life of 8–11 hours.

Adverse effects include skin rashes, pruritus, nausea, epigastric pain and glossitis. Megaloblastic anemia, leukopenia, granulocytopenia can occur due to the inhibition of the human dihydrofolate reductase. Folinic acid, the reduced form of tetrahydrofolate is sometimes used to prevent these effects.

II.e.3. Combinations of Sulfonamides and Trimethoprim

As said before, on the basis of their mechanisms of action combinations of trimethoprim with a sulfonamide are synergistic. Co-trimoxazole, trimethoprim combined with sulfamethoxazole, has been widely used as a broad-spectrum antibacterial agent. Indications include treatment of urinary tract infections and chronic prostatitis. However of major importance is the use of co-trimoxazole for the treatment and prophylaxis of Pneumocystis carinii infections in patients with AIDS. Both compounds have similar elimination half-lives. However, trimethoprim has a larger volume of distribution (±1 l/kg) than sulfamethoxazole (±0.25 l/kg). Trimethoprim and sulfamethoxazole are given in a 1 in 5 ratio, resulting in peak plasma concentrations with a ratio of 1:20. This ratio is in accordance with relative activities of the two drugs *in vitro*. Resistance especially among Enterobacteriaceae is increasing.

Note that in addition to the adverse events due to trimethoprim the combination trimethoprim–sulfamethoxazole may cause all of the untoward reactions associated with sulfonamides. In HIV positive patients the incidence of rashes can increase to 50%. Desensibilisation with increasing doses of co-trimoxazole has been successful.

II.f. Quinolones

The first-generation fluoroquinolones include ciprofloxacin, norfloxacin, ofloxacin, enoxacin, lomefloxacin and pefloxacin. Newer analogues include grepafloxacin, levofloxacin, sparfloxacin, gemifloxacin, moxifloxacin, gatifloxacin, sitafloxacin, trovafloxacin and alatrofloxacin, the parental prodrug of trovafloxacin. They are fluorinated analogues of nalidixic acid. Nalidixic acid itself is very rapidly excreted in the urine where about 20% of it is effective the other 80% being inactive glucuronides. It is therefore only useful in urinary tract infections. The quinolones act by inhibiting DNA gyrase, and thus have a bactericidal effect by interfering with the cutting and ligation of bacterial DNA, required for transcription. They have a broader anti-bacterial spectrum than nalidixic acid and are active against gram positive and gram negative bacteria. Anaerobes are less susceptible. They are used in urinary tract, gynecological, respiratory and some soft-tissue infections.

They are well absorbed after oral administration with a bioavailability of 70–80%. They have a rather low protein binding, 20–40%, and are widely distributed in tissues, body fluids and bone. They are eliminated mainly by glomerular filtration and tubular secretion with a half-life of 3–7 hours. Up to 40% of the dose is metabolized by the liver.

The most frequent adverse reactions are gastrointestinal complaints like abdominal pain, nausea, vomiting and diarrhoea. CNS effects include headache, dizziness and insomnia but also, although rarely, hallucinations and seizures. Hypersensitivity reactions vary from rashes and urticaria to Stevens–Johnson syndrome and anaphylaxis.

The initial enthusiasm for the quinolones has been diminished considerably in the last few years. In the fall of 2004, the FDA upgraded the warnings found within the package inserts for all drugs within this class regarding rare but such serious adverse reactions like spontaneous tendon ruptures, peripheral neuropathy and pseudomembranous colitis. Trovafloxacine and alatrofloxacine were withdrawn from the market because of serious liver toxicity. Grepafloxacin was withdrawn due to its side effect of lengthening the QT interval leading to sudden death. In 2006 the manufacturer of gatifloxacin stopped production of the antibiotic because of life threatening side-effects.

The quinolones are relatively contraindicated in pregnant women and children as animal studies have show cartilage damage.

II.g. Other Antibacterials

II.g.1. Amphenicols

Chloramphenicol is a bacteriostatic antibiotic with a broad spectrum. It shows activity against a wide range of gram-negative as well as gram-positive microorganisms but not against *Pseudomonas* and it is ineffective against *chlamydia* and *mycoplasma*. However, due to its potential for lethal toxicity, vide infra, its indications for systemic use are limited to CNS infections not responsive to other antibacterial regimens and typhoid fever. In the West, the main use of chloramphenicol is in eye drops or ointment for bacterial conjunctivitis.

Chloramphenicol is able to inhibit the peptidyl transferase reaction and so bacterial protein synthesis by binding reversibly to the 50s ribosomal subunit. Resistance can occur due to the plasmid-mediated enzyme chloramphenicol acetyltransferase which inactivates the drug by acetylation. Such resistance is often a part of plasmid-mediated multidrug resistance. Resistance can also occur by an altered bacterial permeability. However in most instances resistance to chloramphenicol only develops slowly and remains partial.

Absorption after oral administration is rapid and complete. Chloramphenicol is widely distributed to nearly all tissues and also to the CNS. Chloramphenicol is extensively glucuronidated in the liver.

Mostly chloramphenicol is well tolerated with only mild gastrointestinal disturbances. However this antibiotic inhibits mitochondrial protein synthesis in red blood cell precursors in the bone marrow and thus may cause dose-dependent anemia. This dose dependent reaction should not be confused with the idiosyncratic aplastic anemia which is dose-independent and usually fatal. The onset of this idiosyncrasy which has an incidence of about 1:20 000–1:50 000 may be during the treatment or weeks to months after therapy.

The gray-baby syndrome occurs in babies which are still deficient in glucuronyl-transferase. The syndrome is characterized by distension of the abdomen, anorexia, progressive cyanosis, vasomotor collapse, hypothermia and shock.

II.g.2. Glycopeptide Antibacterials: Vancomycin

The glycopeptides include vancomycin and teicoplanin. They are bactericidal antibiotics. Their mechanism of action is based on inhibition of bacterial cell-wall synthesis by blocking the polymerization of glycopeptides. They do not act from within the peptidoglycan layer, as the beta-lactam antibiotics do, but intracellularly. The indications are mainly restricted to the management of severe or resistant staphylococcal infections, especially those caused by coagulase negative staphylococcal species such as *S. epidermidis*.

Vancomycin is not absorbed after oral administration and must be given intravenously. Oral administrations are used for intraluminal gastrointestinal infections such as antibiotic-associated pseudomembranous colitis produced by *Clostridium difficile*. Vancomycin is widely distributed in the body but does not cross the blood brain barrier and does not penetrate into bone. It is excreted mainly via the urine, resulting in accumulation in patients with renal insufficiency. Its elimination half-life is 4–11 hours but can increase to 6–10 days in renal failure.

Vancomycin can cause "red-man syndrome" consisting of diffuse flushing, presumably mediated by histamine-release. This problem can be prevented by limiting the infusion rate. The most serious adverse reactions are ototoxicity and nephrotoxicity. The toxicity for both organ systems is potentiated by aminoglycosides. Vancomycin will cross the placenta barrier and has the potential to cause fetal ototoxicity.

II.g.3. Steroid Antibacterials: Fusidic Acid

Fusidic acid is a product of, among others, the fungus *Fusidium coccineum*. It has a steroidal structure and has mainly bacteriostatic activity. Its mechanism of action is based on inhibition of bacterial protein synthesis. Its indications are limited to the treatment of severe staphylococcal infections, usually in combination with another antistaphylococcal agent to prevent the emergence of resistance.

It is rather slowly absorbed after oral administration with peak plasma concentrations after 2–4 hours. Protein binding is about 95%. Fusidic acid is mainly excreted in the bile with an elimination half-life of approximately 10 hours. It is generally well tolerated with mild gastrointestinal reactions. Hepatotoxicity has been described.

II.g.4. Polymyxins

Polymyxins acts as an antibiotic by damaging the cytoplasmic membrane of bacteria. Polymyxins have a bactericidal effect on gram-negative bacilli, especially on *Pseudomonas* and coliform organisms. Polymyxin antibiotics are highly neurotoxic and nephrotoxic, and very poorly absorbed from the gastrointestinal tract. Polymyxins also have antifungal activity. The most important representative is colistin. Colistin is used to treat *Pseudomonas aeruginosa* infections in cystic fibrosis patients. It is also available as an aerosol.

II.g.5. Oxazolidinones

These antibiotics are considered as a choice of last resort where every other antibiotic therapy has failed. The first and only commercially available oxazolidinone antibiotic is linezolid which was introduced in 2002. Its mechanism of action is inhibition of bacterial protein synthesis. It is available for intravenous administration and also has the advantage of having excellent oral bioavailability. Linezolid is used for the treatment of infections caused by multi-resistant bacteria including streptococcus and methicillin-resistant *Staphylococcus aureus* (MRSA).

II.g.6. Nitrofurantoin

Nitrofurantoin is an bactericidal antibiotic. It is used in treating urinary tract infection. The drug works by damaging bacterial DNA. Nitrofurantoin is rapidly reduced by nitrofuran reductase inside the bacterial cell to multiple reactive intermediates that attack among others ribosomal proteins and DNA. Resistance to nitrofurantoin may be chromosomal or plasmid mediated and involves inhibition of nitrofuran reductase. Nitrofurantoin and its metabolites are excreted mainly by the kidneys. In renal impairment, the concentration achieved in urine may be subtherapeutic. It is active against *E. coli, Klebsiella* species, staphylococci and entercocci. The drug has very poor tissue penetration and should therfore only be used for the treatment of cystitis.

Nitrofurantoin can cause nausea and vomiting, fever, rash, hypersensitivity pneumonitis. When given for long periods of time, nitrofurantoin can cause progressive pulmonary interstitial fibrosis.

II.g.7. Daptomycin

Daptomycin is a newly-approved antibacterial agent, the first lipopeptide agent to be released onto the market. It is used in the treatment of infections caused by gram-positive organisms. Its distinct mechanism of action means that it may be useful in treating infections caused by multi-resistant bacteria. It binds to the membrane and causes rapid depolarisation, leading to inhibition of protein, DNA and RNA synthesis. Daptomycin is used for the treatment of skin and skin structure infections caused by Gram-positive bacteria, *Staphylococcus aureus* bacteraemia and right-sided *S. aureus* endocarditis.

Daptomycin can give quite a few adverse reactions. The primary toxicities associated with daptomycin use are myopathies. Significant rates of cardiovascular, central nervous system, dermatological, gastrointestinal and hematological side effects have also been reported.

III. ANTIMYCOBACTERIALS

III.a. Drugs for Treatment of Tuberculosis

Tuberculosis can be an extremely difficult disease to manage. Most cases are infected with *Mycobacterium tuberculosis*. These organisms are different from other microorganisms in several aspects. They have another sensitivity spectrum and their growth rate is very slow. The mycobacterium can remain dormant for extended periods of time. Furthermore tuberculosis is an intracellular infection and the mycobacterium is therefore difficult to reach by antimycobacterials. All these factors contribute to the fact

that for manifest tuberculosis prolonged periods of treatment are required.

Increasingly the existence of multiresistant strains is reported, especially in the United States but also elsewhere. Also the occurrence of infections with difficult to treat, so called atypical mycobacteria like *Mycobacterium avium intracellulare* and *Mycobacterium kansasii* is on the rise. These infections are especially seen in patients with a compromised immune system. *In vitro* these atypical mycobacteria often show resistance against first-choice drugs. However this *in vitro* lack of sensitivity does not always correspond with *in vivo* responses.

Among the antimycobacterials often a differentiation is made between first-choice and second-choice agents. The first-choice agents include isoniazid, rifampicin, ethambutol, pyrazinamide and streptomycin or as alternatives the other aminoglycosides amikacine or kanamycine. The second-choice agents include the quinolones ciprofloxacin and ofloxacin and also the rifamycin derivative rifabutin.

III.a.1. Hydrazides

Isoniazid (INH) is a synthetic derivative of isonicotinic acid. It has bactericidal activity against both intra- and extra-cellular mycobacteria. It also displays anti-bacterial activity in caseous lesions, but only in proliferating cells. Losing genes which code for catalase and peroxidase is the major mechanism through which resistance occurs. Single mutations can rapidly result in such resistance if isoniazid is used alone. Its mechanism of action is presumably based on inhibition of the synthesis of mycolic acids, unique and essential components of the mycobacterial cell wall.

Absorption is reduced by food and antacids and the drug should be taken on an empty stomach. Peak plasma concentrations are reached within 1–2 hours. It is widely distributed to all tissues and fluids, including the CNS. INH has a low protein binding of less than 10%. It is eliminated mainly by acetylation in the liver. In rapid acetylators half-lives of 0.5–1.6 hours are found while slow acetylators show half-lives of 2–5 hours. A minor metabolic pathway is via hydroxylation.

Isoniazid can induce a wide variety of potentially serious adverse reactions. Some hepatotoxicity can manifest itself as transient elevations of liver enzymes and this occurs in 10–20% of patients. Progressive and potentially fatal liver damage is age dependent with a very low incidence below the age of 20 years, increasing to higher than 1% in patients over 50 years. Although slow acetylators are considered to be at increased risk this influence of acetylator phenotype on hepatotoxicity is controversial. However as INH is normally given in combination with other antimycobacterials which can cause hepatotoxicity such as pyrazinamide and rifampicin determination of which drug was responsible is usually difficult.

CNS toxicity occurs because isoniazid has structural similarities to pyridoxine (vitamin B_6) and can inhibit its actions. This toxicity is dose-related and more common in slow acetylators. Manifestations include peripheral neuropathy, optic neuritis, ataxia, psychosis and seizures. The administration of pyridoxine to patients receiving INH does not interfere with the tuberculostatic action of INH but it prevents and can even reverse neuritis. Hematological effects include anaemia which is also responsive to pyridoxine. In some 20% of patients antinuclear antibodies can be detected but only in a minority of these patients drug-induced lupus erythematosus becomes manifest.

Isoniazid inhibits cytochrome P450 enzyme function and thus can interact with drugs that are subject to cytochrome P450 mediated metabolism like warfarin and the antiepileptic agents phenytoin and carbamazepine.

Ethionamide is an analog of isoniazid and also inhibits mycolic acid synthesis. Its usefulness is limited by the rapid development of resistance. It can cause intense gastric pain and, like isoniazid, may also be neurotoxic.

III.a.2. Antibiotics

Rifampicin, a semisynthetic derivative of the antimicrobial agent rifamycin B obtained from *Streptomyces mediterranei*, is bactericidal for intra- and extracellular bacteria. Bacterial RNA synthesis is inhibited by binding to the beta-subunit of DNA-dependent RNA polymerase. Human polymerases are not affected. It has activity against gram-positive and gram-negative cocci, chlamydia as well as mycobacteria. It is used in combination with dapsone for leprosy.

Resistance occurs by two mechanisms. Changes in bacterial permeability can hinder penetration of the drug or changes in the bacterial RNA polymerase can diminish drug binding to the enzyme. It is almost completely absorbed after oral administration with peak plasma concentrations reached after 2–4 h. It

is widely distributed in body fluids and tissues including the CNS. Protein binding is about 85%. It is metabolized in the liver, in part to the active metabolite desacetylrifampicin, and excreted into the bile. Significant entero-hepatic recirculation occurs. The elimination half-life which is 3–5 h at the start of treatment reduces through auto-induction to 2–3 h.

Patients should be warned that rifampicin colors urine, tears and other body fluids reddish-orange. Adverse effects further include rashes and pruritus and gastrointestinal complaints like nausea, anorexia and diarrhoea. With intermittent therapy a probably allergic hypersensitivity reaction can occur which mostly manifests itself as a flu-like syndrome with fever but can also result in nephritis and acute tubular necrosis. Elevation of serum transaminase levels occur frequently but clinical hepatitis is rare. Fatal outcome has been reported however.

Rifampicin is a potent inducer of cytochrome P450 enzymes and thus can diminish the activity of a multitude of other agents such as warfarin, glucocorticosteroids, cyclosporin, oral contraceptives and sulphonylurea-type oral antidiabetic agents.

Rifabutin, a semi-synthetic derivative of rifamycin S, is a bactericidal antibiotic primarily used in the treatment of tuberculosis. Its effect is based on blocking the DNA-dependend RNA-polymerase of the bacteria. Rifabutin is used in the treatment of infections with *Mycobacterium avium intracellulare*. Rifabutin is well tolerated in patients with HIV-related tuberculosis, but patients with low CD4 cell counts have a high risk of treatment failure or relapse due to acquired rifamycin resistance.

III.a.3. Other Tuberculostatics

Ethambutol is a synthetic agent and not related to any of the other tuberculostatics. Its mechanism of action is not well understood but in actively dividing mycobacteria it appears to be an inhibitor of mycobacterial RNA synthesis. It also has effects on bacterial phosphate metabolism and on polyamine synthesis. It is an bacteriostatic agent and its main function in combination therapy is to delay the occurrence of resistance, mainly against isoniazid and rifampicin. It is well absorbed after oral administration. It is widely distributed, except to the CNS. Protein binding is about 20–30%. It is mainly excreted unchanged in the bile and urine with an elimination half-life of 3–4 h. Ethambutol is concentrated in erythrocytes and thus provides a depot for continuous release.

Its most important adverse effects are visual disturbances. This ocular toxicity is dose dependent and has an incidence of lower than 1% at low doses but can reach 5% at high dose regimens. Ocular toxicity manifests itself as retrobulbar neuritis usually after the second month of use. If therapy is discontinued immediately it is mostly reversible but not always. During the treatment visual function should periodically be tested. Age under 8 years is a relative contraindication as visual symptoms are difficult to monitor.

Pyrazinamide is a nicotinamide derivative. It has mycobactericidal activity with a high specificity for Mycobacterium tuberculosis. Its mechanism of action is not well understood.

Pyrazinamide can only be administered orally. It has a protein binding of 10–20% and is widely distributed, also to the CNS. Pyrazinamide undergoes deamination and oxidation in the liver with urinary excretion of the metabolites. Its elimination half-life is approximately 10 h. Combination with other drugs is mandatory as resistance occurs rapidly.

Its main adverse effect is hepatotoxicity which is dose dependent but still occurs in some 5% of the patients. Hyperuricemia is seen in almost all patients. When gout becomes manifest it does not respond to treatment with probenecid.

The aminoglycoside (see Section II.c) streptomycin was the first antimycobacterial antibiotic. It has activity against extracellular mycobacteria with a high growth rate. The macrolide antibiotics azithromycin and clarithromycin (see Section II.d.1) were approved for the treatment of disseminated mycobacterial infections due to *Mycobacterium avium* complex.

Terizidone is a cycloserine analogue. It has activity against *M. tuberculosis* but also against many gram-negative and gram-positive organisms. Apart from the fact that it reaches high concentrations in urine little is know about its pharmacokinetics. Renal impairment is a contraindication as serious CNS effects including convulsions and psychiatric disturbances may occur.

Thioacetazone is a tuberculostatic agent with limited activity but still used on a large scale for the first-line management of tuberculosis in developing countries because it is extremely cheap.

III.b. Drugs for Treatment of Leprosy

Agents used for the management of leprosy are dapsone, rifampicin, clofazimine and recently thalido-

mide. Dapsone has for a long time been the principal drug for the treatment of leprosy. However increasing resistance necessitates the use of dapsone in combination with other agents. An other indication of dapsone is for the treatment of pneumocystis carinii infections. It is a sulfone and has a similar mechanism of action as the sulfonamides (see Section II.e.1). The efficacy which it sometimes displays in dermatitis herpetiformis must be based on another mechanism. Dapsone is concentrated in the skin but also in liver, kidney and muscle.

Gastrointestinal disturbances are common. Its adverse reactions also include severe hemolytic anemia in people with G6PD deficiency. Skin reactions vary from erythema nodosum to toxic epidermal necrolysis. However its most serious adverse reaction is potentially fatal agranulocytosis.

Rifampicin (see Section III.a.2) has bactericidal activity against Mycobacterium lepra and is employed in combination with clofazamine and dapsone.

Clofazimine is a phenazine dye with some mycobactericidal activity. It is only used in combination with dapsone to reduce the emerging resistance against dapsone. Its efficacy in the management of erythema nodosum leprosum is based on its anti-inflammatory activity.

In 1998, the FDA approved the use of thalidomide for the treatment of lesions associated with erythema nodosum leprosum. Because of thalidomide's potential for causing birth defects, the distribution of thalidomide was permitted only under tightly controlled conditions. Nevertheless, because of its use for patients with leprosy thalidomide has been identified again as a current teratogen, now in South America.

IV. ANTIVIRAL AGENTS

Viruses are obligate intracellular organisms as their replication is based on DNA and RNA dependent processes and protein synthesis of the host. Antiviral therapy can therefore not be as selective as antibacterial treatments and anti-viral agents tend to inhibit host cell function and can cause major toxicity. An other problem with antiviral therapy is the fact that active viral replication mostly takes place before symptoms become manifest. Our armamentarium against most viral infections is limited.

Five steps can be distinguished in virus replication. First the organism has to penetrate the host cell. Then some early protein synthesis, e.g. RNA polymerase synthesis, takes place. The third step is the synthesis of RNA or DNA which is followed by the synthesis of structural proteins. The fifth step is the assembly and release of virus particles.

Antibodies against the virus but also amantadine and derivatives, interfere with host cell penetration. There are nucleoside analogues such as aciclovir and ganciclovir, which interfere with DNA synthesis, especially of herpes viruses. Others like zidovudine and didanosine, inhibit reverse transcriptase of retroviruses. Recently a number of non-nucleoside reverse transcriptase inhibitors was developed for the treatment of HIV infections. Foscarnet, a pyrophosphate analogue, inhibits both reverse transcriptase and DNA synthesis. Protease inhibitors, also developed for the treatment of HIV infections, are active during the fifth step of virus replication. They prevent viral replication by inhibiting the activity of HIV-1 protease, an enzyme used by the viruses to cleave nascent proteins for final assembly of new virons.

IV.a. Viral Uptake Inhibitors

Amantadine (see Chapter 21, Section III.b.1) is a tricyclic symmetric adamantanamine. It inhibits the uncoating stage which takes place for binding of the virus to cells, of the influenza-A virus. It is used prophylactically for influenza-A infection, and when given within 24 hours of onset for active influenza-A. It shows good oral absorption and is excreted in the urine with an elimination half-life of about 12 hours. The adverse effects are mainly on the CNS and include insomnia, restlessness, nervousness and depression.

Rimantadine is an alternative for amantadine. It has a longer half-life and less central nervous system effects. It is eliminated by the liver.

IV.b. Nucleic Acid Synthesis Inhibitors

Ribavirin can inhibit the replication of both RNA and DNA viruses. It is a nucleoside analog which blocks guanosine monophosphate by inhibiting the enzyme inosine monodehydrogenase. Its main indication is severe respiratory syncytial virus infections in infants but it has also shown activity against influenza A and influenza B infections. It is administered by aerosol spray. No serious adverse effects occur when used as aerosol.

Idoxuridine inhibits the replication of herpes simples virus in the cornea and is topically applied for herpetic keratitis.

Vidarabine (adenine arabinoside, ara-A) is phosphorylated in the cell to the triphosphate derivative which blocks DNA synthesis by inhibiting DNA polymerase. It is indicated for infections with herpes simplex virus and varicella-zoster however its use has to a large extend been surpassed by aciclovir. It is administered topically or intravenously. It is inactivated rapidly by adenosine deaminase which for systemic use necessitates constant infusion of the drug. Vidarabine is the least toxic of the purine analogues. Nausea and vomiting are the most frequent adverse effects and neurotoxicity may occur.

Aciclovir has activity against herpes viruses. It is a guanosine analogue and is like vidarabine a prodrug which has to be phosphorylated intracellularly by thymidine kinase to the active triphosphate. The selective toxicity is explained by a greater affinity of the drug for the viral enzyme. Aciclovir triphosphate inhibits viral DNA polymerase but it is also built into viral DNA where it acts as a chain-terminator. Aciclovir has the same indications as vidarabine. Drug resistance may develop after prolonged treatment via two mechanisms. A mutation in viral thymidine kinase which prevents the conversion of aciclovir to the triphosphate may induce resistance. An other mechanism for resistance is a mutation in viral DNA polymerase preventing the binding of the drug. Oral bioavailability of aciclovir is 15–30%. The drug is also used topically for skin lesions, or intravenously for encephalitis or neonatal disease. It is widely distributed and crosses to some extend the blood–brain barrier. Aciclovir is eliminated by urinary excretion with a half-life of 2–3 h. Generally oral aciclovir is well tolerated. Some complaints of headache, nausea, vomiting, diarrhoea and dizziness may occur as well as transient increases of liver enzymes. However intravenous administration can be nephrotoxic. There have been reports of central nervous system toxicity manifesting itself as encephalopathy with lethargy, confusion and convulsions.

Valaciclovir is a prodrug of acyclovir with a higher bioavailability. In the body it is rapidly transformed in aciclovir and the amino acid L-valine.

Valganciclovir is a pro-drug of ganciclovir. Ganciclovir, a guanine analogue, is also a pro-drug of which the triphosphate is the active form which inhibits viral DNA polymerase. The ganciclovir triphosphate derivative is also incorporated into DNA for which it competes with deoxyguanosine triphosphate. Its activity against herpes simplex and varicella-zoster is similar to that of aciclovir. However, the *in vitro* activity of ganciclovir is 100-fold greater against cytomegalovirus (CMV) and 10-fold greater against Epstein–Barr virus (EBV) than that of acyclovir. Furthermore, in CMV-infected cells levels of ganciclovir triphosphate are ten-fold higher than in uninfected cells and this agent is therefore specifically indicated for immunocompromised patients with cytomegalovirus infections. Both diminished phosphorylation and mutations of viral DNA polymerase may induce resistance against ganciclovir. Although the oral bioavailability is less than 5% there is an oral formulation available. Ganciclovir is widely distributed. It crosses the blood-brain barrier and also reaches intraocular fluids. It is eliminated by urinary excretion with a half-life of 2–4 h. Myelosuppression is the most important adverse effect. Neutropenia occurs in approximately 40% of patients.

Foscarnet sodium is an pyrophosphate analogue. It inhibits viral DNA polymerase and reverse transcriptase. Its main indication is cytomegalovirus retinitis in AIDS patients which have contraindications for ganciclovir.

Newer agents of this class are famciclovir and cidofovir. Famciclovir is a prodrug of penciclovir with improved oral bioavailability. It is labelled for the suppression of recurrent episodes of genital herpes in immunocompetent adults and for the treatment of recurrent mucocutaneous herpes simplex infections in HIV-infected patients.

In 1996 cidofovir was approved for the treatment of AIDS-related cytomegalovirus retinitis. It is already a monophosphate and does not need activation by viral enzymes.

Fomivirsen does not belong to this class but it is also specifically indicated for CMV retinitis. In 1998 the FDA approved fomivirsen, the first drug using antisense technology, for patients who are intolerant of or have a contraindication to other treatments for CMV retinitis or who were insufficiently responsive to previous treatments for CMV retinitis. Antisense drugs work by blocking a specific gene from producing the protein it codes for. This drug is injected directly into the eye, and is given monthly.

IV.c. Neuramidase Inhibitors

Zanamivir was the first orally active neuraminidase inhibitor commercially developed. It acts as a

transition-state analogue inhibitor of influenza neuraminidase, preventing progeny virions from emerging from infected cells. It is used in the treatment and prophylaxis of both Influenzavirus A and Influenzavirus B. A combination of factors has resulted in the limited commercial success of zanamivir. However zanamivir led to the development of other members of this class.

Oseltamivir, also a neuraminidase inhibitor, is a prodrug which is hydrolysed hepatically to the active metabolite, the free carboxylate of oseltamivir. It has activity against Influenzavirus A and Influenzavirus B. With increasing fears about the potential for a new influenza pandemic oseltamivir is now stockpiled by many governments. Common adverse drug reactions include nausea, vomiting, diarrhea, abdominal pain, and headache. However there are concerns that oseltamivir may cause dangerous psychological side effects in some people. In 2006 the FDA amended the warning label to include the possible side effects of delirium, hallucinations, or other related behavior and in 2007 a warning was issued in Japan that oseltamivir should not be given to children aged 10–19.

IV.d. Interferons

Interferons are natural proteins produced by the cells of the immune system in response to challenges by foreign agents such as viruses, parasites and tumor cells. Interferons assist the immune response by inhibiting viral replication within host cells. There are three major classes of interferons, interferon type I, interferon type II and interferon type III. They bind to a differen cell surface receptor complexes. The type I interferons in humans are IFN-α, IFN-β and IFN-ω. IFN-γ is human interferon type II. All classes of interferon are important in fighting RNA virus infections and endogenous interferons are secreted when abnormally large amounts of dsRNA are found in a cell.

Pegylated interferon alpha-2b was approved in 2001, polyethylene glycol being added to increase the duration of action, and pegylated interferon alpha-2a in 2002. The pegylated forms are injected once weekly, rather than three times per week for conventional interferon-alpha. Pegylated interferon alfa-2b is a treatment for hepatitis C while pegylated interferon alpha-2a is approved around the world for the treatment of chronic hepatitis C (including patients with HIV co-infection) and has also been approved for the treatment of chronic hepatitis B.

The most frequent adverse effects are flu-like symptoms: increased body temperature, feeling ill, fatigue, headache, muscle pain, convulsion, dizziness, hair thinning and depression. Erythema, pain and hardness on the spot of injection are also frequently observed. Interferon therapy may cause immunosuppression. Also various interferon induced autoimmune syndromes were reported.

IV.e. Reverse Transcriptase Inhibitors

The virus that causes AIDS, the Human Immune Deficiency Virus (HIV) is a retrovirus. Instead of double-stranded DNA it uses single-stranded RNA to store its genetic information. HIV uses the enzyme reverse transcriptase to convert its RNA into DNA in order to replicate.

IV.e.1. Nucleoside Analogue Reverse Transcriptase Inhibitors (NRTIs)

By inhibiting the enzyme that is crucial for the conversion of viral RNA into DNA the nucleoside reverse transcriptase inhibitors block virus replication.

The present NRTIs available for the treatment of HIV are zidovudine (azidothymidine, AZT), stavudine (d4T), didanosine (ddI), lamivudine (3TC), dideoxycytidine (ddC, zalcitabine) and abacavir, emtricitabine and tenofovir disoproxil. Combination formulations are abcavir combined with zidovudine and lamivudine and the abacavir–lamivudine combination.

Zidovudine was the first drug of the class. It is a dideoxythymidine analog. It has to be phosphorylated to the active triphosphate. This triphosphate is a competitive inhibitor of HIV reverse transcriptase. By incorporation into viral DNA it also acts as a chain-terminator of DNA synthesis. Mutations in viral reverse transcriptase are responsible for rapidly occurring resistance. Zidovudine slows disease progression and the occurrence of complications in AIDS patients. It is readily absorbed. However, first pass metabolism reduces its oral bioavailability with some 40%. It readily crosses the blood–brain barrier. Plasma protein binding is about 30%. Zidovudine is glucuronidated in the liver to an inactive metabolite. Its elimination half-life is 1 hour.

Its adverse effects are dose dependent. Hematological effects include anaemia and leucopenia. Other effects are nausea, headache, myalgia, insomnia, and rarely, myopathy and hepatotoxicity. CNS toxicity can manifest itself as seizures, confusion

or mania. It has been argued that drugs that may compete for the glucuronidation pathway, like paracetamol or trimethoprim, could potentiate zidovudine toxicity.

Stavudine is an other thymidine analogue with a similar mechanism of action and activity as zidovudine. It can be used in AIDS patients who responded insufficiently to zidovudine or who cannot tolerate zidovudine. Its most prominent dose dependent toxicity is d4T induced neuropathy.

Didanosine (2′3′-dideoxyinosine or ddI) is a dideoxynucleoside purine analogue. Its mechanism of action is identical to that of zidovudine and resistance to didanosine is known to occur rapidly in patients who were already treated with zidovudine. Didanosine shows in vitro synergy with zidovudine while their toxicity profiles are different. Oral absorption is decreased by food and didanoside penetrates into the brain to a limited extend. Pancreatitis is the most serious complication. Other adverse reactions include peripheral neuropathy, diarrhoea and other gastrointestinal disturbances.

Additional nucleoside analogues like the purine dideoxynucleosides lamivudine (3TC) and dideoxycytidine (ddC, zalcitabine) act in the same way as AZT. Resistance against these agents may show different patterns. They are generally less toxic than AZT. Adverse effects include diarrhoea and other gastrointestinal disturbances, headache, anxiety, restlessness and insomnia. Also hepatotoxicity can occur, probably because some of these drugs might have also some affinity for human DNA polymerases in the liver.

A potentially fatal hypersensitivity, or allergic reaction, has been associated with the use of abacavir, a nucleoside analogue reverse transcriptase inhibitors recently approved for treatment of AIDS in adults and children, in at least 5% of patients. Symptoms of this reaction may include skin rash, fever, nausea, abdominal pain and severe tiredness.

Adefovir dipivoxil is an orally-administered nucleotide analog reverse transcriptase inhibitor. However it is used for treatment of hepatitis B and failed as a treatment for HIV.

IV.e.2. Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

Although the NNRTI are active at the same site as the NRTI inhibitors and also prevent the conversion of RNA to DNA, their mechanism of action is not identical. The NNRTIs inhibit virus replication by binding directly to reverse transcriptase.

This group includes nevirapine, efavirenz and delavirdine. Nevirapine was the first agent of this new class of drugs. It has convincingly been shown that combinations of AZT and ddI with nevirapine were more effective than AZT and ddI alone. It was also shown that the use of nevirapine alone rapidly induced resistance. The most frequently occurring adverse reaction to nevirapine is rash and it is advised to discontinue nevirapine in patients who develop a severe rash.

IV.f. Protease Inhibitors

Protease Inhibitors (PIs) interrupt the HIV reproduction cycle and prevent the virus from being assembled by interfering with the HIV protease enzyme. As a result, copies of HIV are not able to infect new cells.

This class of antiretrovirals may be considered the most potent therapeutic agents for HIV to date. Protease inhibitors are used in combination regimens and combinations of reverse-transcriptase inhibitors and protease inhibitors have been proven most effective to decrease viral load and prolong survival. However, the protease inhibitors generally show poor penetration into the CNS and thus have no effect on aids dementia. The present PIs available for the treatment of HIV are indinavir, ritonavir, nelfinavir, saquinavir and (fos)amprenavir, atazanavir and lopinavir (in combination with ritonavir as ritonavir improves the bioavailability of lopinavir by inhibiting its metabolism in the liver by CYP3A).

In 1995 the FDA approved saquinavir, the first protease inhibitor, for use in combination with other nucleoside analogue medications. In 1999 a soft gel capsule formulation of saquinavir with considerably improved absorption characteristics was developed. Ritonavir and indinavir have been approved for use alone or in combination with nucleoside analogue medications in people with advanced HIV disease. Nelfinavir is the first protease inhibitor labeled for use in children. Amprenavir is the newest of the protease inhibitors. Amprenavir can be taken with or without food, but it should not be taken with a high-fat meal because the fat content may decrease the absorption of the drug. The most disturbing adverse reactions to protease inhibitors consist of the lipodystrophy syndrome with severe hyperlipidemia and unpredictable fat redistributions over the body

which can pose serious cosmetic problems to the patient. Frequently reported adverse events are nausea, diarrhea, vomiting, and rash. Indinavir and nelfinavir are associated with taste disturbances. Severe and life-threatening skin reactions, including Stevens–Johnson syndrome, have occurred in patients treated with amprenavir. Acute hemolytic anemia, diabetes mellitus and hyperglycemia may also be associated with amprenavir.

The protease inhibitors are partially metabolized by the cytochrome P450 oxidase system and have a potential for serious interactions with a large number of commonly prescribed drug products metabolized by the same pathway.

V. SYSTEMIC ANTIFUNGAL AGENTS

Systemic mycoses are mostly opportunistic infections and their prevalence increased as a consequence of increased use of immunosuppressive regimens in organ transplantation and in the treatment of malignancies, and the AIDS epidemic. However, most fungi are completely resistant to antibacterial drugs. Only few chemicals are known with activity against fungi and most of these are relatively toxic. The principal agents used for systemic mycoses are amphotericin B, a polyene antibiotic, and the synthetic antifungal agents, flucytosine and the azole derivatives such as ketoconazole, itraconazole and fluconazole. Griseofulvin and terbenafine can be administered systemically but their indications are limited to the treatment of dermatophytic infections of the skin, nails and hair. Nystatin, a polyene antibiotic structurally similar to amphotericin-B, is too toxic for systemic use and the same holds true for haloprogin. Clotrimazole and miconazole are topical azole antifungals which are also too toxic for systemic use. Similar topical azoles include econazole, oxiconazole and sulconazole. Ciclopirox olamine, tolnaftate and naftifine are other topical antifungal agents.

V.a. Antibiotics

Amphotericin-B, an amphoteric polyene macrolide remains the most effective for severe systemic mycoses. It is indicated for systemic mycoses such as disseminated candidiasis, cryptococcosis, aspergillosis, mucormycosis, coccidioidomycosis, histoplasmosis, extracutaneous sporotrichosis and blastomycosis. It is a fungicidal antibiotic without antibacterial activity. It binds to ergosterol in the cell wall of fungi and thus increases its permeability and induces cell lysis. Resistance may result from changes in ergosterol structure and decreased amounts of ergosterol in the fungal membrane which makes it less susceptible to the drug.

Combinations of amphotericin-B with flucytosine are sometimes used to reduce the occurrence of resistance. Amphotericin-B is not absorbed from the gastrointestinal tract which necessitates intravenous administration. It is 90% protein bound and widely distributed, except for the CNS. For the treatment of fungal meningitis therefore only intrathecal drug administrations can be effective. Amphotericin-B is eliminated very slowly in urine, mainly in an inactive form, with an elimination half-life of about 24 hours which can increase to up to 15 days with repeated doses.

Amphotericin-B is highly toxic as ergosterol is very similar to cholesterol and amphotericin has thus cross-reactivity to cholesterol in human cell membranes. Adverse effects include chills, fever, dyspnea, hepatotoxicity and anemia. However, nephrotoxicity is the most common complication, although adequate hydration can reduce the risk for this toxicity to some extend. Amphotericin induced nephrotoxicity may be irreversible. Liposomal preparations have shown to be therapeutically effective with little or no renal damage.

Griseofulvin is isolated from *Penicillium griseofulvum*. Although it is given systemically it only works on superficial fungi. It presumably inhibits the replication of fungi by binding to microtubules in the cells. Fatty meals can increase the oral absorption of griseofulvin. It is concentrated in the skin and other tissues that contain keratin as griseofulvin binds to keratin. Adverse effects include allergic reactions, headache and gastrointestinal disturbances.

V.b. Azole Derivatives

The azole derivatives for systemic administration include the imidazoles ketoconazole and miconazole and the triazoles fluconazole, itraconazole, posaconazole and voriconazole. They are broad spectrum antifungals and have activity against several dermatophytes, *Candida*, *Cryptococcus* and other fungi that cause deep-seated infections.

The mechanism of action is based on blocking the fungal Cytochrome P450 mediated synthesis of ergosterol from lanosterol, thus inhibiting fungal growth. There is however cross-reactivity with human Cytochrome P450 enzymes which explains

their potential for inhibition of steroid synthesis in humans and for interaction with other hepatically metabolized drugs.

Ketoconazole is indicated for non-life-threatening blastomycosis, histoplasmosis and coccidioidomycosis chronic mucocutaneous candidiasis. The emergence of drug resistance is rare. For its anti-androgenic effects ketoconazole has been used to treat prostate cancer. It is given orally and is then readily absorbed. Raising the pH in the stomach with e.g. antacids or cimetidine can markedly decrease absorption. It is widely distributed. Ketoconazole is metabolized by liver Cytochrome P450 enzymes. As with the other azoles vomiting, diarrhoea and rashes can occur. However, adverse effects also include gynecomastia due to its anti-androgenic activity and hepatotoxicity which can be fatal. Ketoconazole inhibits also human cytochrome P450 enzymes and serious interactions have occurred, e.g. with cyclosporin.

Fluconazole is particularly useful for treatment for cryptococcal meningitis. It is active against *Candida albicans*. However, other candida species are not sensitive for it. Given orally it is well absorbed. It can also be administered intravenously. Fluconazole readily enters the CNS. Its main adverse effect is hepatotoxicity. Due to cytochrome P450 inhibition drug interactions with phenytoin, cyclosporin, warfarin and hypoglycemic agents have been reported.

Itraconazole has a broader spectrum than ketoconazole and also the incidence of averse reactions is less. Like the other azoles it is a cytochrome P450 inhibitor.

V.c. Other Antimycotics for Systemic Use

Flucytosine is an oral antifungal pro-drug. It has to be enzymatically deaminated by the fungi to the active metabolite, fluorouracil. Fluorouracil inhibits thymidylate synthetase and DNA synthesis. Its indications are treatment of cryptococcal meningitis and serious systemic candidiasis. Resistance develops rapidly, due to altered drug-permeability. For this reason Amphotericin B and flucytosine are often given in combination as they have synergistic effects.

Oral flucytosine is well absorbed and widely distributed, also in the cerebrospinal fluid. It is actively secreted and concentrated into the urine with an elimination half-life of 2.5–6 hours.

Adverse effects include diarrhoea, nausea and vomiting and skin rashes. Less frequently CNS effects occur like confusion and drowsiness. Severe liver damage is rare. the most serious adverse event is bone marrow depression which is concentration dependent and may be fatal.

Impairment of renal function by amphotericin may increase the potential for bone marrow toxicity.

Terbinafine is an n-allylamine which is highly active against dermatophytes. Next to a cream formulation there is also an oral formulation. Terbinafine acts by inhibiting squalene epoxide, a key enzyme in fungal sterol biosynthesis, which results in ergosterol deficiency and squalene accumulation, with cell death. Unlike the azole antifungals such as itraconazole and ketoconazole, terbinafine does not interact with other drugs as a metabolizing enzyme inhibitor. The drug is generally well tolerated.

Caspofungin is the first of a new class termed the echinocandins. It was approved in the US and in Europe in 2001. It shows activity against infections with Aspergillus and Candida, and works by inhibiting $\beta(1,3)$-D-Glucan of the fungal cell wall. Compared to amphotericin B, caspofungin seems to have a relatively low incidence of side-effects.

VI. ANTIPARASITIC AGENTS

Three types of potential targets for antiparasitic chemotherapy can be discerned. Firstly, enzymes unique for the parasite could be present. Secondly, enzymes for which alternative pathways exist in the host may be targeted. And thirdly, in principle similar biochemical functions for parasite and host can differ enough to provide, if pharmacologically influenced, some selectivity. Apart from these three types of mechanisms there are antiparasitic agents for which the mechanism has not been identified.

VI.a. Antiprotozoals

VI.a.1. Agents Against Amoebiasis and Other Protozoal Diseases

Most of the agents against amoebiasis are not effective against the cyst stage. Tissue amoebicides kill organisms in the bowel wall, the liver and other extraintestinal tissues and are often only partially effective as luminal amoebicides. They include the nitroimidazoles and the emetines. Chloroquine is also a tissue amoebicide but is only active in the liver. Luminal amoebicides act in the bowel lumen and are not effective against organisms in the bowel wall or other tissues. They include the dichloroacetamides and the halogenated hydroxyquinolines.

Tetracycline and erythromycin have some amoebicidal activity in the bowel wall and lumen. They act indirectly by their effects on the bacterial flora which the amoebae need for survival.

Metronidazole is a nitro-imidazole. It is a mixed amoebicide, i.e. it acts at all sites of infection. It has to be activated in the parasite. By reduction in the amoeba of its nitro group reactive intermediates are formed, resulting in oxidative damage and ultimately cell kill. It is effective against many parasitic intestinal and tissue infections such as trichomoniasis, giardiasis and amoebiasis. It is the drug of choice for amoebic dysentery and amoebic liver abscess.

Oral bioavailability is almost 100%. Metronidazole is protein bound for less than 20% and is widely distributed, including the CNS. It is metabolized in the liver with an elimination half-life of 8 hours. Common adverse effects include nausea, headache and taste disturbances. With alcohol a severe disulfiram-like reaction, with flushing, sweating and abdominal cramps will occur.

Nimorazole, secondizole, ornidazole and tinidazole are newer, longer- acting nitroimidazole agents with a similar spectrum of activity as metronidazole. They may be somewhat less effective but can be administered with a longer dosing interval.

The emetines include emetine and dehydroemetine. These drugs act only against trophozoites. Their mechanism of action is based on eukaryote protein synthesis. They are parenterally administered because oral preparations are absorbed erratically and may induce severe vomiting. They are widely distributed and accumulate in liver, lungs and other tissues. The emetines are slowly elimination via the kidneys. Local side-effects in the area of the intramuscular injection are pain, tenderness and muscle weakness. Serious toxicity is common if the drugs are given for more than 10 days. Side effects include nausea, vomiting, diarrhoea but also cardiotoxicity.

Of the dichloroacetamides diloxanide furoate, clefamide, teclozan and etofamide the most frequently used agent is diloxanide furoate. It is the luminal amoebicide of choice in chronic intestinal amoebiasis, however it lacks efficacy acute intestinal amoebiasis. Its mechanism of action is unknown. Given orally, diloxanide is formed by bacterial hydrolases. Diloxanide is for 90% absorbed and then metabolized to diloxanide glucuronide. The remaining 10% remains in the intestine as the active drug. Diloxanide is generally well tolerated. Adverse effects include flatulence, nausea and abdominal cramps.

The halogenated hydroxyquinolines include iodoquinol and clioquinol. Their mechanism of action is unknown. These agents can produce severe neurotoxicity and clioquinol is believed to have been responsible for the neurotoxic syndrome subacute myelo-optic neuropathy (SMON).

VI.a.2. Antimalarials

VI.a.2.1. Aminoquinolines. The aminoquinolines currently used as antimalarials include the 4-aminoquinolines chloroquine and mefloquine and the 8-aminoquinoline primaquine.

Chloroquine is a rapidly acting blood schizonticide with some gametocytocidal activity. It is used with primaquine for *Plasmodium vivax* and *Plasmodium ovale* infections. It has been widely used prophylactically by traveler's to endemic areas. Its mechanism of action is unclear. It is believed to hinder the metabolism of hemoglobin in the parasite. Presumably chloroquine prevents the formation in the plasmodia of polymers out of free heme which then builds up and becomes toxic. Resistance occurs as a consequence of the expression of a membrane phospho-glycoprotein pump in the plasmodia which is able to expel chloroquine from the parasite. *Plasmodium falciparum* is the most likely to become resistant.

Chloroquine is rapidly absorbed and widely distributed. Tissue binding, especially to melanin containing cells, and the fact that the drug is taken up in the lysosomes of cells results in an apparent volume of distribution of over 200 l/kg. Its distribution half-life is 2–6 days. Chloroquine concentrates in plasmodium-infected erythrocytes up to 500 times the plasma concentration. It is metabolized in the liver, mainly by deethylation, with an elimination half-life of 30–60 days. Chloroquine is generally well-tolerated. Adverse effects include gastrointestinal disturbances, and headache. Less frequent but more serious adverse reactions are retinopathy, myopathy and ototoxicity. Especially after large cumulative doses this latter toxicity can be irreversible. After parenteral doses hypotension and cardiac arrest have been reported. Hemolysis may occur in glucose-6-phosphate dehydrogenase (G6PD) deficient persons.

Mefloquine is also a 4-aminoquinoline. It is a blood schizonticide active against the asexual stages of all malaria parasites. Mefloquine is currently the prophylactic agent of choice for short-term travellers. Resistance of *P. falciparum* against mefloquine has occurred in South-East Asia. Only an oral

formulation of mefloquine exists because of intense local irritation with parenteral use. It is well absorbed orally and notwithstanding a high protein binding of about 98% it is distributed throughout the body. Mefloquine is metabolized in the liver and eliminated slowly, mainly in bile and faeces with an elimination half-life of 10–30 days. Adverse effects include gastrointestinal pain and other disturbances and also, sinus bradycardia. More serious are CNS effects like dizziness and vertigo and more rarely neuropsychiatric disturbances, seizures.

Primaquine, an 8-aminoquinoline derivative, is a tissue schizonticide effective against the intrahepatic forms of all human malaria parasites and their gametocytes. It eradicates latent parasites from the liver and is used for the cure of *P. vivax* and *P. ovale* infection following treatment with a blood schizonticide. It is extensively deaminated in liver to a metabolite which gains higher concentrations than the parent compound. Both the metabolite and the parent compound are active. Its adverse effects include gastrointestinal disturbances, headache and pruritus. Hemolytic anemia may occur in patients with G6PD deficiency.

VI.a.2.2. Biguanides. Proguanil is a dihydrofolate reductase inhibitor. It is a slow acting blood schizonticide and not effective on its own. It has also a marked effect on the primary tissue stages of *Plasmodium falciparum*. It is used in combination with chloroquine for the prophylaxis of chloroquine-resistant *Plasmodium falciparum*.

It is slowly absorbed orally with peak plasma levels about 4 hours after dosing. Its protein binding is about 75%. It is metabolized in the liver to its triazine metabolite, the active compound cycloguanil, with an elimination half-life of on average 16 hours, however, with a wide interindividual variation. It is excreted in urine and faeces as unchanged drug and metabolites.

Proguanil is well tolerated. Gastrointestinal and allergic reactions are rare.

Chlorproguanil-dapsone (sold commercially as Lapdap™) is a fixed dose combination pill containing chlorproguanil and dapsone, which act synergystically against falciparum malaria. Although developed in collaboration with WHO for use in Sub-Saharan Africa, it is a controversial agent because of the risks of hemolytic anemia associated with dapsone use in areas with a high prevalence of G6PD deficiency.

VI.a.2.3. Quinine alkaloids. The quinine alkaloids include quinine and quinidine. Quinidine, the dextrorotatory diastereoisomer of quinine, is mainly used for the parenteral treatment of cardiac arrhythmias but it can be an alternative antimalarial in regions where *Plasmodium falciparum* is resistant to both chloroquine and antifolate-sulfonamide combinations.

Quinine is the principal alkaloid derived from the bark of the cinchona tree. It has been used for malaria suppression for over 300 years. By 1959 it was superseded by other drugs, especially chloroquine. After widespread resistance to chloroquine became manifest quinine again became an important antimalarial. Its main uses are for the oral treatment of chloroquine-resistant falciparum malaria and for parenteral treatment of severe attacks of falciparum malaria. Quinine is a blood schizonticide with some gametocytocidal activity. It has no exoerythrocytic activity. Its mechanism of action is not well understood. It can interact with DNA, inhibiting strand separation and ultimately protein synthesis. Resistance of quinine has been increasing in South-East Asia.

Quinine is rapidly and almost completely absorbed orally with peak plasma levels after 1–3 hours. Protein binding is about 80%. It is extensively metabolized in the liver and excreted in urine with a half-life of about 11 hours which can be prolonged to up to 18 hours in malaria.

Hypersensitivity is most frequently manifested by pruritus and skin rashes. Severe drug induced immune thrombocytopenia can occur. Hemolysis may occur in patients with G6PD deficiency.

Cinchonism characterized by giddiness, headache, tinnitus with hearing deficits, nausea, diarrhoea and blurring of vision becomes manifest if serum levels exceed 10 μg/ml. Rapid intravenous administration may cause cardiotoxicity with hypotension and arrhythmias.

VI.a.2.4. Diaminopyrimidines. Pyrimethamine is a dihydrofolate reductase inhibitor, like the biguanides, and is structurally related to trimethoprim. It is seldom used alone. Pyrimethamine in fixed combinations with dapsone or sulfadoxine is used for treatment and prophylaxis of chloroquine-resistant falciparum malaria. The synergistic activities of pyrimethamine and sulfonamides are similar to those of trimethoprim/sulfonamide combinations. Resistant strains of *Plasmodium falciparum* have appeared world wide. Prophylaxis against falciparum

malaria with pyrimethamine alone is therefore not recommended. Most strains of *Plasmodium vivax* have remained sensitive. Pyrimethamine is also used in combination with a sulfonamide for the treatment of Toxoplasmosis.

It is slowly absorbed from the gastrointestinal tract with peak plasma levels 4–6 hours after dosing. Pyrimethamine is bound to plasma proteins and is extensively metabolized before excretion. Its elimination half-life is 3–5 days.

Used for malaria chemoprophylaxis and treatment the dihydrofolate reductase inhibitors do not cause pharmacological side-effects in the host. In the higher dose used for toxoplasmosis macrocytic anaemia and other adverse effects may occur.

Fansidar is the fixed dose combination of pyrimethamine with sulfadoxine. This formulation is well absorbed with peak plasma levels of the components 2–8 hours after dosing.

Sulfadoxine is excreted by the kidneys with an elimination half-life of 170 hours. Because Fansidar is only slowly active, seriously ill patients should also be treated with quinidine. Generally single dose treatments with Fansidar are well tolerated. Sulfonamide allergic reactions or reactions of the hematologic, gastrointestinal, central nervous system, dermatologic or renal systems are rare. Fansidar should not be used for continuing prophylaxis because of severe reactions including erythema multiforme, Stevens–Johnson syndrome and toxic epidermal necrolysis.

Maloprim, the fixed dose combination of pyrimethamine with dapsone, is not recommended for routine prophylaxis because of the potential for fatal agranulocytosis.

VI.a.2.5. Artemisinin and derivatives. Artemisinin is a sesquiterpene lactone endoperoxide isolated from Artemisia annua. Artemisinin and its derivatives are effective blood schizonticides against all types of malaria including chloroquine-resistant falciparum malaria. Whereas most of the antimalarials work at the late trophozoite and schizont stage of the malaria parasite, artemisinin derivatives also act already at early trophozoite stages and ring stages. Thus far no *in-vivo* resistance has been described. Characteristic for artemisinin and its derivatives is their rapid onset of action with clearance of parasites from the blood within 48 hours in most cases. A meta-analysis showed a slight survival-benefit with artemisinin drugs compared to quinine in the treatment of severe (complicated or cerebral) malaria. A disadvantage of the artemisinin drugs is the occurrence of recrudescences when given in short course monotherapy regimens. Therefore combination with a longer acting antimalarial drug is usually recommended. Artemisinin is given alongside lumefantrine to treat uncomplicated falciparum malaria. Lumefantrine has a half-life of about 3 to 6 days. Such a treatment is called ACT (artemisinin-based combination therapy); other examples are artemether–lumefantrine, artesunate–mefloquine, artesunate–amodiaquine, and artesunate–sulfadoxine–pyrimethamine. The World Health Organisation has recommended that a switch to artemisinin-based combination therapy (ACT) should be made in all countries where the malaria parasite has developed resistance to chloroquine. It has been shown that ACT is more than 90% effective, with a recovery of malaria after three days, especially for the chloroquine-resistant *Plasmodium falciparum*. In 2006 WHO called for an immediate halt to provision of single-drug artemisinin malaria pills. The term "co-artemether" is sometimes used to describe the administration of lumefantrine with artemether and this ATC was actively promoted by WHO.

The action of the artemisinin derivatives is based on an unique mechanism. Haem or Fe^{2+} in the parasite catalyzes the opening of the peroxide bridge in artemisinin, leading to the formation of free radicals which are lethal (see Fig. 1).

Artemisinin is very poorly soluble in water or oil and can thus only be administered orally. Active derivatives have been synthesized such as artemether, arteether and beta-arteether (Artemotil), artelinic acid and artesunate, which are used for oral, intramuscular, rectal and intravenous administration. Dihydroartemisinin is the active metabolite of all artemisinin compounds and is also available as a drug in itself (see Fig. 2).

Oral formulations of artemisinin and its derivatives are absorbed rapidly but incompletely. Peak plasma concentrations are reached in 1–2 h. A relative bioavailability of 43% was found for oral artemether compared to intramuscular administration. The absolute bioavailability of artesunate, the only derivative for which an intravenous formulation exists, was about 15%. Artesunate is extensively hydrolyzed to dihydroartemisinin in the gastro-intestinal lumen before first-pass metabolism in the gut wall and liver takes place. Artesunate acts like a prodrug with fast transformation into

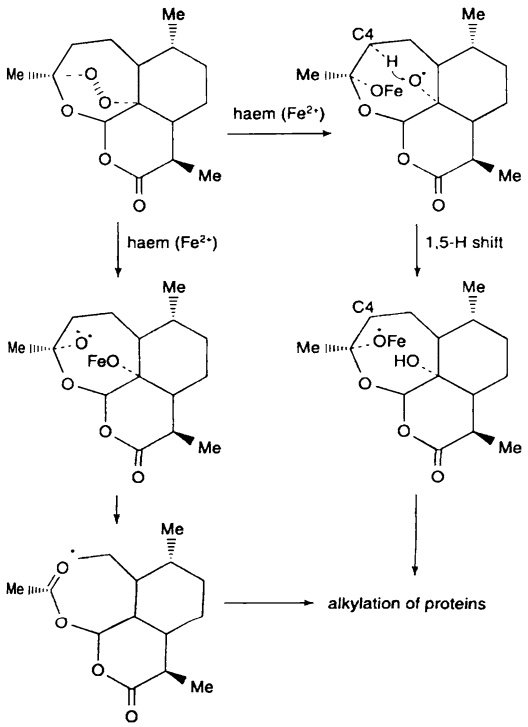


Fig. 1. Mechanism of action of artemisinin. By the reduction of the peroxide bridge two radical anions can be formed which will both lead to alkylation of proteins and parasite death. (From van Agtmael et al. Trends Pharmacol Sci 1999;20:199, reproduced with permission from Elsevier Science.)

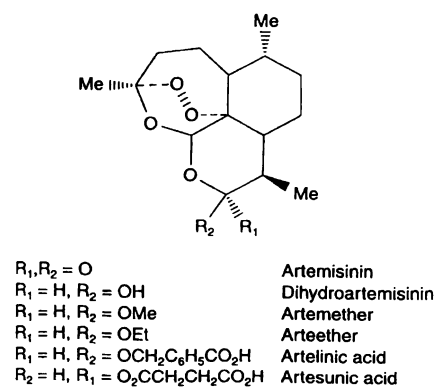


Fig. 2. Structure of artemisinin derivatives. (From van Agtmael et al. Trends Pharmacol Sci 1999;20:202, reproduced with permission from Elsevier Science.)

the also active compound dihydroartemisinin. Less dihydroartemisinin is seen after intramuscular administration of artemether than with the oral route, which suggests that dihydroartemisinin formation is subject to a first pass effect. Artusenate has an elimination half life of less than half an hour. Most compounds have short elimination half-lives of 1–3 h after oral intake. For arteether an elimination half-life of about 24 hours was found after intramuscular administration. Although the metabolic routes are not known for the artemisinin derivatives, strong suggestions were found that the enzyme CYP3A4 of the cytochrome P450 family plays a role in the first-pass elimination of artemether. In multiple dose studies of artemisinin analogues a time dependent decrease in plasma concentrations was observed which probably has to be explained by autoinduction.

Thus far no major adverse effects have been reported for artemisinin and its derivatives. Although neurotoxicity can occur in animals, it has never been reported in humans. However, subclinical cumulative neurotoxicity could occur with each treatment course for separate episodes of malaria. This possible risk prohibits the use of artemisinin drugs for malaria prophylaxis.

VI.a.2.6. Other antimalarials. Doxycycline (see Section II.b) is a useful and effective short-term prophylactic agent for travellers to chloroquine-resistant areas and can be used as an alternative when mefloquine or proguanil is unavailable or mefloquine is contraindicated. In combination with quinine also tetracycline is used as an antimalarial.

Halofantrine, a 9-phenanthrenemethanol derivative, is a blood schizonticide and is active against *Plasmodium vivax* and chloroquine sensitive as well as chloroquine resistant strains of *Plasmodium falciparum*. As no parenteral preparation is available it cannot be used for severely ill patients. Oral absorption is slow and incomplete and is increased by a fatty meal.

The major metabolite is as active as the parent drug but has a longer half-life. The elimination half-life of halofantrine is 1–2 days and of its metabolite 3–5 days.

Halofantrine is usually well tolerated. Gastrointestinal complaints as well as pruritus and skin rashes may occur. It can prolong the QTc interval which can result in ventricular dysrythmias. Lumefantrine has many similarities to halofantrine but seems not to prolong QTc. It is thus far only used in a fixed dose combination with artemether (see Section VI.a.2.5).

Quinacrine, a 9-aminoacridine, is a blood schizonticide with activity against all four types of

human malaria. It can effect radical cures of Plasmodium malariae and non resistant strains of *Plasmodium falciparum*. It is not used for prophylactic purposes. Drug deposits can color the skin yellow. Although rarely psychotic reactions can occur.

Atovaquone is a hydroxy-1,4-naphthoquinone, an analog of ubiquinone, with antipneumocystic activity. Since 2000 atovaquone is available as a fixed dose preparation (Malarone) with proguanil for the oral treatment of falciperum malaria. Its activity probably is based on a selective inhibiton of mitochondrial electron transport with consequent inhibition of pyrimidin synthesis. Malarone should not be used to treat severe malaria, when an injectable drug is needed.

VI.a.3. Agents against Trypanosomiasis and Leishmaniasis

Drugs used for trypanosomiasis include nifurtimox, suramin, melarsoprol and pentamidine. The first choice agent for treating leishmaniasis is sodium stibogluconate. Alternatives are amphotericin B (see Section V.a) and pentamidine.

Nifurtimox, a nitrofuran derivative, has been found to be a potent inhibitor of trypanothione reductase, an enzyme found only in the parasite. It is active against intracellular amastigotes as well as against the trypomastigotes. Nifurtimox has been used to treat Chagas disease. Since the drug causes oxidative stress its use should be avoided in cases of glucose-6-phosphate dehydrogenase deficiency. Nifurtimox has also been used to treat African sleeping sickness. Unfortunately, when nifurtimox is given on its own, about half of all patients will relapse, but the combination of melarsoprol with nifurtimox appears to be efficacious.

Suramin is a non-specific inhibitor of many enzymes. Suramin can only be given intravenously. Toxic reactions are frequent and sometimes severe, including gastrointestinal complaints, nephrotoxicity, peripheral neuritis and exfoliative dermatitis.

Melarsoprol is a trivalent arsenical. It reacts with sulfhydryl groups. Melarsoprol is used for the late stage of sleeping sickness. It has to be administered intravenously. Slow i.v. injection is recommended. It is widely distributed and enters the CNS. It has a very short elimination half-life as it is biotransformed to a pentavalent arsenical. Adverse effects include hypersensitivity reactions and gastrointestinal toxicity causing severe vomiting and abdominal pain. CNS reactions are most serious as the encephalopathy may be fatal. Hemolytic anemia may be seen in patients with glucose-6-phosphate dehydrogenase deficiency.

Sodium stibogluconate is a pentavalent antimonial compound. It is a prodrug as the pentavalent antimonial has to be reduced to a trivalent antimony compound. Sodium stibogluconate is used to treat leishmaniasis and is only available for administration by injection. It is excreted in the urine. In general it is tolerated fairly well. Adverse effects include pain at the injection site and gastrointestinal complaints. Cardiac arrhythmias can occur and renal and hepatic function should be monitored.

Pentamidine is an aromatic diamidine sometimes used to treat sleeping sickness and leishmaniasis. It has activity against the hematologic stage of *Trypanosoma brucei gambiense* and is used for prevention and treatment of sleeping sickness in combination with suramin. It is not active against *Trypanosoma cruzi*. Its most important indication is the prevention and treatment of pneumocystis carinii infections in patients for whom co-trimoxazole is contraindicated where it is administered as an aerosol and has low toxicity. It is taken up by an energy dependent high-affinity system. It may act as a type II topoisomerase inhibitor but also interferes with polyamine biosynthesis. Pentamidine is administered intramuscularly. Intravenous administration is not recommended as it may induce shock by histamine release. The drug concentrates in the liver, spleen and kidneys from where it is slowly released and excreted via the kidneys for months. Only trace amounts enter the CNS.

Pentamidine can cause serious renal toxicity and is toxic to pancreatic beta-cells. Its adverse reactions further include hypotension, dizziness and rashes. After inhalation bronchoconstriction can occur.

VII. ANTHELMINTICS

VII.a. Antitrematodals

VII.a.1. Quinoline Derivatives

Praziquantel is the agent of choice against all trematodes apart from *Fasciola hepatica* where bithionol is the drug of first choice. It is also an anticestodal agent and, as also niclosamide, is a first choice drug for intestinal tapeworm infestations by *Taenia solum* (pork tapeworm), *Taenia saginata* (beef tapeworm), *Taenia latum* (fish tapeworm) and *Hymenolepis nana* (dwarf tapeworm) and it is a second choice drug af-

ter albendazole for cysticercosis caused by *Taenia solum* (see Table 2).

The mechanism of action of praziquantel is based on the induction of contraction with consequent paralysis of helminths by increasing permeability of the helminthic cell membrane for calcium. In susceptible parasites it will also lead to vacuolization and disintegration. It is readily absorbed and then hydroxylated and conjugated in the liver with an elimination half-life of 1–1.5 hours.

The adverse effects are usually mild and transient. Frequent reactions include non-specific gastroin-

Table 2. Drugs used in helminthic diseases

Helmints	Drugs of first choice	Alternatives
Nematodes		
Ascaris lumbricoides (round worm)	Albendazole or mebendazole or pyrantel	Piperazine
Enterobius vermicularis (pinworm, threadworm)	Albenzdazole or mebendazole or pyrantel	Piperazine
Trichuris trichiura (whipworm)	Mebendazole	Albendazole
Ancylostoma duodenale *Necator americanus* (hookworms)	Albendazole or mebendazole or pyrantel	
Strongyloides stercoralis	Thiabendazole	Albendazole Mebendazole
Ancylostoma braziliense (cutaneous larva migrans)	Thiabendazole	Albendazole
Toxocara canis/cati (visceral larva migrans)	Diethylcarbamazine or thiabendazole	Mebendazole
Wuchereria brancofti	Diethylcarbamazine	
Brugia malayi	Diethylcarbamazine	
Loa loa	Diethylcarbamazine	
Onchocerca volvulus (filarial infections)	Ivermectin	
Trematodes		
Schistosoma haematobium	Praziquantel	Metriphonate
Schistosoma mansoni (bilharzia)	Praziquantel	Oxamniquine
Cestodes		
Taenia saginata (beef tapeworm)	Niclosamide or praziquantel	Albendazole or mebendazole
Taenia solium (pork tapeworm)	Niclosamide or praziquantel	Albendazole or mebendazole
Cysticercosis (pork tapeworm larval stage)	Praziquantel or albendazole	
Diphyllobothrium latum (fish tapeworm)	Niclosamide or praziquantel	
Hymenolepsis nana (dwarf tapeworm)	Praziquantel	Niclosamide
Echinococcus granulosis	(Surgery)	
Echinococcus muiltilocularis (hydatid disease)	Albendazole	Mebendazole

From Katzung (1997), *Basic and Clinical Pharmacology*, reproduced with permission from McGraw-Hill.

testinal disturbances, headache, dizziness and general malaise. Less frequent are urticaria, eosinophilia and arthralgia.

Oxamniquine is a second choice agent against *Schistosoma mansoni*. It is ineffective against other Schistosoma species. It shows activity against both the early developmental as well as the mature stages of *Schistosoma mansoni*. Its mode of action is not well understood.

Its absorption is delayed by food. It is extensively metabolized with an elimination half-life of 1–2.5 hours. Its adverse effects include transient dizziness, headache, nausea and diarrhoea.

Less frequent are skin rashes, fever, hallucinations and convulsions.

VII.a.2. Organophosphorus Compounds

Metrifonate is an alternative for treatment and prophylaxis of schistosomiasis caused by *Schistosoma haematobium*. It is a prodrug and has to be activated to dichlorvos. Its mechanism of action is not clear but is thought to be related to its function as a long-acting irreversible cholinesterase inhibitor. Metrifonate is well absorbed orally with peak levels 1–2 hours after dosing. It is eliminated via its nonenzymatic transformation to dichlorvos with an elimination half-life of 1.2 hours. Metrifonate is generally well tolerated. Some mild cholinergic symptoms such as nausea and bronchospasm may occur. Plasma cholinesterase activity is rapidly depressed and may need several weeks to return to normal. It is therefore strongly advised, at least during the first 48 after treatment not to use depolarizing neuromuscular blocking agents. Its potential to enhance central nervous system cholinergic neurotransmission led to clinical trials for the treatment of people with Alzheimer's disease. However due to neuromuscular dysfunction with life-threatening respiratory failure and death its further development for this indication was stopped in 1999.

VII.b. Antinematodal Agents

VII.b.1. Benzimidazole Derivatives

Mebendazole is a broad spectrum anthelmintic and of special use for mixed worm infestations. Its mechanism of action is based on inhibition of microtubule synthesis and decreased transport of vesicles and organelles thus irreversibly blocking glucose uptake.

About 5–10% is absorbed orally but systemic bioavailability is even less because of first-pass metabolism in the liver. For extraintestinal infections absorption can be markedly increased by fatty meals. It is metabolized, mainly in the liver with an elimination half-life of 2–9 hours in patients with impaired liver function this half-life can increase considerably.

Adverse effects are very rarely seen after doses needed for antinematodal effects. Some nausea and diarrhoea may occur. After the high doses which are needed for hydatid disease skin rashes, renal toxicity and blood dyscrasias are reported.

Albendazole has an even broader spectrum of activity than mebendazole. Its indications include pinworm infection, ascariasis, trichuriasis, strongyloidiasis and hookworm infections. It is the preferred agent for inoperable cases of hydatid disease.

Albendazole selectively blocks glucose uptake and depletes glycogen stores. ATP formation is thus inhibited. It should be administered on an empty stomach for intraluminal parasites and with a fatty meal for tissue parasites. It is metabolized to an active sulfoxide metabolite resulting in very low Albendazole blood levels. Albendazole sulfoxide is excreted in the urine with an elimination half-life of about 8 h. Used for 1–3 days in doses recommended for intestinal worms the incidence of adverse effects is similar in treatment and control groups. Hepatotoxicity may occur, especially after the higher doses that are needed for hydatid disease. Also alopecia has been reported.

Tiabendazole is the drug of choice against strongyloidiasis and cutaneous larva migrans. It also has shown efficacy in the therapy of visceral larva migrans. The action of tiabendazole is based on blocking microtubule synthesis. It may also interfere with sources of energy in the parasite by inhibiting fumarate reductase in susceptible helminths. It is rapidly and almost completely absorbed after oral administration. It is metabolized in the liver with an elimination half-life of 1–2 hours.

Frequently occurring adverse events are anorexia, nausea, vomiting and dizziness.

Less frequent are skin rashes, tinnitus and liver function disturbances. Erythema multiforme and Stevens–Johnson syndrome have been reported.

VII.b.2. Piperazine and Related Agents

A large number of piperazine compounds have anthelmintic action. Piperazine itself is available as the hexahydrate and as various salts. It is used in ascariasis. Pinworm infection is no longer considered an indication. Piperazine acts as a GABA agonist, blocking acetylcholine at myoneural junctions causing paralysis of *Ascaris*. It has hardly any pharmacological activity in the host.

Oral doses of piperazine are readily absorbed with peak plasma levels 2–4 hours after dosing. The drug is excreted in the urine with an elimination half-life of about 3 hours. However large interindividual differences were found for the excretion rate of both unchanged drug and its metabolites.

Dose-related adverse effects are generally rare and include mild gastrointestinal complaints. Some neurotoxicity is mostly seen in children. Hypersensitivity reactions can occur.

Diethylcarbamazine is an anthelmintic drug that does not resemble other antiparasitic compounds although it has some relationship with piperazine derivatives and it has been useful in the management of filariasis due to *Wuchereria bancrofti* or *Brugia malayi* and *Loa loa* and of tropical eosinophilia. It is a lipoxygenase inhibitor and alters the surface structure of the parasite making it more susceptible to destruction by the host. It is well absorbed and widely distributed. It is eliminated with an half-life of 5–13 hours both by metabolism and excretion unchanged in the urine.

It is generally well tolerated although prolonged use may lead to ocular damage.

When used for the treatment of onchocerciasis a potentially fatal 'Mazotti' reaction may occur, with severe skin reactions, tachycardia, hypotension and fever.

VII.b.3. Tetrahydropyrimidine Derivatives

Pyrantel is a drug of first choice for the treatment of a number of round-, thread- and hookworm infestations. However, it has no activity against whipworm. Its mechanism of action is based on triggering the release of acetylcholine in helminths causing a depolarizing neuromuscular blockade that leads to spastic paralysis.

It is poorly absorbed from the gastrointestinal tract and is therefore mainly useful for treatment of luminal intestinal infections. It is mainly excreted unchanged in faeces and not more than 15% of the dose is excreted in the urine, either as unchanged drug or in the form of metabolites.

Its adverse effects are mild and may include gastrointestinal distress, drowsiness, headache, rashes and fever.

VII.b.4. Other Antinematodal Agents

Ivermectin, a semisynthetic macrocyclic lactone, is a mixture of avermectin B_{1a} and avermectin B_{1b}. It acts on chloride channels associated with GABA receptors and amplifies GABA functions paralyzing the nematode. Although its spectrum of activity is rather broad it is only considered as drug of first choice in onchocerciasis. It is then given in single oral doses according to body weight. It is well absorbed reaching peak plasma levels after 4–5 hours. It is excreted in the feces with an elimination half-life of about 24 hours. Ivermectin has no pharmacological effects in humans and it does not cross the blood–brain barrier.

Levamisole (see Chapter 26, Section III.e and Chapter 28, Section III) is an imidazothiazole derivative and the L isomer of D,L-tetramisole. It has activity against *Ascaris* and *Trichostrongylus* but is mainly used for its immunomodulating effects in Rheumatoid Arthritis and as adjunct therapy in some anti-cancer regimens.

VII.c. Anticestodals

Agents used in the treatment of cestodal infections include praziquantel (see Section VII.a.1), niclosamide and the benzimidazoles such as albendazole and mebendazole (see Section VII.b.1). Niclosamide and praziquantel are effective against *Taenia solum* (pork tapeworm), *Taenia saginata* (beef tapeworm), *Taenia latum* (fish tapeworm) and *Hymenolepis nana* (dwarf tapeworm). Praziquantel is a second choice drug after albendazole for cysticercosis caused by *Taenia solum*. Albendazole and mebendazole are alternatives.

Niclosamide is a salicylamide derivative. Its mechanism of action could be based on inhibition of oxidative phosphorylation or on its ATPase stimulating action. The scolices and segments, but not segments of the ova, are rapidly killed. Niclosamide is minimally absorbed from the gastrointestinal tract and excreted, mostly unchanged, in the faeces. It is generally well tolerated with occasional gastrointestinal disturbances. Skin eruptions have been reported.

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Chapter 26

Analgesics, Antirheumatics and Drugs for the Treatment of Gout[1]

Chris J. van Boxtel

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III. Disease modifying antirheumatic drugs (DMARDs) 440
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I. OPIOID ANALGESICS

I.a. Introduction

The Greek word opium refers to the active ingredients extracted from the juice of the poppy, *Papaver somniferum* and opiates are those drugs derived from opium. On the other hand all exogenous substances, natural or synthetic, that have morphine like properties are called opioids. Endogenous opioids are the enkephalins, endorphins and dynorphins. The word narcotic comes from the Greek word for stupor and is often interchangeably used with opiate. The legal term narcotic refers to any dependence inducing substance.

Opioids are used for the management of both acute and chronic pain. However, in addition to pain relieve, opioids have a wide variety of other effects. Some of these side effects can be particularly harmful, such as respiratory depression and the induction of dependency. Gastrointestinal effects like obstipation, nausea and vomiting can limit their use.

I.b. Opioid Receptors

Opioid receptors are found in the dorsal horn as well as in other areas throughout the spinal cord and brain. Three major classes of opioid receptors exist: mu receptors (μ), kappa receptors (κ) and delta receptors (δ), nowadays also called OP3, OP2 and OP1 receptors respectively. Most opioids bind to the μ-opioid receptor, of which there are three subtypes: $\mu 1$ receptors are responsible for analgesia and $\mu 2$ receptors for respiratory depression, bradycardia, and inhibition of gastrointestinal motility. Stimulation of the κ receptors, $\kappa 1$, $\kappa 2$ and $\kappa 3$, also produces analgesia. These receptors are also mainly located in the spinal cord. Agonists for these receptors produce less miosis and respiratory depression (see Table 1). Stimulation of δ receptors, $\delta 1$ and $\delta 2$, leads to analgesia, euphoria and physical dependence.

Next to these three classical receptor families a additional opioid receptor has been identified. This receptor is known as the nociceptin receptor or ORL 1 receptor. Its natural ligand is known

Table 1. Main responses of the two best-characterized opioid receptor subtypes

Response	Receptor	
	μ	κ
Analgesia	Supraspinal	Spinal
Respiration	Depression	Depression?
Behavior	Euphoria	Sedation, dysphoria
Pupil	Miosis	Miosis?
Morphine withdrawal	Abstinence syndrome	No effect
Antagonized by naloxone	Yes	Yes

[1] For agents used in the therapy of migraine see Chapter 19, Section II.a.

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Table 2. Agonists, antagonists and partial agonists for the various opioid receptors

Opioid	Receptor		
	μ	κ	δ
Morphine	Ag	Ag	Ag
Naloxone	Ant	Ant	Ant
Nalorphine	Ant	Ag	–
Pentazocine	pAg	Ag	–
Buprenorphine, dezocine	pAg	Ant	–

Ag = full agonist, pAg = partial agonist, Ant = antagonist.

alternately as nociceptin. The relatively new drug buprenorphine, a partial agonist at μ receptors and a antagonist at κ receptors, is also a partial agonist at ORL 1 receptors while its metabolite norbuprenorphine is a full agonist at these receptors.

Agonists as well as antagonists, agonist-antagonists and partial agonists for the various opioid receptors exist (see Table 2). Antagonists have no effect when given to individuals not exposed to an opioid. They will antagonize all effects of morphine-like opioids and in opioid dependent subjects they can precipitate a severe abstinence syndrome. Examples are naloxone, naltrexone and nalmefene.

Agonist-antagonists have analgesic effects but will precipitate withdrawal in dependent subjects. Nalorphine, cyclazocine and nalbuphine are competitive μ antagonists and agonists at κ receptors. Partial agonists have less efficacy than full agonists and have less abuse potential. As already said, buprenorphine is a partial μ agonist and also a κ-opioid receptor antagonist. Pentazocine is partial μ agonist with full κ-agonist activity and thus can produce dysphoria and withdrawal symptoms in dependent subjects.

Mainly on the basis of affinity differences opioid analgesics may be usefully classified as weak acting, e.g. codeine and detropropoxyphene, intermediate acting agents like dipipanone, dihydrocodeine and tilidine, and the strong acting opioids like morphine and related agents like buprenorphine, dextromoramide, hydromorphone, methadone, nicomorphine, oxycodon, meperidine and piritramide. It should be noted here that in most countries the prescription of dextromoramide is avoided due to its abuse potential and its use is mainly limited to terminal care. Many countries have put severe limits on the use of meperidine or curtailed it outright due to its toxicity. By 2006 dextropropoxyphene, especially in combination products, was taken of the market in several European countries because of unacceptable mortality rates.

I.c. Morphine and Related Opioid Agonists

CNS effects include decreased pain perception, altered reaction to pain, euphoria and hypnosis, nausea and vomiting, respiratory depression and suppression of cough reflexes. Increased tone of the gastrointestinal tract is primarily mediated by μ receptors in the bowel.

Opioids can be administered orally, rectally, parenterally as well as intrathecally and into the epidural space. Also formulations for dermal administration exist. Most opioids are rapidly metabolized in the liver. The lower the rate of hepatic metabolism, the more effective oral doses will be. Morphine is rapidly metabolized and 3–6 times higher doses are required orally compared to i.v. doses. On the other hand, methadone is only slowly metabolized and oral doses are almost as effective as parenteral doses. Lipid solubility determines the rate at which an opioid crosses the blood–brain barrier. Drugs that enter the brain very rapidly, such as the lipid soluble diacetylmorphine (heroin) and its metabolite 6-monoacetylmorphine (6-MAM), produce a more intense state of euphoria and are more prone to be addictive. Both active and toxic metabolites can be formed. Morphine-6-glucuronide, although it has more difficulties to cross the blood–brain barrier, is still more active than morphine itself and contributes towards its effects. As the glucuronide is eliminated by the kidney dangerous accumulation can occur in patients with impaired renal function. Morphine-6-glucuronide may also accumulate during repeated administration of codeine to patients with impaired renal function. Accumulation of normeperidine, a metabolic demethylation product of meperidine (synonym is pethidine) may cause seizures and the repeated administration of dextropropoxyphene may lead to naloxone-insensitive cardiac toxicity caused by the accumulation of norpropoxyphene.

The opium alkaloid morphine is representative for this group of opiates and also for other opioid analgesics. Morphine is a full agonist for both the μ and the κ receptors. It is used to relieve severe acute pain, or chronic pain in terminally ill patients. Its oral bioavailability varies from 15% to 35% and its

elimination half-life is between 2 and 3 hours. Analgesic effects occur within 20 minutes (parenterally) and last some 4–5 hours.

As for all opioids common adverse effects are constipation, slowed gastric emptying and biliary spasm. Urinary retention may occur. There is an increased risk of respiratory depression in young children and in the elderly. Allergic reactions are rare, but wheals and pain at the injection site due to histamine release may occur. CNS depressants will potentiate the depressant effects of morphine and that of other opioids.

The most important other opium alkaloid is codeine. In contrast to morphine, codeine has a high oral–parenteral potency ratio due to less first-pass metabolism. Codeine is considered a prodrug, since it is metabolised *in vivo* to the primary active compounds morphine and codeine-6-glucuronide. Approximately 10% is demethylated to morphine. The analgesic effect of codeine is due to the formation of these metabolites as codeine itself has a very low affinity for opioid receptors. The half-life of codeine in plasma is 2–4 hours.

Many synthetic or semisynthetic opioids have been developed, all with various advantages and disadvantages. Meperidine is sometimes preferred over morphine since it is less spasmogenic, in biliary, bowel or ureteric colic. However the dangers of its toxic metabolite have already been pointed out. Dipipanone, dihydrocodeine and tilidine are between the high-potency and the low-potency groups and could be considered before resorting to stronger agents. As already mentioned buprenorphine and also nalbuphine have lower abuse and dependency potential, as well as less respiratory depressant potential. Pentazocine has an intermediate potency. However pentazocine has a tendency to raise pulmonary blood pressure and its complex interactions with the various opioid receptors make its effects less predictable. Fentanyl, remifentanil, alfentanil and sufentanil are mainly used as intra-operative analgesics. Fentanyl patches for dermal administration are used for chronic pain.

I.d. Opioid Antagonists

Small changes in molecular structure can reverse agonist actions of an opioid into antagonistic activity for one or several opioid receptors. Sometimes a molecule is produced that is an competitive antagonists at μ receptors but an agonist for κ receptors. Nalorphine and levallorphan are examples. For example in patients with postoperative pain the analgesic effects of 10 mg of nalorphine is about the same as 10 mg of morphine. On the other hand naloxone and naltrexone seem to have no agonistic activity and some antagonistic affinity for all types of opioid receptors. Although antagonists could be expected to have effects by altering the actions of endogenous opioid peptides mostly such effects are not discernable.

Opioid antagonists can be useful for the diagnosis of opioid dependence and as therapeutic agents in the treatment of compulsive users of opioids. Naloxone is a drug used to counter the effects of opioid overdose while naltrexone and nalmefene are used in dependence treatment. Compared with naloxone, oral doses of naltrexone are more active and it has a much longer duration of action. Advantages of nalmefene relative to naltrexone include longer half-life and a greater oral bioavailability.

II. NSAIDS AND MISCELLANEOUS AGENTS

The first generation of nonsteroidal antiinflammatory drugs (NSAIDs) available on the market inhibit prostaglandin synthesis by inhibiting both cyclooxygenase 1 (COX-1) as well as cyclooxygenase 2 (COX-2). The effects produced by local or parenteral injections of small amounts of prostaglandins are very similar to those of inflammation. Prostaglandin E2 (PGE2) and prostacyclin (PGI2) cause erythema by an increase in local blood flow. It is important to realize that COX-2 is induced 10–80 fold in inflammatory conditions and it is therefore believed that the inhibition of COX-2 is mainly responsible for the antipyretic, analgesic, and antiinflammatory action of NSAIDs. The simultaneous inhibition of COX-1 results in unwanted side effects, such as gastric ulcers and renal toxicity, that result from decreased prostaglandin and thromboxane formation.

While aspirin is equipotent at inhibiting COX-2 and COX-1 enzymes *in vitro* and ibuprofen demonstrates a sevenfold greater inhibition of COX-1, other NSAIDs appear to have partial COX-2 specificity, particularly meloxicam. A search for COX-2-specific inhibitors resulted in promising candidates such as valdecoxib, celecoxib and rofecoxib. A 30–300 higher potency for inhibiting COX-2, than COX-1, suggested the possibility of relief from pain

and inflammation, without gastrointestinal irritation. Celecoxib and rofecoxib were introduced in 1999 and rapidly became the most frequently prescribed new drugs in the United States. Two large trials, the CLASS study for celecoxib and the VIGOR study for rofecoxib, concluded in 2000 that COX-2 specific NSAIDs were associated with significantly fewer adverse gastrointestinal effects. However in 2002 it was published that adequate analysis of the CLASS trial indicated that selective COX-2 inhibitors are not superior to traditional non-steroidal anti-inflammatory drugs in this respect. In 2004 rofecoxib was withdrawn voluntarily from the market, due to an increased risk of myocardial infarction and stroke. In 2005 valdecoxib was also removed from the market due to concerns about possible increased risk of heart attack and stroke. Etoricoxib is approved in more than 60 countries worldwide but in 2007 the FDA asked the manufacturer to provide more test results showing that the drug's benefits outweigh its risks. In 2006 lumiracoxib received marketing approval for all European Union countries but as of 2007, the FDA has not yet granted approval for its sale in the US. At present it is unclear whether the cardiovascular adverse effects are really a class effect. However, regulatory authorities worldwide now require warnings about cardiovascular risk of COX-2 inhibitors still on the market. Although this story probably has not ended yet, for the moment one could conclude that the benefits of COX-2 specific NSAIDs are not substantiated and that the risks could be prohibitive.

Most of the NSAIDs are organic acids but they form a heterogeneous group of compounds with few further chemical relationships. At least 10 different groups can be distinguished. Some of the most frequently used groups are listed in Table 3. The prototype is aspirin and therefore the term aspirin-like drugs is frequently used.

Apart from their anti-inflammatory activity the NSAIDs also show, dependent on the condition and the type of pain, considerable analgesic efficacy. In some forms of postoperative pain the NSAID's can be as efficacious as opioids, especially when prostaglandins, bradykinin and histamine, which are released by inflammation, have caused sensitization of pain receptors to normally painless stimuli. In Table 4 some advantages and disadvantages of NSAID's and opioids are compared. Although analgesic effects at peripheral or central neurons cannot be excluded completely, most studies indicate that

Table 3. Chemical classification of some of the most frequently used groups of NSAIDs

Salicylates	
Acetylated	Aspirin
Non-acetylated	Diflunisal
	Choline salicylate
	Choline-magnesium trisalicylate
	Sodium salicylate
	Salsalate
	Magnesium salicylate
Acetic acid derivatives	Indomethacin
	Sulindac
	Toletin
	Etodolac
	Diclofenac
Propionic acids	Fenoprofen
	Flurbiprofen
	Ibuprofen
	Carprofen
	Naproxen
	Oxaprozin
Enolic acids	Piroxicam
	Meloxicam
	Tenoxicam
Pyrazolon derivatives	Phenylbutazone
	Oxyphenbutazone
Fenamic acids	Meclofenamate
Non-acidic compounds	Nabumetone

the analgesic effects of NSAIDs are also the result of inhibition of prostaglandin synthesis. As it is well known that PGE2, by increasing cyclic AMP, stimulates the hypothalamus to rise body temperature also the antipyretic action of NSAID's can be explained by prostaglandin synthesis inhibition.

All NSAIDs except aspirin inhibit cyclooxygenase reversibly. Inhibition by aspirin, caused by the covalent acetylation of the enzyme, is irreversible. In platelets most NSAIDs block thromboxane synthesis more than that of prostacyclin and the overall effect is therefore inhibition of platelet aggregation. This effect is already noticeable at low doses. Because of the irreversible nature of the enzyme inhibition by aspirin and the fact that in platelets the novo enzyme synthesis is not possible the aggregation inhibitory effects of aspirin last several days.

NSAIDs share several unwanted side effects. The most notorious is the risk for serious adverse gastrointestinal events including gastric or intestinal ulceration. For gastrointestinal bleeding associated

Table 4. Comparison of some advantages and disadvantages of NSAIDs and opioids

Analgesic	Advantages	Disadvantages
Opioid	All levels of pain intensity	Drowsiness Tolerance
	Best for sharp intense pain	Physical dependence Euphoria (abuse) Respiratory depression
Non-opioid	Best for dull throbbing pain due to inflammation	Only mild to moderate pain

with the use of NSAIDs a relative risk of 10 has been estimated. And the attributable fraction of this risk among exposed cases is 90%. Two mechanisms can be held responsible: a local erosive action of orally administered agents and inhibition of the biosynthesis of the cytoprotective prostaglandins PGI2 and PGE2 in the gastric mucosa.

Due to inhibition of PGE2 and prostacyclin synthesis, both of which help to maintain kidney blood-flow, NSAIDs have the potential for nephrotoxicity. They may promote aldosterone release and therefor have a tendency for increased water retention. Hypersensitivity presenting itself as rashes, urticaria or bronchoconstriction, is seen in up to 15% of patients and then often shows cross-reactivity between all of the NSAIDs as a group. It probably is a form of pseudo allergy and not an immune response. It may be due to activation of the lipoxygenase pathway for the metabolism of arachidonic acid, resulting in the accumulation of leukotrienes LTC4, LTD4 and LTE4. Anaphylaxis, although rare, can occur. Hepatotoxicity has been explained by glucuronidation of carboxylic acid moieties and the formation of reactive carboxy-glucuronidate metabolites. It has to be appreciated that this mechanism differs from that of the liver necrosis that will result from overdoses of paracetamol.

Apart from the salicylates NSAIDs include several classes of weak acids like propionic acid derivatives such as ibuprofen, carprofen, fenbufen, fenoprofen, flurbiprofen, ketorolac, loxoprofen, naproxen, oxaprozin, tiaprofenic acid and suprofen. Phenylbutazone is the most important representative of the pyrazolon derivatives which have a bad reputation for their risk of potentially fatal bone-marrow toxicity. To the acetic acid derivatives belong indomethacin, diclofenac and sulindac. Sulindac is a pro-drug with less toxicity than indomethacin. The enolic acids include piroxicam, droxicam and tenoxicam. Meloxicam is an analog of piroxicam and has a high selectivity for COX-2.

II.a. Salicylates

The salicylates, with acetylsalicylic acid, i.e. aspirin, as its best known representative, is the oldest group of NSAIDs. Aspirin is a weak acid with a pKa of 3.5 and its absorption is favored by a low pH. It is hydrolyzed to salicylic acid in the liver which is then conjugated with glucuronic acid and glycine and excreted in the urine. At high anti-inflammatory doses, its elimination half-life is increased from 2 to 3 hours to about 12 hours. It is mainly used as an antipyretic, for pain relieve and for prophylaxis against myocardial infarctions. Tinnitus is often a first sign of toxicity later followed by, nausea, vomiting, dizziness and confusion. Children are especially sensitive for life threatening salicylate toxicity which is characterized by metabolic acidosis compensated by hyperventilation.

Aspirin is epidemiologically associated with Reye's syndrome, a rare but often fatal consequence of infection with varicella, influenza and various other viruses, and salicylates are therefore contraindicated in children with chicken pox or influenza.

Carbasalate calcium is a platelet aggregation inhibitor. It is a mixture of calcium acetylsalicylate and urea.

II.b. Paracetamol

Paracetamol, synonym acetaminophen, is world wide probably the most popular analgesic and antipyretic. Its mechanism of action is not well understood. It is not really an NSAID as it is only a very weak inhibitor of cyclo-oxygenase and has hardly any anti-inflammatory activity. For the same reason paracetamol gives only negligible gastrointestinal irritation and gives hardly any blockade of platelet aggregation. Paracetamol concentrations in plasma reach a peak in 30–60 minutes, and the half-life in plasma is about 2 hours. Almost 100% of

the drug is excreted in the urine, conjugated mainly with glucuronic and sulfuric acid. A small fraction, approximately 5% of the dose undergoes cytochrome P450 (Cyp-2E1)-mediated hydroxylation to form a highly reactive free-radical. This metabolic product is responsible for the often fatal paracetamol hepatotoxicity with overdose, when stores of reduced glutathione as free radical scavenger are depleted. Chronic alcohol consumption increases the levels of CYP-2E1 and at the same time depletes body stores of NADPH, a co-enzyme for glutathione reductase which normally reduces glutathione in the liver. Alcohol abuse therefor considerably increases the risks for paracetamol hepatotoxicity.

II.c. Miscellaneous Agents Used for Pain Relieve

Ziconotide is a non-opioid, non-NSAID, non-local anesthetic used for the amelioration of chronic pain. In December 2004 the FDA approved ziconotide for intrathecal administration. The drug is derived from a marine snail toxin. Its mechanism of action has not yet been elucidated. Due to serious side effects or lack of efficacy when delivered through more conventional routes ziconotide must be administered intrathecally. It's use is considered appropriate only for management of severe chronic pain in patients for whom intrathecal therapy is indicated.

Capsaicin acts by interfering with substance P, which enhances the pain of inflammation. Elevated concentrations of substance P are found in areas of nociceptive stimulation. Topical application of capsaicin causes the release and depletion of substance P in C fibers. This mechanism limits the use of capsaicin to areas of localized pain.

Tramadol is a central-acting analgesic, effective for mild to moderate acute and chronic pain. It impairs nociception by a unique mechanism that is not completely understood. In animal models, it binds to the μ opioid receptor and is a weak inhibitor of serotonin and norepinephrine reuptake, actions similar to those ascribed to the SSRIs and TCAs. Seizures have been reported in patients taking tramadol. Abuse potential is low, but does exist.

Baclofen, labeled as a skeletal muscle relaxant binds to GABA receptors and depresses excitation. It is also useful in the treatment of paroxysms of trigeminal neuralgia. Baclofen is effective in patients with carbamazepine-resistant pain and has been used successfully to relieve attacks in patients previously unresponsive to carbamazepine or phenytoin.

The benzodiazepines bind to a specific GABA receptor site to affect mood, spasticity, seizures and sleep. The benzodiazepines are reported to be effective in certain chronic pain syndromes characterized by muscle spasm, concomitant chronic pain and anxiety.

Antiepileptic drugs as a class have been widely studied and prescribed for the relief of acute and chronic pain. In general, there is the greatest support for the efficacy of antiepileptics in the treatment of trigeminal neuralgia and diabetic neuropathy and for migraine prophylaxis.

Tricyclic antidepressants are used for treatment of chronic pain. The mechanism of action supposedly is related to their activity at the sodium channel. It also is hypothesized that tricyclic antidepressants affect norepinephrine release and, possibly, serotonin release, thereby altering spinothalamic transmission of pain. However patients who require higher doses often find that the pain relief obtained is not adequate to justify the adverse effects.

Selective serotonin reuptake inhibitors have not been well studied in patients with chronic pain, nor has the role of serotonin been elucidated. However some clinical experience suggests that the perception of pain is diminished with selective serotonin reuptake inhibitors.

III. DISEASE MODIFYING ANTIRHEUMATIC DRUGS (DMARDS)

Most often Rheumatoid Arthritis (RA) can be managed with NSAIDs alone. However a minority of patients needs second-line medications, also called slow-acting or disease modifying drugs (DMARDs). These agents generally belong to much more toxic groups of compounds such as gold salts, chloroquine and hydroxychloroquine, penicillamine, adrenocorticosteroids (see Chapter 24), and other immunosuppressives, especially methotrexate (see Chapter 28). Frequently also sulfasalazine (see Chapter 23) is used for this purpose. A new group of agents is added to this category, the so-called biologicals or biological-DMARDs. These biological-DMARDs include infliximab, etanercept, adalimumab, anakinra and abatacept.

DMARDs seldom induce complete remission and relapses frequently occur. However, oral combina-

tions of DMARDs generate better outcomes compared to single drug therapy. Their use is associated with a high rate of adverse effects and consequently discontinuation with long-term therapy. However there is a tendency to use these agents earlier than in the past, because the maximal damage occurs in the first 2 years of the disease.

III.a. Gold Compounds

Gold compounds reduce symptoms and may slow the progression of articular destruction. Members of this group are auranofin, aurothioglucose, disodium aurothiomalate, sodium aurothiosulfate and sodium aurothiomalate. Preparations of gold are all compounds in which the gold is attached to sulfur. The more water-soluble formulations, of which aurothioglucose and aurothiomalate are examples, are used for parenteral administration. Auranofin is available for oral administration. However, the accumulation of gold in target tissues during treatment with auranofin is much less than with the injectable preparations and there are indications that auranofin is less effective. Gold compounds are rather rapidly absorbed after intramuscular injection and more slowly if suspended in oil. Plasma protein binding is high. The pharmacokinetic behavior is dose and time dependent. During therapy the elimination half-life increases from several days to more than two months. After continued therapy considerable deposits can be detected in the synovium of affected joints. The mechanism of action is unknown although alteration of macrophage function and inhibition of lysosomal enzymes are considered to play a role.

Adverse effects resulting from gold-accumulation in tissues can include lesions of the mucous membranes, skin eruptions varying from erythema to severe exfoliative dermatitis, proteinuria and nephrosis. A serious hematologic reaction is aplastic anemia. A rather high incidence of gastrointestinal disturbances is seen in patients on auranofin.

Combination with penicillamine is contraindicated as penicillamine is a metal chelator. However penicillamine can be used to treat gold toxicity. N-acetylcysteine can also increase the excretion of gold.

III.b. Aminoquinoline Derivatives (See Also Chapter 25)

Chloroquine but especially hydroxychloroquine is used for RA that has proved to be refractory to NSAID treatment alone. They may be used concurrently with NSAIDs. It mostly takes 1–3 month for their anti-inflammatory action to become apparent. The pharmacodynamics of these antimalarials in RA is uncertain. Possible mechanisms include decreased leukocyte chemotaxis, stabilization of lysosomal membranes, inhibition of DNA and RNA synthesis and trapping of free radicals.

Corneal deposits during the long-term treatment of RA are not uncommon but the most prominent concern is the danger of producing irreversible retinal damage. At the usual antirheumatic doses these risks seem to be less for hydroxychloroquine than for chloroquine.

III.c. Penicillamine

Penicillamine is an analog of cysteine. Only the d-isomer is used. In patients with progressive rheumatoid arthritis which is refractory to treatment with gold compounds it may retard progression of articular cartilage and bone destruction. For these effects to become apparent a latency period of 3–4 month often is needed. Its mechanism is unknown but it supposedly interferes with the synthesis of DNA, collagen and mucopolysaccharides.

Adverse reactions include alteration of taste perception in a high proportion of patients, drug fever, proteinuria and immune complex nephritis and an increased incidence of autoimmune diseases. Most feared are blood dyscrasias for which blood tests should be done regularly.

III.d. Biological-DMARDs

III.d.1. Tumor Necrosis Factor alpha (TNFα) Blockers

Infliximab is the first chimeric monoclonal antibody against TNFα to be marketed for clinical use. It blocks the action of TNFα by binding to it and preventing it from signaling the receptors for TNFα. Infliximab is administered by intravenous infusion, typically at 6–8 week intervals. It has been approved for treating ankylosing spondylitis, Crohn's disease, fistulizing Crohn's disease, psoriatic arthritis, psoriasis, rheumatoid arthritis, and ulcerative colitis. Adverse reactions include serious and sometimes fatal blood disorders, infections among which tuberculosis ranks high, rare reports of lymphoma and solid tissue cancers, rare reports of serious liver injury, rare reports of drug induced lupus and rare reports of demyelinating central nervous system disorders.

Etanercept is a recombinant human soluble tumor necrosis factor-alpha (TNFα) receptor fusion protein that binds to TNFα and decreases its role in disorders involving excess inflammation. It is approved for subcutaneous use in the treatment of patients with moderate to severe active rheumatoid arthritis, juvenile rheumatoid arthritis, psoriatic arthritis, ankylosing arthritis and plaque psoriasis. To the adverse reactions mentioned for infliximab, rare reports of congestive heart failure should be added.

Adalimumab is a recombinant, fully human anti-tumor necrosis factor monoclonal antibody approved in the US and Europe for the treatment of adult patients with moderate to severe, active rheumatoid arthritis. It has to be injected subcutaneously. The most common side effects of adalimumab are injection site reactions. Adalimumab increases the risk of rare serious infections. Rare side effects include: worsening or initiation of congestive heart failure, a lupus-like syndrome, a promotion of lymphoma, medically significant cytopenias, and worsening or initiation of a multiple sclerosis like neurological disease.

III.d.2. Other Biological-DMARDs

Anakinra is the first biologic drug that has been developed specifically as an interleukin (IL)-1 receptor antagonist and is derived from an endogenous IL-1Ra. The drug blocks the activity of IL-1 in synovial joints, reducing the inflammatory and joint destructive processes associated with rheumatoid arthritis. It is administered subcutaneously and is generally well tolerated. Injection-site reactions are the most commonly reported adverse event.

Abatacept is a newly approved treatment for rheumatoid arthritis refractory to other agents. Abatacept is a fusion protein of the cytotoxic T-lymphocyte antigen (CTLA) molecule and immunoglobulin (Ig) G1 that blocks CD28. Specifically, abatacept blocks the CD80 and CD86 ligands on the surface of antigen-presenting cells that must interface with the T-cell's CD28 receptor to activate T cells. Abatacept seems to be more immunosuppressive than tumor necrosis factor alpha blockers. Overall, abatacept has a more acceptable safety and tolerability profile, with fewer serious adverse events, serious infections, acute infusional events and discontinuations due to adverse events than infliximab.

III.e. Immunosuppressives and Other Agents

For immunosuppressive effects methotrexate is most frequently used in RA but also azathioprine and cyclosporin are employed. Methotrexate doses for this indication can be lower than those used for cancer chemotherapy but significant toxicity such as nausea, cytopenias and mucosal lesions, and with long-term therapy slowly progressive hepatotoxicity may still be seen.

Short-term use of corticosteroids such as prednisone or predisolone is indicated for relapses and for intra-articular administration. Symptomatic improvement is rapidly obtained but any progression of the destruction of bone and cartilage is not influenced by corticosteroids.

The anti-helminthic agent levamisole has immunostimulant properties. It increases chemotaxis and phagocytosis of macrophages and polymorphonuclear leukocytes and stimulates lymphocytes function. It has proved to be effective in treating RA. Its most common adverse effect is the occurrence of rashes.

Sulfasalazine has been used for the management of RA and ankylosing spondylitis with apparently similar effectiveness as penicillamine and with less toxicity. While 5-aminosalicylic acid is the active agent in inflammatory bowel disease, it is believed that sulfapyridine is mostly responsible for the antirheumatoid effects. Gastrointestinal complaints, dizziness and photosensitivity are the most frequently observed adverse events. With levamisole and also with sulfasalazine and olsalazine a delay of 2–3 months is to be expected before positive responses will be observed.

Minocycline is a member of the broad spectrum tetracycline antibiotics. It inhibits apoptosis via attenuation of TNF-alpha and downregulating pro-inflammatory cytokine output. Minocycline is an effective DMARD in patients with early seropositive RA. Pigmentation is a common side effect in patients receiving minocycline therapy for more than 3 months.

Leflunomide is an immunomodulatory drug inhibiting dihydroorotate dehydrogenase, an enzyme involved in de novo pyrimidine synthesis. It has also anti-inflammatory effects. Leflunomide is able to slow progression of the disease and to cause remission/relief of symptoms of rheumatoid arthritis and psoriatic arthritis such as joint tenderness and decreased joint and general mobility in patients. The combined use of leflunomide with methotrexate may

lead to severe or even fatal hepatotoxicity.

IV. DRUGS FOR THE TREATMENT OF GOUT

All NSAIDs are effective in the management of pain and inflammation in acute episodes of gout. Oral glucocorticoids, or intra-articular glucocorticoids are also effective for pain relieve. However, the use of corticosteroids or prostaglandin inhibitors can only be considered as symptomatic treatment. There is no evidence that prostaglandins contribute to the pathogenesis of the gouty inflammation of joints. As an acute attack of gout results from an inflammatory reaction to the deposition of sodium urate crystals in joint tissue, especially in an acid environment, there are several strategies for causal treatment. As hyperuricemia contributes to the risks for gout, reducing the concentration of uric acid in plasma is one of these strategies. For this purpose uricosuric drugs which increase the excretion of uric acid can be used and as aspirin inhibits the excretion of uric acid already at low doses it must be obvious that this drug is contra-indicated. With allopurinol the terminal step of the biosynthesis of uric acid is selectively inhibited. Finally, since a low pH results from lactate production by leukocytes associated with the inflammatory process, favoring further formation of urate crystals, the use of a drug like colchicine which inhibits the local infiltration of granulocytes, is warranted.

IV.a. Uricosuric Agents

In the proximal tubule probenecid, sulfinpyrazone and benzbromarone enhance the excretion of uric acid Although they compete with uric acid for active secretion by the proximal tubules, resorption of uric acid in the proximal tubules is also inhibited with as a net effect the promotion of uric acid excretion. Indications for the use of uricosurics are repeated attacks of gout, the presence of renal impairment associated with hyperuricaemia and the presence of chronic gouty arthropathy or tophi.

The uricosurics are most effective when used during the first few weeks after an acute attack of gout. It is to be expected that in this period high serum levels of uric acid exist with insufficient excretion of urate in the urine. Oral doses of both probenecid and sulfinpyrazone are completely absorbed. Benzbromarone has an oral bioavailability of approximately 50%. Probenecid is eliminated, mainly by glucuronidation with a half-life which shows dose dependency and ranges from 5 to 8 hours while sulfinpyrazone is excreted unchanged in the urine as well as metabolized to an also uricosuric acting metabolite. Benzbromarone is also metabolized to active metabolites, i.e. benzarone and bromebenzarone.

The adverse effect of formation of urate stones in the kidney can be reduced by adequate hydration and alkalinization of the urine.

Especially with sulfinpyrazone and benzbromarone gastrointestinal disturbances can occur. The most frequent adverse reaction of probenecid is allergic dermatitis. Treatment with benzarone or benzbromarone can be associated with fulminant hepatic injury.

IV.b. Xanthine Oxidase Inhibitors and Similar Agents

Allopurinol, a xanthine-oxidase inhibitor, may decrease tissue urate deposits in patients who are "overproducers" of uric acid, i.e. patients with primary hyperuricaemia, in myeloproliferative neoplastic diseases and in hyperuricaemia resulting from tissue breakdown after cancer chemotherapy or radiation therapy. Allopurinol may also be recommended, in certain circumstances, in "undersecretors" of uric acid.

Allopurinol is well absorbed after oral administration and is mainly metabolized in the liver with a short half-life of 1–3 hours. However its active metabolite oxipurinol has an elimination half-life of up to 24 hours.

Hypersensitivity, probably as a manifestation of pseudo-allergy is not infrequent. Especially in patients with impaired renal function various skin eruptions can be followed by a potentially fatal syndrome with fever, hepatic and renal dysfunction and eosinophilia.

Rasburicase is a recombinant form of an enzyme, urate oxidase. This enzyme catalyses the conversion of uric acid to allantoin, a more soluble molecule, easily cleared by kidney. Monthly infusions of rasburicase appear to be a possible therapy for severe gout not treatable by other means. The most important adverse events are allergy and the development of antibodies which compromise rasburicase effectiveness.

Febuxostat is a non-purine inhibitor of xanthine oxidase. It seems to be an alternative that is supe-

rior to allopurinol at reducing serum urate levels, but not at reducing attacks of gout. It is expected to be approved in 2009.

IV.c. Colchicine

Colchicine is an alkaloid of *Colchicum autumnale*. Colchicine can produce dramatic relief from acute gout. Its mechanism of action is based on disappearance of microtubules in granulocytes, thereby inhibiting their migratory capacity, which is brought forward by the ability of colchicine to bind to tubulin. Colchicine is rapidly absorbed after oral administration and then metabolized to several metabolites which are excreted in the bile. Elimination from the body is slow.

Nausea, vomiting, diarrhea, and abdominal pain are the most common side effects which result from the antimitotic effects of colchicine on the gastrointestinal mucosal cells. They can also be the forebode of serious overdose.

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Chapter 27

Antineoplastic Agents

Chris J. van Boxtel

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I. INTRODUCTION

Many agents are available for the management of malignant diseases. The indications for the use of these agents should almost always be made by specialists. However knowledge about the various classes of anti-tumor medicaments is also of importance for non-specialist practitioners as they are often involved in the overall care of patients receiving such therapy and they should be familiar with the potentially very serious adverse effects and drug interactions that are associated with these treatments.

Although the ideal is to selectively kill malignant cells such selective toxicity is rarely possible to the same degree as can be obtained with antibacterial chemotherapy since the differences between normal and malignant cells are much more elusive. Anticancer agents are therefor toxic for all proliferating cells, including bone marrow, gastrointestinal and germinal epithelia and also hair follicles. Another difference with antimicrobial regimens is that for infectious diseases drug treatment only has to remove a certain number of bacteria in support of an active immune system. However in general tumor cells are not very immunogenic and the host does not have as strong an immune response to cancer cells as to bacterial cells. Furthermore, many anticancer agents have considerable immunosuppressive activity which further inhibits any immune response to the tumor.

The sensitivity of cancer cells to a given drug is often dependent upon their stage in the cell cycle. The activity of cell-cycle dependent drugs strongly depends on the stage of cell-proliferation. They can roughly divided in S-phase drugs which affect DNA synthesis and M-phase drugs which affect mitosis or the mitotic spindle. Cell-cycle independent drugs directly damage DNA and for their activity they do not depend as strongly on cell-proliferation.

Some tumors may be intrinsically resistant to a given drug treatment. Such primary resistance, i.e. resistance without any exposure to the drugs, can be seen in for example colon cancer and lung cancers. However, as often the tumor consists of a heterogeneous population of cells also selection can give rise to a resistant subpopulation. This acquired resistance is common and can have different mechanisms. Activation in cancer cells of a phospho-glycoprotein pump which actively pumps out the anti-cancer agents is a frequently occurring mechanism. These pumps work on many drugs and thus can result in multi-drug resistance. In some tumors glutathione transferase is triggered to inactivate cytotoxic agents which are then excreted via glutathione-specific pumps. These tumors can also up-regulate glutathione production.

For the above reasons combination therapies are often employed. This can also have the advantage that doses of the individual agents can often be decreased reducing toxicity. The combination of cell-cycle dependent agents with cell-cycle independent drugs can have synergistic activity.

Many cytostatics inhibit nucleic acid synthesis or functions such as replication or transcription. There

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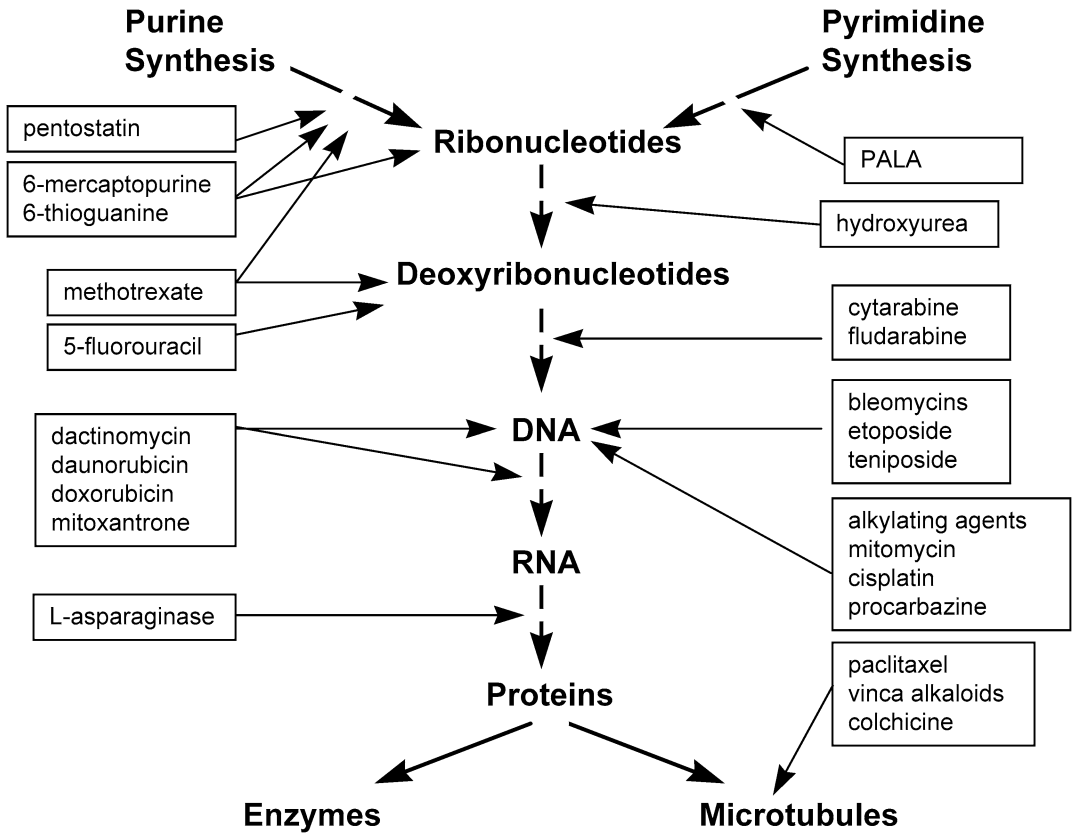


Fig. 1. Sites of action of cytostatic agents. PALA = N-phosphonoacetyl-L-aspartate.

are agents that interfere early in the process of nucleic acid synthesis by obstructing the synthesis of purine and pyrimidine bases. The metabolism of ribonucleotides or of deoxyribonucleotides can be interfered with. DNA template disruption will disturb nucleic acid synthesis. Inhibition of various enzymes such as polymerases, nucleases, ligases and topoisomerases I and II will inhibit nucleic acid synthesis or protein synthesis.

In Fig. 1 various targets of some important cytostatic agents are depicted. Their main mechanisms of action can be briefly summarized as follows. Pentostatin blocks purine nucleotides by inhibiting adenosine deaminase. 6-Mercaptopurine and 6-thioguanine inhibit purine ring biosynthesis and they inhibit nucleotide interconversions. Methotrexate by inhibiting dihydrofolate reduction blocks thymidine monophosphate and purine synthesis. 5-Fluorouracil also blocks thymidine monophosphate synthesis. Dactinomycin, daunorubicin, doxorubicin and mitoxantrone intercalate with DNA and inhibit RNA synthesis. L-asparaginase deaminates asparagine and inhibits protein synthesis. N-phosphonoacetyl-L-aspartate (PALA) inhibits pyrimidine ribonucleotide biosynthesis. Hydroxyurea inhibits ribonucleotide reductase. Cytarabine and fludarabine inhibit DNA synthesis. The bleiomycins and etoposide and teniposide damage DNA and prevent DNA repair. The alkylating agents and mitomycin, cisplatin and procarbazine form adducts with DNA. Finally, paclitaxel, de vinca alkaloids and colchicine inhibit mitosis by interfering with microtubule function.

II. CYTOSTATIC AGENTS

II.a. Alkylating Agents

The alkylating agents have in common that, through intramolecular cyclization to form an ethyleneiminium ion, they become strong electrophiles which may directly or via formation of a carbonium ion intermediate transfer of an alkyl group to cellular target molecules. These reactions result in the

formation of covalent linkages by alkylation of various nucleophilic moieties such as phosphate, amino, sulfhydryl, hydroxyl, carboxyl and imidazole groups. Especially guanine residues in DNA chains are susceptible to the formation of covalent bonds. The chemotherapeutic and cytotoxic effects are directly related to the alkylation of DNA causing interstrand cross-links and disruption of DNA synthesis. Other effects include abnormal base pairing, obstruction of DNA transcription, DNA strand breakage and base-pair deletions.

The alkylating agents can be considered to be cell-cycle independent drugs. They are used for the management of leukemias, lymphomas, multiple myeloma and some carcinoma's and soft tissue tumors, generally as components of drug combination regimens. Cyclophosphamide is also used for its marked immunosuppressant properties.

Acquired resistance to alkylating agents is a common event. Such resistance against the cytostatic activity can occur through at least three mechanisms. Increased thiol production can inactivate the agents. Also a decreased cell permeability to the drug can play a role. Increased capacity for DNA repair can mitigate cytotoxic activity.

Bone marrow suppression with severe thrombocytopenia and leukopenia belongs to the dose limiting adverse reactions. Nausea and vomiting occur with varying incidence depending on the agent used. Both local effects through loss of gastrointestinal mucosa cells and direct stimulation of the chemoreceptor trigger zone in the brain can be responsible for the nausiating effects. Also alopecia and gonadal dysfunction are reported especially with cyclophosphamide. Unique to alkylating agents is the risk for secondary malignancies, often with a delay of many years. Among these secondary malignancies leukemias and lymphomas are the most common.

II.a.1. Nitrogen Mustard Analogues

The nitrogen mustard analogues are nitrogen derivatives of sulfur mustard, used as poison gas in World War I. Agents include cyclophosphamide, mechlorethamine, chlorambucil, melphalan, ifosfamide, uramustine and estramustine.

Cyclophosphamide, probably one of the most frequently used anti-cancer drugs, is a pro-drug. It can be given orally as well as intravenously. It is converted by the liver microsomal cytochrome P450 mixed-function oxidase system to its active forms 4-hydroxycyclophosphamide and aldophosphamide. In both normal and tumor tissues these metabolites are further non-enzymatically transformed in the cytotoxic molecules phosphoramide mustard and acrolein. Acrolein is toxic to the bladder when excreted with risk for hemorrhagic cystitis. The severity of cystitis can be diminished by aggressive hydration before and during therapy.

Mechlorethamine was the first nitrogen mustard. It is directly toxic. With its half-life of only a few minutes infusion directly into arteries supplying the tumor is the preferred mode of administration. Its spectrum of adverse effects is similar to that of cyclophosphamide.

With chlorambucil and melphalan, although administered orally complaints of nausea and vomiting are minimal. The other toxic effects are comparable to those of cyclophosphamide. Chlorambucil has marked immunosuppressant activity.

Ifosfamide, similar to cyclophosphamide, has to be activated in the liver by hydroxylation. However, the activation of ifosfamide proceeds more slowly and a number of inactive matabolites are formed which might explain why higher doses of ifosfamide are required for equitoxic effects.

Uracil mustard or uramustine is an alkylating agents that is used in lymphatic malignancies such as non-Hodgkin's lymphoma. Chemically it is a derivative of nitrogen mustard and uracil. It is preferentially taken up in cancer cells that need uracil to make nucleic acids during their rapid cycles of cell division.

Estramustine is used to treat prostate cancer. It is a derivative of estradiol with an nitrogen mustard-carbamate ester moiety.

II.a.2. Ethylene Imines

Since the formation of the ethyleniminium ion is crucial for the cytotoxic activity of the nitrogen mustards, it is not surprising that stable ethylenimine derivatives have antitumor activity. Thiophosphoramide or thiotepa is the best known compound of this type that has been used clinically. Both thiotepa and its primary metabolite, triethylenephosphoramide (TEPA), to which it is rapidly converted by hepatic mixed-function oxygenases form cross-links with DNA. It is mainly used as an intravesicular agent in bladder cancer. Thiotepa produces little toxicity other than myelosuppression.

II.a.3. Alkyl Sulphonates

The alkyl sulphonates in clinical use include busulfan and treosulfan.

Busulfan is well absorbed after oral administration. In conventional doses busulfan has few pharmacological actions other than myelosuppression. At low doses, selective depression of granulocytopoiesis is evident, leading to its primary use in the chronic phase of chronic myelogenous leukemia. Busulfan suppresses all blood elements, particularly stem cells, and may produce a prolonged and cumulative myelosuppression lasting for months. High dose regimens are for this reason used in allogenic bone marrow transplantation programs. Adrenal insufficiency, increased skin pigmentation and pulmonary fibrosis may occur.

Treosulfan is also administrated orally. It is used as a last resort palliative treatment for carcinoma of the ovary. Bone marrow depression constitutes its main toxicity.

II.a.4. Nitrosoureas

The nitrosoureas carmustine (BCNU), lomustine (CCNU) and semustine (methyl CCNU) all require for their activity nonenzymatic biotransformation. As they are highly lipid-soluble and readily cross the blood–brain barrier they are useful agents in the treatment of brain tumors. Their mechanism is based on the formation of cross-linkages through alkylation of DNA. There appears to be no cross-resistance with other alkylating agents. Carmustine is usually administered intravenously. The advantage of lomustine and semustine is that they have good oral bioavailability. Their spectrum of clinical activity, including primary brain tumors, melanoma, and gastrointestinal cancers, and their toxicities, including delayed myelosuppression and late renal and pulmonary effects, are similar to those of carmustine.

Streptozotocin is particularly toxic to the insulin-producing beta cells of the pancreas. Streptozotocin is a glucosamine-nitrosourea and is similar enough to glucose to be transported into the cell by the glucose transport protein GLUT2, a protein which is concentrated in beta cells. Due to its substantial risk of toxicity it is only used for treating metastatic pancreatic cancer to reduce hypoglycemia due to excessive insulin secretion.

II.a.5. Other Alkylating Agents

Procarbazine is a methylhydrazine derivative. In combination with other agents it is an important agent for the treatment of Hodgkin's disease and non-Hodgkin's lymphomas. It is a methylating agent but has to undergo metabolic activation to generate the cytotoxic reactants which methylate DNA. Induction of microsomal enzymes by e.g. phenytoin and other agents enhances the rate of conversion of procarbazine to its active metabolites. Its most common toxic effects are leukopenia and thrombocytopenia. Mild nausea and vomiting occur in most patients. Procarbazine has sedative activity. The ingestion of alcohol can cause the acetaldehyde syndrome as produced by disulfiram.

Dacarbazine also has methylating activity after metabolic activation in the liver. It is used for the treatment of malignant melanoma, Hodgkin's disease and adult sarcomas. Dacarbazine is administered intravenously. Toxicity frequently includes nausea and vomiting. Myelosuppression is usually mild to moderate. A flulike syndrome, consisting of chills, fever, malaise, and myalgias, may occur during treatment. Hepatotoxicity, alopecia, facial flushing, neurotoxicity, and dermatological reactions have been reported.

Temozolomide is an imidazotetrazine derivative of the alkylating agent dacarbazine. It is an oral alkylating agent used for the treatment of refractory anaplastic astrocytoma. Apart from myelosuppression the most common adverse effects are nausea and vomiting.

II.a.6. Alkylating-Like Agents

The platinum compounds are discussed here as their mechanism of action resembles that of the alkylating agents.

Cisplatin (*cis*-Diamminedichloroplatinum) is a divalent water-soluble platinum containing complex. It reacts directly with DNA, resulting in both intra- and inter-strand cross-links. It also causes DNA breaks and it inhibits DNA replication and RNA transcription. A mechanism for the occurrence of resistance appears to be an increased of the levels of DNA-excision repair enzymes. Cisplatin is used in combination therapies with other anticancer drugs in the treatment of testicular and ovarian cancers and it has also shown high activity against cancers of the bladder, head, neck and endometrium. It is administered intravenously by rapid injection or by continuous infusion. It is for more that 90% bound to

plasma proteins. It is slowly eliminated by excretion in the urine.

Its most important adverse effects are nephrotoxicity and ototoxicity. The risks for nephrotoxicity can be limited by adequate hydration. Marked nausea and vomiting are frequent. Only mild-to-moderate myelosuppression is seen. Pseudo-allergic reactions may occur which respond to intravenous epinephrine and corticosteroids or antihistamines.

Carboplatin is a platinum complex in which platinum is incorporated into a more complex molecule. Its mechanism of action and spectrum of anti-tumor activity are similar to those of cisplatin. However carboplatin is better tolerated that cisplatin.

Oxaliplatin is a newer platinum-based agent. It is most frequently administered in combination with fluorouracil and leucovorin for the treatment of colorectal cancer. Oxaliplatin has less ototoxicity and nephrotoxicity than cisplatin and carboplatin.

II.b. Antimetabolites

Anti-metabolites are cell-cycle dependent drugs and are in principle S-phase specific. They exert their effects on DNA synthesis. These drugs are often used in combination with alkylating agents. Efficacy has been shown among others against head and neck carcinomas and against lung, breast and intestinal cancers, osteogenic sarcoma, choriocarcinoma and leukemia. Their common adverse effects are bone marrow suppression, nausea and vomiting.

II.b.1. Folic Acid Antagonists

Folic acid antagonists are of historical interest as a representative of this group, i.e. methotrexate, produced the first, although temporary, remissions in leukemia and the first cure of a solid tumor, choriocarcinoma.

Methotrexate is a folic acid analogue. Its mechanism of action is based on the inhibition of dihydrofolate reductase. Inhibition of dihydrofolate reductase leads to depletion of the tetrahydrofolate cofactors that are required for the synthesis of purines and thymidylate (see Fig. 2). Enzymes that are required for purine and thymidylate synthesis are also directly inhibited by the polyglutamates of methotrexate which accumulate with dihydrofolate reductase inhibition. The mechanisms that can cause resistance include decreased transport of methotrexate into the tumor cells, a decreased affinity of the antifolate for dihydrofolate reductase, increased concentrations of intracellular dihydrofolate reductase and decreased thymidylate synthetase activity.

Methotrexate at low doses is well absorbed from the gastrointestinal tract. High doses should be administered intravenously. Approximately 50% is

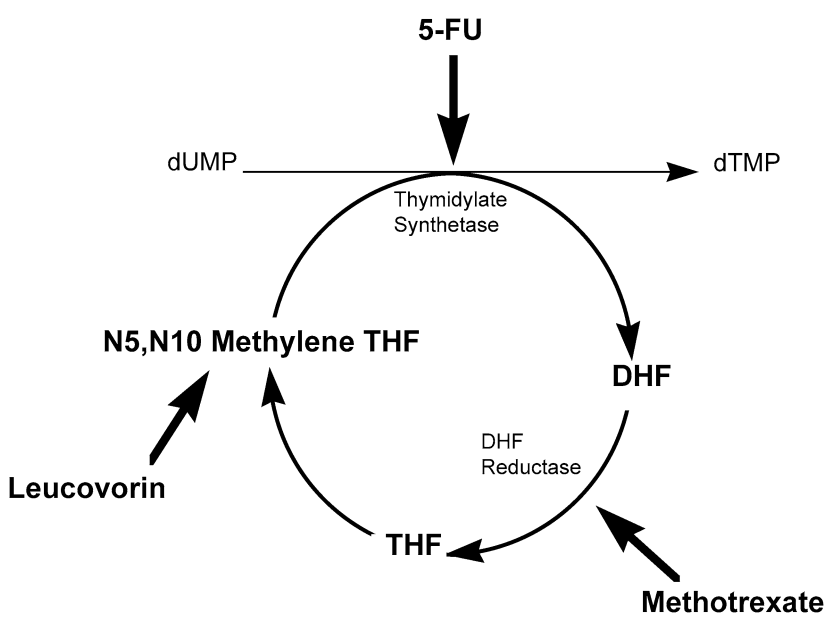


Fig. 2. Target enzymes for methotrexate and 5FU. 5-FU = 5-Fluorouracil; THF = tetrahydrofolic acid; DHF = dihydrofolic acid; dUMP = deoxyuridine-monophosphate; dTMP = deoxythymidine-monophosphate.

protein bound and may be displaced from plasma albumin by a number of drugs. Concentrations in the spinal fluid are only 3% of those in the systemic circulation at steady state and neoplastic cells in the CNS are probably not killed by standard dosage regimens. Methotrexate is slowly distributed into the pleural or peritoneal cavity and ascites or pleural effusion can markedly increase the volume of distribution giving rise to prolonged elevation of plasma concentrations and severe toxicity. Methotrexate is mainly cleared by glomerular filtration and active tubular secretion with a terminal half-life of approximately 8–10 hours. The concurrent use of drugs that reduce renal blood flow such as non-steroidal anti-inflammatory agents, that are nephrotoxic, or that are weak organic acids can delay drug excretion and lead to severe myelosuppression.

Clinical applications include childhood acute lymphoblastic leukemia, choriocarcinoma, osteosarcom, non-Hodgkin's lymphoma and Burkitt's lymphoma. However methotrexate is also frequently used as an immunosuppressant in diseases such as psoriasis, rheumatoid arthritis and others.

The adverse effects of methotrexate include gastrointestinal complaints, bone marrow suppression, alopecia and nephrotoxicity. The toxic effects of methotrexate may be terminated by administering the fully reduced folate coenzyme leucovorin (folinic acid). Leucovorin rescue permits the administration of high doses of methotrexate, for example in situations where partially resistance has occurred or to obtain cytotoxic concentrations of methotrexate in the CNS.

Pemetrexed is chemically similar to folic acid. It inhibits three enzymes used in purine and pyrimidine synthesis – thymidylate synthetase, dihydrofolate reductase, and glycinamide ribonucleotide formyl transferase. By inhibiting the formation of precursor purine and pyrimidine nucleotides, pemetrexed prevents the formation of DNA and RNA. In 2004 it was approved for treatment of malignant pleural mesothelioma and as a second-line agent for the treatment of non-small cell lung cancer. Adverse effects include gastrointestinal complaints, bone marrow suppression, alopecia, allergic and neurotoxic reactions.

Raltitrexed is a folic acid analogue which inhibits thymidylate synthetase. Intracellularly formed raltitrexed polyglutamates are even stronger inhibitors of thymidylate synthetase than the parent compound. Similar to methotrexate polyglutamates these polyglutamates can retain raltitrexed in the tissues for long periods. Raltitrexed is used in the management of carcinomas of the colon. It is administred intravenously and eliminated mainly via renal excretion with an elimination half-life of almost 200 hours. Raltitrexed is reasonably well tolerated. However life threatening myelosuppression may occur.

II.b.2. Purine Antagonists

Mercaptopurine (6-MP) and thioguanine are analogs of the natural purines hypoxanthine and guanine. Both thioguanine and mercaptopurine are substrates for hypoxanthine-guanine phosphoribosyltransferase and are converted to the ribonucleotides 6-thioguanosine monophosphate (6-thioGMP) and 6-thioinosine monophosphate (T-IMP). The accumulation of these monophosphates inhibits several vital metabolic reactions. Some metabolites also act as pseudofeedback regulators of purine synthesis. These purine antagonists are both effective agents for the therapy of human leukemias. Azathioprine is a prodrug of mercaptopurine and is exclusively used for its immunosuppressive activity. Two compounds which are resistant to deamination by adenosine deaminase are the adenosine analog fludarabine (2-F-AraAMP) and the purine analogue cladribine. They both show substantial activity in patients with refractory chronic lymphocytic leukemia and low-grade lymphomas. Pentostatin inhibits adenosine deaminase which leads to accumulation of intracellular adenosine and deoxyadenosine nucleotides blocking DNA synthesis. It is effective against certain leukemias and lymphomas. In 2004 clofarabine was approved by the FDA under accelerated approval regulations requiring further clinical studies. It is used in paediatrics to treat refractory acute lymphoblastic leukaemia.

For the purine antagonists the most common mechanism of resistance is a deficiency or complete lack of the enzyme hypoxanthine-guanine phosphoribosyltransferase. In addition, resistance can result from decreases in the affinity of this enzyme for its substrates. Increased levels of alkaline phosphohydrolase can inactivate active metabolites of mercaptopurine.

Mercaptopurine is well absorbed after oral administration. First pass metabolism in the liver results in 5–37% bioavailability. It is eliminated by xanthine oxidase, thus allopurinol can considerably increase its blood levels and potentiate its effects.

Mercaptopurine is generally well tolerated. Adverse effects include bone marrow depression, anorexia, nausea, vomiting and sometimes jaundice associated with hepatic toxicity.

Absorption of thioguanine is incomplete and erratic. It is eliminated mainly by S-methylation. Thioguanine can be administered concurrently with allopurinol without reduction in dosage, unlike mercaptopurine and azathioprine.

Fludarabine phosphate is a fluorinated nucleotide analog of the antiviral agent vidarabine. Its cytotoxicity is not well understood. It is rapidly dephosphorylated at the cell membrane level and then rephosphorylated intracellularly by deoxycytidine kinase to the active triphosphate derivative. It inhibits DNA polymerase and DNA primase. It is also incorporated into DNA and RNA. Fludarabine is administered intravenously by infusion over 30–120 min. It is eliminated by renal excretion with a terminal half life 10 hours. Adverse effects include myelosuppression, nausea, vomiting, chills and fever. The number of CD4 positive cells is reduced and the incidence of opportunistic infections is increased.

Cladribine, or 2-chlorodeoxyadenosine, is resistant to adenosine deaminase and after intracellular phosphorylation by deoxycytidine kinase, it is incorporated into DNA. It is considered the drug of choice in hairy cell leukemia because of high activity combined with acceptable toxicity. Cladribine shows variable oral absorbtion and is usually administered intravenously. Its concentration-time course is biphasic with plasma half-lives of 35 minutes and 6.7 hours. Excretion is primarily by the kidneys. Its most prominent dose-limiting toxicity is myelosuppression.

The adenosine deaminase inhibitor pentostatin is a natural product derived from *Streptomyces* and structurally it resembles the transition state of adenosine as it is hydrolyzed by adenosine deaminase.

II.b.3. Pyrimidine Antagonists

The pyrimidine antagonists inhibit the biosynthesis of pyrimidine nucleotides or interfere with vital cellular functions, such as the synthesis or function of nucleic acids. The analogues of deoxycytidine and thymidine that are used are inhibitors of DNA synthesis while 5-fluorouracil (5-FU) an analogue of uracil, is an inhibitor of both RNA function and of the synthesis of thymidylate (see Fig. 2). PALA (N-phosphonoacetyl-L-aspartate), an inhibitor of aspartate transcarbamylase, an enzyme that is of importance early in the pyrimidine biosynthesis has shown some synergistic activity with 5-FU in experimental systems. The best known pyrimidine antagonists are the halogenated pyrimidines like 5-fluorouracil and 5-fluorodeoxyuridine (5-FudR or floxuridine). In cytarabine (AraC) the ribose of cytidine is replaced by arabinose. Two other cytidine analogues are 5-azacytidine, an inhibitor of DNA methylation as well as a cytidine antimetabolite, and difluorodeoxycytidine (gemcitabine).

Fluorouracil is activated in the tumor by uridine kinase to its active metabolite, 5-fluorodeoxyuridine monophosphate (5-FdUMP) which inhibits thymidylate synthetase thus depriving the cell of thymidylate. 5-Fluorouracil is also incorporated into both RNA and DNA. Resistance can occur through a decrease of uridine kinase and thus a decreased bioactivation of 5-FU. Mutations in or increased levels of thymidylate synthetase can induce a reduced sensitivity. Clinical applications include metastatic breast carcinomas and also ovarian, prostate, pancreatic and hepatic carcinomas. 5-Fluorouracil can be an effective adjuvant in the treatment of colorectal carcinomas. 5-FU has to be administred intravenously. Capecitabine is a pro-drug that can be given orally and is enzymatically converted to 5-fluorouracil in the tumor. 5-FU is inactivated by reduction of the pyrimidine ring by dihydropyrimidine dehydrogenase. Patients deficient in this activity show increased sensitivity to 5-FU. It is considerably more toxic than the purine analogues. Adverse effects often occur with a considerable delay. Myelosuppression is seen 9–14 days after the first injection. Other adverse effects include anorexia, nausea, stomatitis, diarrhea and alopecia. An acute cerebellar syndrome and also cardiac toxicity have been reported.

Tegafur-uracil is an oral agent which combines uracil, a competitive inhibitor of dihydropyrimidine-dehydrogenase, with the 5-FU prodrug tegafur in a 4:1 molar ratio. Excess uracil competes with 5-FU for dihydropyrimidine-dehydrogenase, thus inhibiting 5-FU break down. The drug is used in the treatment of bowel cancer. Gastrointestinal disturbances and myelosuppression, are the main side effects.

5-FUdR, or floxuridine, is converted by thymidine or deoxyuridine phosphorylases into 5-FU. It is therefore not surprising that the pharmacology and toxicity of both agents are similar. Floxuridine is also administered parenterally, since oral absorption is unpredictable and incomplete. It is primarily used

by continuous infusion into the hepatic artery for treatment of metastatic carcinoma of the colon. The drug is eliminated mainly by metabolism in the liver and many other tissues.

Cytarabine is structurally an analogue of deoxycytidine. It has to be converted by deoxycytidine kinase to the active metabolite AraCTP which inhibits DNA polymerase during the S-phase. Resistance may occur through a decreased uptake of AraC by the tumor cell or a decrease of deoxycytosine kinase levels resulting in decreased conversion of AraC to AraCTP. Also an increased deoxycytosine deaminase activity can increase the breakdown of AraCTP. The most important clinical application of AraC is remission induction in acute myelocytic leukemia. After oral administration only approximately 20% is absorbed due to metabolism in the gastrointestinal tract and the drug is therefor administered intravenously. The adverse effects of AraC include myelosuppression, gastrointestinal disturbances and reversible hepatic dysfunction. Neurotoxicity can occur when the drug is administered in high doses.

Gemcitabine is intracellularly activated by nucleoside kinases to diphosphate and triphosphate nucleosides. Gemcitabine diphosphate inhibits DNA synthesis by inhibiting ribonucleotide reductase while gemcitabine triphosphate competes with deoxycytidine triphosphate for incorporation into DNA. Gemcitabine is used for the treatment of non-small cell lung carcinoma and of adenocarcinoma of the pancreas. It has to be administred intravenously and is eliminated by metabolism with an elimination half-life of approximately 50 minutes. Its spectrum of adverse effects is comparable to that of 5-FU.

II.c. Plant Alkaloids

II.c.1. Vinca Alkaloids

The vinca alkaloids comprise vincristine and vinblastine. These complex, heterocyclic alkaloids are derived from the periwinkle plant. Vindesine and vinorelbine are semisynthetic analogues. These drugs are M-phase specific. Binding specifically to tubulin they inhibit the polymerization of microtubules. The consequent ineffective chromosome segregation initiates apoptosis for both normal and malignant cells.

In principle there is no cross-resistance among the individual vinca alkaloids. However cells which are multidrug-resistant due to an activated efflux pump may display cross-resistance to vinca alkaloids, the epipodophyllotoxins, anthracyclines, dactinomycin and colchicine. Only vinorelbine can be given orally. Its bioavailability is approximately 30%. The other three are administered intravenously. They are all metabolized by the liver and excreted in the bile and in urine with elimination half-lives between 12 and 40 hours. Of vinblastine an active metabolite, desacetylvinblastine, is known.

Despite their structural similarities there are important differences in antitumor activity and toxicity. Vincristine is used, mostly in combination drug regimens, against childhood leukemias, Hodgkin's and non-Hodgkin's lymphoma, testicular and ovarian carcinomas, brain tumors and neuroblastoma. The main indication for vinblastine is, in combination with bleomycin and cisplatin, the treatment of metastatic testicular cancer. It has also activity against lymphomas, Kaposi's sarcoma and neuroblastoma. Vindesine is used in childhood leukemias and with cisplatin for the treatment of lung cancer. Vinorelbine has activity against non-small cell lung cancer and breast cancer.

Vincristine displays limited myelosuppression but its neurotoxicity is dose limiting. On the other hand the most important toxicity of vinblastine is myelosuppression while it lacks serious risks for neurotoxicity. The toxicity spectrum of vindesine and of vinorelbine is between these two extremes. The vinca alkaloids can cause inappropriate secretion of antidiuretic hormone.

II.c.2. Taxanes

The taxanes include paclitaxel and docetaxel. Paclitaxel (taxol) was first isolated from the bark of the Western yew tree but it can now be semisynthesized from yew tree leaves. It is a diterpinoid compound with a complex taxane ring. Further derivatisation has led to the more potent analogue docetaxel. The taxanes are also M-phase specific. They bind specifically to b-tubulin and promote, in contrast to the vinca alkaloids, the polymerization of microtubules thereby stabilizing the mitotic spindle during metaphase. Thus they cause metaphase arrest by prohibiting the tumor cells from passing through metaphase. The mechanism of clinical drug resistance is not known but could involve altered b-tubulin. Paclitaxel is used in combination with cisplatin for the management of metastasized ovarian carcinomas. The taxanes are further used against breast cancer and sometimes against head and neck carcinomas.

The taxanes are practically insoluble in water and solubility is limited to mixtures of ethanol with polyethoxylated castor oil. They are generally administered in 3–24 hour infusions. The taxanes are for 90–95% plasma protein bound and primarily metabolized by P450 enzymes in the liver. Less than 10% is excreted in the urine as parent compounds. The elimination half-life of docetaxel is approximately 10 hours while that of paclitaxel has been varyingly reported between 5 and 50 hours. Inhibitors of the cytochrome P450 isoenzyme Cyp3A4, like ketoconazole and erythromycine, are contraindicated.

The most frequently occurring adverse effects are bone marrow suppression alopecia and hypersensitivity reactions. Patients must be protected with corticosteroids and H1 antihistamines. For mucositis also H2 antagonists are sometimes recommended. Neurotoxicity and cardiotoxicity are mostly mild but can pose serious problems.

II.d. Cytotoxic Antibiotics

The capacity of the antibiotics used for their antitumor activity to bind to DNA is responsible for their cytotoxicity. In varying degree they are able to inhibit DNA-dependent RNA polymerases and DNA polymerases. In addition they can cause single-strand breaks in DNA. Except bleomycin they are cell-cycle non-specific (CCNS) although, as might be expected of compounds that inhibit DNA function, maximal toxicity occurs during the S-phase. Resistance usually results from removal of the agents from the tumor-cells by phosphoglycoprotein pumps.

II.d.1. Actinomycines

The first antitumor antibiotic was actinomycin A which was isolated from a *Streptomyces* species. The actinomycins are chromopeptides containing a planar chromophore, responsible for the bright color of the compounds, with peptide side chains. The most important representative of this group which is in clinical use is actinomycin D, or dactinomycin.

Its mechanism of action is based on intercalation in the minor groove of double stranded DNA, interference with RNA polymerase and with topoisomerase II. Its primary indications are rhabdomyosarcoma and Wilms' tumor in children. In combination with methotrexate, it is used in the treatment of choriocarcinoma.

Dactinomycin is administered intravenously. It is excreted in bile and urine as parent compound with an elimination half-life of some 35 hours. Dactinomycin does not cross the blood–brain barrier.

Its adverse effects include anorexia, nausea, vomiting, bone marrow suppression, alopecia.

Severe local toxicity can occur as a result of extravasation during administration.

II.d.2. Anthracyclines

The anthracycline antibiotics include doxorubicin, daunorubicin, epirubicin and the synthetic agents idarubicin, mitoxantrone and valrubicin. The natural products are derived from *Streptomyces peucetius.* They have tetracycline ring structures attached to the sugar daunosamine. Quinone and hydroquinone groups allow them to function as oxidants and reductive agents. They intercalate with DNA, blocking both replication and transcription. Strand breaks also occur, probably via free radical mechanisms or via topoisomerase II. Doxorubicin has a broad-spectrum and is used in combination chemotherapy regimens against many tumors. The spectrum of daunorubicin and idarubicin is more narrow and they are mainly used against acute leukemias. Epirubicin is a stereoisomer of doxorubicin and also has a very broad spectrum. Mitoxantrone is used for the treatment of acute myelogenous leukemia, non-Hodgkin's lymphomas and breast cancer. Valrubicin is a semisynthetic analog of the anthracycline doxorubicin, and is used to treat bladder cancer. It is administered by infusion directly into the bladder.

The anthracyclines, apart from valrubicin, are administered intravenously. Doxorubicin is rapidly distributed to tissues and slowly eliminated in faeces and urine with an elimination half-life of several days. Daunorubicin undergoes extensive metabolism in the liver, among others to the active daunorubicinol, and is eliminated as inactive products with an elimination half-live of approximately 30 hours. Epirubicin and idarubicin have similar kinetic profiles as daunorubicin with respectively epirubicinol and idarubicinol as their major metabolic products. The kinetic behavior of mitoxantrone resembles more that of doxorubicin with a very slow elimination from the body mainly as parent compound or as inactive metabolites. The anthracyclines do not cross the blood–brain barrier.

Adverse effects include myelosuppression, alopecia and gastrointestinal disturbances. Most important is the dose related cardiac toxicity which is cumulative and can become manifest by congestive heart failure weeks or moths after termination

of treatment. This congestive heart failure is unresponsive to digitalis and has a high mortality rate. Advised maximal cumulative doses for doxorubicin and daunorubicin are 550 mg/m^2, for mitoxantrone 160 mg/m^2 and for epirubicin 900 mg/m^2. Dexrazoxane is used to protect the heart against the cardiotoxic side effects of anthracyclines and tissues after extravasation. It is a derivative of EDTA and chelates iron but the mechanism of its protective effects is not known.

II.d.3. Other Cytotoxic Antibiotics

Bleomycin is a naturally occurring fermentation product of *Streptomyces verticillus*. It is a basic glycoprotein, complexed with Cu^{++}. It intercalates between DNA base pairs, and it also chelates iron, generating oxygen radicals which further damage the DNA. It is the only cell-cycle specific agent among the antibiotics as it causes accumulation of cells in the G2 phase of the cell cycle.

Bleomycin is partially inactivated by bleomycin hydrolase present in various tissues. Some bleomycin-resistant cells contain high levels of hydrolase activity. Bleomycin is used in combination regimens for the treatment of lymphomas and in treating testicular, ovarian cancers and other solid tumors.

Bleomycin is administered parenterally. It is eliminated in the urine with an elimination half-life of approximately 3 hours.

Adverse effects include hyperthermia, headache, nausea and vomiting. Bleomycin has minimal myelosuppressive activity. It can display sever cutaneous and pulmonary toxicity which can be explained by the low hydrolase activity in these tissues. The pulmonary toxicity may progress to life-threatening pulmonary fibrosis.

Mitomycin is an antibiotic isolated from *Streptomyces caespitosus.* It is intracellularly activated to a reduced quinone and then becomes an alkylating agent. It cross-links DNA and inhibits DNA synthesis. Part of the resistance to mitomycin can be ascribed to inactivation of the reduced quinone. Mitomycin is used in combination regimens against carcinomas of the cervix, colon, rectum, breast, bladder, head and neck, and lung.

Mitomycin is administered intravenously or may be instilled directly into bladder to treat bladder carcinoma. It undergoes extensive metabolism in the liver.

Bone-marrow suppression is its most pronounced toxicity. Neprotoxicity and also pulmonary toxicity may occur.

Mithramycin (also known as MIT and plicamycin) is an antibiotic that binds to DNA to regulate transcription. It attaches to specific regions of DNA that are rich in guanine and cytosine. It appears to lower serum calcium concentrations by blocking the hypercalcemic action of Vitamin D. After IV administration about 25% of the drug is excreted in the urine after 2 hours, and 40% after 15 hours. The main indications are treatment of testicular tumors and control of hypercalcemia and hypercalciuria.

Myelosuppression, electrolyte disturbances and loss of appetite are its main side effects. Extravasation may lead to tissue necrosis.

II.e. Topoisomerase Inhibitors

II.e.1. Topoisomerase I Inhibitors

The topoisomerase I inhibitors include irinotecan and topotecan. They are water-soluble camptothecin analogues. Both are administered by intravenous infusion. Their cytotoxicity effects are exerted through interaction with the topoisomerase I-DNA complex, eventually leading to cell death.

Irinotecan has demonstrated a broad spectrum of activity *in vitro* and *in vivo*, and synergistic effects have been observed when it is administered in combination with other antineoplastic agents. Clinically irinotecan is now an active agent in patients with colorectal carcinoma. Irinotecan is metabolized by carboxylesterase to an active metabolite. It is cleared by hepatic metabolism and biliary excretion with a terminal elimination half-life of approximately 15 hours. The principal toxicities associated with irinotecan are diarrhoea and leucopenia.

Topotecan has been approved for the treatment of ovarian cancer refractory to other treatments. However, topotecan has also shown marked activity against other cancers such as neuroblastoma in children, hematologic malignancies, rhabdomyosarcoma and small-cell lung cancer. Topotecan undergoes clinically significant oxidative metabolism via cytochrome P450 and renal elimination with an elimination half-life of 2–3 hours. The most commonly observed toxicities are dose limiting myelosuppression and nausea and vomiting.

II.e.2. Topoisomerase II Inhibitors

The topoisomerase II inhibitors etoposide and teniposide are semisynthetic derivatives of podophyllotoxin. They form a complex with topoisomerase II and DNA which results in double-stranded DNA

breaks and ultimately cell death. Cells in the S and G2 phases of the cell cycle are most sensitive. Etoposide and teniposide have a similar spectrum of antitumor activity. They are used in leukemias, lymphomas and etoposide in testicular malignancies and small cell carcinoma of the lung.

Etoposide is eliminated mainly by urinary excretion with an elimination half-life of 6–12 hours. In contrast teniposide is for some 80% metabolized before excretion in the urine. Both drugs are highly protein bound and display increased toxicity in patients with low plasma albumin.

The dose-limiting toxicity of etoposide is leukopenia. Alopecia is frequent. Secondary leukemia has been reported after combination regimens with etoposide. Myelosuppression, nausea, and vomiting are the primary toxic effects of teniposide.

II.f. Other Cytostatic Agents

Amsacrine (m-AMSA) is a synthetic aminoacridine which intercalates into DNA and inhibits DNA topoisomerase II. m-AMSA is not cross-resistant to anthracyclines and has been particularly active in acute non-lymphocytic leukemia. Amsacrine is administred by intravenous infusion. It is metabolized in the liver and eliminated in the bile with an elimination half-life of 6–9 hours. Its major toxicity is bone marrow depression. Gastrointestinal disturbances are frequent. Neurotoxicity and cardiotoxicity may occur.

Asparaginase is a bacterial enzyme isolated from *Escherichia coli*. The enzyme deprives tumor cells which have low or deficient levels of asparagine synthetase and thus require an external source of asparagine necessary for protein synthesis. It is used in combination regimens to treat childhood acute leukaemia. It is administered intravenously and eliminated with a variable half-life of 4–20 hours. Allergy, including anaphylaxic reactions may occur. Gastrointestinal complaints are frequent. Other adverse effects include neurotoxicity, hepatotoxicity and, through inhibition of protein synthesis also disturbances of hemostasis. Pegaspargase is a form of L-asparaginase which has undergone PEGylation.

Hydroxycarbamide (hydroxyurea) is an inhibitor of the enzyme ribonucleoside reductase which catalyzes the conversion of ribonucleotides to deoxyribonucleotides, a crucial step in the biosynthesis of DNA. The drug is S-phase specific. Resistance can occur by an increase of ribonucleotide reductase. Its primary indications are myeloproliferative disorders, including chronic granulocytic leukemia, polycythemia vera, and essential thrombocytosis. It is also used in combination with radiotherapy for head and neck cancer and for carcinoma of the cervix. Hydroxycarbamide is well absorbed after oral administration. It is in part metabolized in the liver and also excreted unchanged in the urine its elimination halflife is 2–5 hours. Its major toxicity consists of short lasting bone marrow depression.

Arsenic trioxide is a chemotheraputic agent used to treat leukemia that is unresponsive to first line agents. It is suspected that arsenic trioxide induces cancer cells to undergo apoptosis. The enzyme thioredoxin reductase has recently been identified as a target for arsenic trioxide. Due to the toxic nature of arsenic, this drug carries significant risks.

Bortezomib is the first therapeutic proteasome inhibitor. It inhibits the activity of the 26S-proteasoom protein complex which regulates protein expression and function and thus plays a role for cell homeostasis. It is used for the treatment of relapsed multiple myeloma. Following intravenous administration bortezomib is mainly metabolised with an elimination halflife of 5–15 h. It is frequently associated with sometimes irreversable neuropathy. Myelosuppression may be dose limiting.

Bexarotene is a member of a subclass of retinoids that selectively activate retinoid X receptors (RXRs). These retinoid receptors have biologic activity distinct from that of retinoic acid receptors (RARs). After oral administration bexarotene is rapidly absorbed. Bexarotene is thought to be eliminated primarily through the hepatobiliary system. It is approved for the treatment of cutaneous T-cell lymphoma in patients who are refractory to at least one prior systemic therapy. Adverse events possibly related to treatment are lipid abnormalities, hypothyroidism, rash, and blood dyscrasias.

III. HORMONAL AGENTS

III.a. Hormones

One of the principles of the use of hormones in oncology is based on the fact that the growth of tumors which occur in hormone-sensitive tissues may be inhibited by hormones with opposing actions, by hormone antagonists, or by agents that inhibit the synthesis of the stimulatory hormone. Other hormone treatments are based on less specific antimitotic effects.

III.a.1. Corticosteroids (see Chapter 24, Section II.b)

Corticosteroids suppress proliferation of lymphocytic cells, thus they are useful at combating acute lymphoblastic or undifferentiated leukemia of childhood, chronic lymphocytic leukemia, Hodgkin's lymphoma, other lymphomas. Therapy is often initiated with a steroid in combination with other agents. There is no evidence of cross resistance to unrelated agents. Mostly prednison is used however at appropriate dosages similar effects can be obtained with other glucocorticosteroids.

III.a.2. Estrogens (see Chapter 24, Section VI.b)

The prostate and the mammary gland are hormone dependent for their growth and function. The estrogens, e.g. diethylstilbesterol, ethinyl estradiol, fosfestrol, *conjugated* estrogens and polyestradiol phophate, are used in regimens to treat breast and prostate cancer. However, breast carcinomas that lack specific estrogen receptors rarely respond to hormonal therapy.

Fosfestrol is indicated in the treatment of carcinoma of the prostate. It is a synthetic non-steroidal estrogen which is dephosphorylated to stilboestrol. Polyestradiol phosphate is an oestrogen with sustained activity that is exclusively used for prostate cancer. It is stored in tissues and slowly dephosphorylated to estrogen.

III.a.3. Progestogens (see Chapter 24, Section VI.c)

In oncology the progestogens are useful as second-line hormonal therapy for metastatic, hormone-dependent breast cancer and in the management of endometrial carcinoma. Progestogens can also be effective in metastatic carcinomas of the prostate and kidney. Progesterone itself has poor oral absorption and has to be given intramuscularly. Also hydroxyprogesterone caproate and medroxyprogesterone acetate are administered intramuscularly. An oral agent is megestrol acetate.

III.a.4. Gonadotropin-Releasing Hormone Analogues (see Chapter 24, Section I.a.1)

The synthetic analogue of gonadotropin-releasing hormone gonadorelin and its more potent and longer acting analogues such as busrelin, goserelin, leuprorelin and triptorelin are used for the management of metastatic testosterone sensitive carcinomas of the prostate. Their mechanism of action is based on depletion and down regulation of gonadotropin producing cells in the anterior pituitary lobe. Initially they can induce a transient flare of disease but this should not be a reason for discontinuation of therapy.

III.b. Hormone Antagonists (see Chapter 24, Section VI.e)

III.b.1. Antiestrogens

Tamoxifen and torimefen competitively bind to estrogen receptors. They can act both as estrogen agonists and antagonists. In oncology their more important antagonist activity is employed. The antiestrogen-receptor complex less readily binds to the estrogen response element which initiates the expression of tumor growth factors. However, because of the estrogenic properties of these agents they may increase the risk of thromboembolic events. Torimefen and especially tamoxifen are used in the treatment of oestrogen-dependent breast cancer. Tamoxifen is slowly absorbed after oral administration. It is metabolized to N-desmethyltamoxifen and further to 4-hydroxy-N-desmethyltamoxifen which has also strong antiestrogenic activity. Tamoxifen has an elimination half-life of 7 days and that of its major metabolite is 14 days.

The most frequent adverse reactions to tamoxifen include hot flushes, nausea, and vomiting. The incidence of endometrial cancer shows a twofold increase in women on longterm treatment with tamoxifen.

Fulvestrant is an estrogen receptor antagonist with no agonist effects, which works both by down-regulating and by degrading the estrogen receptor. It is indicated for the treatment of hormone receptor positive metastatic breast cancer in postmenopausal women with disease progression following antiestrogen therapy. It is administered as a once-monthly injection. The most commonly reported adverse experiences are gastrointestinal symptoms, headache, back pain and hot flushes.

III.b.2. Antiandrogens

The non-steroidal antiandrogens include flutamide, bicalutamide and nilutamide. By binding to the androgen receptor they inhibit translocation of the receptor from the cytoplasm to the nucleus. Flutamide also inhibits the formation of the active dihydrotestosteron from testosteron. These agents are

used in advanced cancer of the prostrate, mostly in combination with a gonadotropin-releasing hormone agonist. Flutamide, bicalutamide and nilutamide are slowly absorbed after oral administration. Flutamide is metabolized to α-hydroxyflutamide which is even more active than the parent compound and it is eliminated in the urine with a half-life of 5–8 hours. Nilutamide and bicalutamide are also metabolized and have elimination half-lives of respectively 2–3 days and 7 days.

The adverse effects of these agents may include occasional diarrhea, nausea, vomiting, variable loss of sexual function and decreased libido.

III.b.3. Aromatase Inhibitors

In the adrenals aminoglutethimide inhibits the conversion of cholesterol to pregnenolone, and thus the synthesis of cortisol. In the periphery it also blocks the conversion of androgens to oestrogens by inhibiting the aromatization of androstenedione to estrone and estradiol. It is used in the management of metastic breast carcinoma, and as a palliative for advanced prostatic carcinoma. Using aminoglutethimide makes substitution with cortisol necessary. Aminoglutethimide is well absorbed after oral administration. It is eliminated in the urine, for $\pm$50% as parent compound, with an elimination half-life of some 15 hours, decreasing as a result of autoinduction to 9 hours after chronic dosing. Drowsiness is a frequently occurring adverse reaction as aminoglutethimide is an analogue of the nowadays obsolete sedative–hypnotic glutethimide. Pruritic, maculopapular rashes are frequent. Aminoglutethimide is a potent inducer of drug metabolizing enzymes.

Formestan, anastrozol and letrozol are specific aromatase inhibitors which also decrease the conversion of androstenedione to estrone without an effect on corticosteroid production. As they interrupt estrogen synthesis they can be useful in metastatic estrogen sensitive breast cancer. Anastrozol and letrozol have the advantage that they can be administered orally while formestan has to be given intramuscularly. Formestan is metabolized in the liver with an elimination half-life of 5–6 days. Anastrozol and letrozol are metabolized with elimination half-lifes of some 40–50 hours. The adverse effects of these agents are mainly caused by their anti estrogenic activity. Letrozol is an inhibitor of cytochrome P450 enzymes and interactions with this agent should be anticipated.

Exemestane is known uniquely as an aromatase inactivator. It acts as a false substrate for the aromatase enzyme, and is processed to an intermediate that binds irreversibly to the active site of the enzyme causing its irreversable inactivation. Exemestane is used for the treatment of hormonally-responsive breast cancer in postmenopausal women. It is generally well tolerated and adverse events are usually mild to moderate. Adverse events include hot flushes, nausea, fatigue and increased appetite.

Testolactone is a synthetic drug related to testosterone. It is used for palliative treatment of advanced breast cancer in postmenopausal women and in women who have had their ovaries removed. The principal action of testolactone is reported to be inhibition of steroid aromatase activity and the reduction in estrone synthesis. The most common adverse effects are nausea, vomiting, and anorexia. An advantage is that it does not cause women to develop male characteristics such as a deep voice or facial hair.

IV. TYROSINE KINASE INHIBITORS

Tyrosine kinases are important mediators of the signaling cascade, determining key roles in diverse biological processes like growth, differentiation, metabolism and apoptosis in response to external and internal stimuli. Recent advances have implicated the role of tyrosine kinases in the pathophysiology of cancer.

Imatinib is the first member of a new class of agents that act by inhibiting particular tyrosine kinase enzymes. In chronic myelogenous leukemia, the Philadelphia chromosome leads to a fusion protein called BCR-ABL. This is a continuously active tyrosine kinase and imatinib decreases BCR-ABL activity, thus inhibiting cell division. Imatinib is used in chronic myelogenous leukemia, gastrointestinal stromal tumors and a number of other malignancies. The drug is metabolised in the liver and the half-lives of the parent compound and of its major metabolite are respectively 18 and 40 hours. Side effects such as edema, nausea, rash and musculoskeletal pain are common but mild. Severe congestive cardiac failure is rare but may occur.

Sorafenib is a kinase inhibitor with both antiproliferative and anti-angiogenic activity. Approved for the treatment of advanced renal cell carcinoma and for the treatment of patients with hepatocellular carcinoma. Peak plasma levels of sorafenib are generally observed 3 hours after oral administration. The

drug is metabolized in the liver with a halflife of approximately 25–48 hours. Adverse drug reactions include skin rash, diarrhea, and hypertension.

Sunitinib inhibits several receptor tyrosine kinase which are involved in tumor growth, angiogenesis and metastasis of cancer. Sunitinib inhibits growth factor receptors (PDGFR-alfa, PDGFR-beta, VEGFR-1, VEGFR-2 and VEGFR-3), the stem cell factor receptor (c-KIT), Fms-*like* tyrosinekinase-3 (FLT-3), colony stimulating factor-1 receptor (CSF-1R) and the neurotrophic factor receptor RET. In 2006 sunitinib was approved for the treatment of renal cell carcinoma (RCC) and imatinib-resistant gastrointestinal stromal tumors. Maximum plasma concentrations (C_{max}) of sunitinib are generally observed between 6 and 12 hours following oral administration. Food has no effect on the bioavailability of sunitinib. Sunitinib is metabolized primarily by CYP3A4, to produce its primary active metabolite. Half-lives of sunitinib and its active metabolite are approximately 40–60 hours and 80–110 hours, respectively. The most common adverse events associated with sunitinib therapy include fatigue, diarrhea, nausea, anorexia, hypertension, and skin discoloration.

Dasatinib is an oral dual BCR/ABL and Src family tyrosine kinases inhibitor approved for use in patients with chronic myelogenous leukemia after imatinib treatment and for the treatment of Philadelphia chromosome-positive acute lymphoblastic leukemia. Maximum plasma concentrations (C_{max}) of dasatinib are observed between 0.5 and 6 hours (T_{max}) following oral administration. Dasatinib is extensively metabolized in humans, primarily by the cytochrome P450 enzyme 3A4. CYP3A4 was the primary enzyme responsible for the formation of the active metabolite. The overall mean terminal half-life of dasatinib is 3–5 hours. Adverse events included mild to moderate diarrhea, peripheral edema, and headache. Neutropenia and myelosuppression were common toxic effects.

Erlotinib specifically targets the epidermal growth factor receptor (EGFR) tyrosine kinase. It binds in a reversible fashion to the adenosine triphosphate (ATP) binding site of the receptor and by inhibiting the ATP, autophosphorylation of EGFR, essential for signal transduction, is no longer possible and the signal stops. Erlotinib has been approved for the treatment of locally advanced or metastatic non-small cell lung cancer and for metastatic pancreatic cancer. Erlotinib is for circa 60% absorbed after oral administration and its bioavailability is substantially increased by food to almost 100%. It is eliminated by biotransformation with a half-life of about 36 hours. The most common adverse reactions in patients receiving single-agent erlotinib were rash and diarrhea.

Gefitinib is a selective inhibitor of epidermal growth factor receptor (EGFR) tyrosine kinase acting in a similar manner to erlotinib. Gefitinib is thus far only indicated for the treatment of locally advanced or metastatic non-small cell lung cancer in patients who have previously received chemotherapy. Gefitinib is absorbed slowly after oral administration with mean bioavailability of 60%. Elimination is by metabolism (primarily CYP3A4) and excretion in feces. The elimination half-life is about 48 hours. Common adverse effects include acne and other skin reactions, gastrointestinal complaints, stomatitis, conjunctivitis, paronychia and asymptomatic elevations of liver enzymes.

V. CANCER IMMUNOTHERAPY AND BIOLOGICALS

Immunomodulators affect the functioning of the immune system. Immune functions may be promoted as well as suppressed by these agents. In this section interferon alpha, BCG, immunocyanin and aldesleukine and the monoclonal antibodies, alemtuzumab, bevacizumab, cetuximab, trastuzumab, rituximab and ibritumomab tiuxetan will be briefly discussed.

Non-glycosylated recombinant human alpha interferons, subtypes 2a and 2b, bind to their specific cell-surface receptor, resulting in the transcription and translation of genes whose protein products have antiproliferative, anticancer, and immune modulating effects. Alpha interferons 2a and 2b are used to treat several types of cancer, such as hairy cell leukemia, melanoma, follicular non-Hodgkin's lymphoma and AIDS-related Kaposi's sarcoma. These interferons are administered intramuscularly or subcutaneously with peak plasmea levels after 4 and 7 hours. They are eliminated by the kidneys with a halflive between 2 and 9 hours with large interindividual variability. The side effects of interferon are not usually severe. These include high temperature, chills and muscle and joint pains. Skin irritation may occur at the injection site.

Bacille Calmette-Guérin (BCG) contains weakened mycobacterium-bovisbacillen prepared from a

culture of Bacillus Calmette-Guérin. BCG is useful in the treatment of non invasive forms of bladder cancer. Intravesicular instillation may result in a remission and prevents recurrence in up to 2/3 of cases of superficial bladder cancer.

Immunocyanin is an effective medicine for the treatment of urinary bladder carcinoma. It is derived from a sea snail protein. The instillation of immunocyanin into the bladder results in a marked immunostimulation of macrophages and hence a specific immune response against tumour cells that are still in the bladder after cancer therapy.

Aldesleukin is a recombinant form of human Interleukin-2 (IL-2). It has been approved for the treatment of malignant melanoma and renal cell cancer. The medicine is administered every 8 hours by a 15-minute intravenous infusion for a maximum of 14 doses. Adverse reactions include hypo- and hypertension, gastrointestinal disturbances, fever, fatigue, lethargy, joint pain, headache. Cardiovascular problems may occur.

Alemtuzumab is a recombinant DNA-derived humanized monoclonal antibody used in the treatment of chronic lymphocytic leukemia and T-cell lymphoma. It targets CD52, a protein present on the surface of mature lymphocytes. Alemtuzumab has been associated with infusion-related events including hypotension, rigors, fever, shortness of breath, bronchospasm, chills, and/or rash. Also reported were syncope, pulmonary infiltrates, cardiac arrhythmias, myocardial infarction and cardiac arrest.

Bevacizumab is a humanized monoclonal antibody against vascular endothelial growth factor (VEGF) that stimulates new blood vessel formation. It was the first commercially available angiogenesis inhibitor. In 2004 it was approved for use in colorectal cancer together with standard chemotherapy. It is given intravenously every 14 days. The main side effects of concern are hypertension and heightened risk of bleeding. Bevacizumab is also used as an intravitreal agent in the treatment of age-related macular degeneration. Also for intraocular use and for the same indication ranibizumab, a Fab fragment derived from the same parent molecule as bevacizumab, has been developed.

Cetuximab is a chimeric monoclonal antibody, against epidermal growth factor receptor (EGFR). It is given by intravenous injection with weekly intervals for the treatment of metastatic colorectal cancer and head and neck cancer. It is given in combination with the chemotherapeutic agent irinotecan. The side effects of cetuximab are generally mild including skin rashes and itching, a feeling of swelling in the tongue or throat, irritation of the nasal passages, wheezing, cough and breathlessness. A very similar drug given for the same indications is panitumumab, the main difference being that cetuximab is an IgG1 and panitumumab an IgG2 antibody.

Trastuzumab, with the trade name Herceptin, is a humanized monoclonal antibody that acts on the HER2/neu (erbB2) receptor. These growth promoting receptors are active in 25–30% of early-stage breast cancers. Cells exposed to trastuzumab undergo arrest during the G1 phase of the cell cycle. Response to trastuzumab therapy can be predicted by the identification of HER-2 overexpression. The drug is given once a week or once every three weeks by intravenous infusion. Trastuzumab is associated with cardiac dysfunction in 2–7% of cases.

Rituximab is a chimeric monoclonal antibody against CD20 which is expressed on B-cells. One of its main mechanisms of action is the induction of apoptosis in CD20+ cells. In oncology it is used for the treatment of B-cell non-Hodgkin's lymphoma and B-cell leukemia. However, there is evidence for efficacy in a whole range of autoimmune diseases. Serious adverse events, which can cause death and disability, include severe infusion reactions, tumor lysis syndrome causing acute renal failure, cardiac arrhythmias and also infections.

Ibritumomab tiuxetan is the combination of the monoclonal mouse IgG1 antibody ibritumomab with the chelator tiuxetan, to which a radioactive isotope is added. This isotope can be either yttrium-90 or indium-111. The antibody ibritumomab is directed against the CD20 antigen on the surface of normal and malignant B-cells. The combination kills the cell to which it is attached by radiation and by antibody-dependent cell-mediated cytotoxicity and antibody induced stimulation of apoptosis. Ibritumomab tiuxetan is administered by a 10 minute intravenous infusion preceded by rituximab. It is used to treat some forms of non-Hodgkin's lymphoma. The most common side effects are myelosuppression, gastrointestinal symptoms, increased cough, dyspnea, anorexia and ecchymosis. Fatalities were associated with an infusion reaction symptom complex that included hypoxia, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation or cardiogenic shock.

VI. OTHER AGENTS USED IN ONCOLOGY

Mitotane, or o,p′-DDD, is an oral medication used in the treatment of adrenocortical carcinoma. Chemically it is an isomere of DDT. Following its metabolism in the adrenal cortex to a reactive acyl chloride intermediate, mitotane covalently binds to adrenal proteins, specifically inhibiting adrenal cortical hormone production. The drug accumulates in fat tissue. It is eliminated mainly by the kidneys with a half-life of 18–159 days. Common side effects include anorexia, nausea, lethargy, sleepiness and skin problems.

Palifermine is a recombinant human keratinocyte growth factor (KGF), produced by *E. coli*. Endogenous KGF is a specific growth factor and is produced by mesenchymal stem cells in response to damage of epithelial cells. It is used to lower the incidence and shorten the duration and severity of oral mucositis in patients with hematologic malignancies who are treated with myeloablative therapy with a high incidence of severe mucositis. Palifermin is given intravenously for 3 days just before the start of chemotherapy/radiation therapy. The half-life ranges from 4 to 6 hours. The most common side effects are skin rash, unusual sensations in the mouth and asymptomatic increases of amylase.

Tretinoin is the acid form of vitamin A. Addition of tretinoin to the treatment of acute promyelocytic leukemia improves prognosis of the disease in terms of survival. The abnormal fusion protein of the promyelocytic leukemia (PML) gene with the retinoic acid receptor (RAR) gene, PML-RAR, is responsible for preventing immature myeloid cells from differentiating into mature cells. Tretinoin acts on PML-RAR to lift this block, causing the immature promyelocytes to differentiate. After oral administration peak levels are reached in 1–2 hours. It is eliminated with an half-life of approximately 0.7 hours. Common side effects include headache, dry or itchy skin, rash, swelling (oedema), fever, sore mouth, and sore eyes. A sometimes fatal retinoic acid syndrome may happen in about 1 in 4 patients within a month of starting treatment, causing heart problems and raised white blood cell count. Tretinoin has teratogenic and embryotoxic effects.

Amifostine is a cytoprotective adjuvant used to reduce the incidence of neutropenia-related fever and infection induced by DNA-binding chemotherapeutic agents. It is an organic thiophosphate prodrug which is dephosphorylated to the active cytoprotective thiol metabolite. The elimination half-life of the parent compound is less than 10 minutes. Amifostine is administred by short lasting intravenous infusions.

Thalidomide was in 2006 approved by the FDA for the treatment, in combination with dexamethasone, of newly diagnosed multiple myeloma patients. Thalidomide was sold in the late fifties as an hypnotic, with the infamous epidemic of birth defects as a result. Thalidomide is racemic and the S enantiomer is teratogenic. However the enantiomers interconvert *in vivo*, so giving only the R enantiomer cannot be a solution. After oral administration peak levels are reached in 2–4 hours. It is eliminated mainly by biotransformation with a halflife of about 6 hours. The most common side effects observed with use of thalidomide in myeloma include drowsiness or fatigue, constipation, dizziness, dry skin or rash, low white blood cell counts, and peripheral neuropathy.

Lenalidomide, a derivative of thalidomide, was introduced in 2004. Patients with multiple myeloma stage II/III, who have undergone at least one previous treatment can be treated with bortezomib or with lenalidomide in combination with dexamethasone. There is good oral absorptin with peak plasma levels at 0.5–4 hours. Lenalidomide is maily eliminated by the kidneys with a half-life of circa 3–9 hours. Teratogenicity cannot be excluded. Side effects include thrombosis, pulmonary embolus, and hepatotoxicity, as well as bone marrow toxicity resulting in neutropenia and thrombocytopenia.

Gardasil was approved by the FDA in 2006. It is a quadrivalent recombinant vaccine against the human papilloma virus (HPV), more specifically against types 6, 11, 16 and 18. It is able to reduce precancerous cervical, vaginal and vulvar lesions, associated with HPV types 16 and 18, as well as condylomas associated with HPV types 6 and 11. With the approval of the first HPV vaccine, cervical cancer now has a primary prevention tool.

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Chapter 28

Drugs Used for Immunomodulation

Chris J. van Boxtel

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I. INTRODUCTION

To initiate a T-cell immune response, antigen presenting cells have to display antigenic peptides complexed with the major histocompatibility complex (MHC) on their cell surface. The T-cell receptor of CD8 cells is specific for the peptide–MHC class I complex while the CD4 cell receptor binds the peptide–MHC class II complex. This binding of the peptide–MHC II complex stimulates CD4 cell proliferation and subsequent lymphokine release. This CD4 cell response can initiate a delayed hypersensitivity reaction. However CD4 activation and the production of various lymphokines is also needed for the generation of cytotoxic T-cells and for the differentiation of plasma cells from B-lymphocytes and the antibody response by these plasma cells. For their role in also the humoral immune response CD4 cells are called T-helper cells.

This primary response takes some 10 days and is accompanied by the generation of 'memory' B- and T-cells for secondary immune responses. It should be noted that immunosuppression is more effective for primary responses than for secondary responses.

The purpose of immunosuppression in tissue or organ transplants is to prevent or slow down a rejection or reactions of the graft against the host, i.e. graft versus host disease (GVHD). In other applications such as auto-immune diseases and inflammatory and vasculitis-like diseases the aim is to reduce the immune response and the resulting inflammation. Immunosuppressants can reduce or prevent an immune response through diverse mechanisms of action. Available agents include a number of cytotoxic agents, azathioprine, cyclosporine, glucocorticoids, anti-lymphocyte and anti-thymocyte immunoglobuline, baziliksimab, muromonab, mycophenolate mofetil, mycophenolic acid, sirolimus, everolimus and tacrolimus.

Cytotoxic agents like cyclophosphamide, methotrexate and the vinca alkaloids achieve their immunosuppressive effect by non-specifically inhibiting lymphocyte proliferation. Azathioprine, which is exclusively used for immunosuppression, also acts through is active metabolite the cytotoxic agent 6-mercaptopurine by inhibiting lymphocyte proliferation. The immunosuppressive mycophenolate mofetil is also a lymphocyte proliferation inhibitor. Due to this non-specific character of the activity of these agents they tend to affect also other rapidly proliferating cells such as bone marrow and gastrointestinal cells.

Immunosuppression in general is associated with two other unwanted effects. Firstly, there is not only an increased risk of bacterial, viral and fungal infections but also various opportunistic infections occur. The second draw back is the risk for secondary tumors, especially lymphomas.

By far the most important indication for the use of immunosuppressive agents nowadays is in organ transplantation. A second indication is the treatment of autoimmune diseases where immunosuppression has been shown to be effective.

Immunomodulating agents can both suppress and stimulate various immune functions. This is a heterogenous group of drugs. Increasingly immunostimulants are employed as a form of immunomodulation. Indications for immunostimulant therapy in-

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clude, immunodeficiency disorders, chronic infectious diseases and various malignancies.

II. IMMUNOSUPPRESIVE AGENTS

II.a. Specific Immunosuppressives

The specific immunosuppressives include cyclosporine and tacrolimus. Although chemically not related and with different biochemical targets they both specifically inhibit cytotoxic T-cell and T-helper cell dependent B-lymphocyte proliferation.

Cyclosporine is at present the most important immunosuppressive agent. It is a cyclic polypeptide derived from the fungus *Tolypocladium inflatum.* It is a specific and reversible inhibitor of T-helper cell proliferation. It also inhibits the production and release of interleukin-2 and is thus interfering with both cellular and humoral immune responses. It does this by binding to a cytoplasmic receptor protein, cyclophilin, thereby ultimately inhibiting serine/threonine phosphatase, an enzyme that is of crucial importance for the transcription of genes coding for specific cytokines, particularly interleukin-2. It is used for the prevention of graft rejection following organ transplantation and is also effective for the prophylaxis of graft-versus-host disease. To reduce doses and thus risks for toxicity in transplantation programs it is often given in combination with other immunosuppressives like steroids, azathioprine or cyclophosphamide. It has also been used in a variety of diseases where dysfunction of immunoregulation might play a role and it has been shown to be effective in acute ocular Behcet's syndrome, endogenous uveitis, atopic dermatitis, rheumatoid arthritis, active Crohn's disease, and for severe chronic plaque-type psoriasis. Since 2002 a topical emulsion of cyclosporine for treating keratoconjunctivitis sicca has been marketed.

Absorption after oral administration is incomplete and variable. Its bioavailability ranges from 20% to 50%. Cyclosporine can also be given intravenously. Plasma protein binding is about 90% and cyclosporine also accumulates in red blood cells. It is extensively metabolized in the gastrointestinal mucosa and in the liver by the cytochrome P450-enzyme system. Its elimination half-life is about 19 hours in adults with a range of 10–27 hours and about 9 hours in children with a range of 3–19 hours. Over 30 different metabolites have been identified, some of which might have immunosuppressive activity. In this metabolism the enzyme CYP3A4, which can be inhibited by inhibitors like erythromycin and ketoconazole, plays an important role. Ketoconazole and erythromycin raise cyclosporine levels. It has been shown that grapefruit juice can increase the oral bioavailability of many drugs including cyclosporine by reducing the 'first pass effect' through specific inhibition of the enzyme CYP3A4 in the gut wall. Inducers like rifampicin and anticonvulsants increase the metabolism of cyclosporine. Cyclosporine metabolites are eliminated mainly via the biliary and faecal route.

Cyclosporine has no myelotoxicity but the drug is nephrotoxic. It is because of this nephrotoxicity that cyclosporine has a narrow therapeutic index that makes blood level monitoring necessary. Other toxicities include hypertension, hepatotoxicity, neurotoxicity, hirsutism, gingival hyperplasia and gastrointestinal disturbances.

Tacrolimus (previously known as FK506) is a macrolide antibiotic which is obtained from the fungus *Streptomyces tsukubaensis*. Tacrolimus binds intracellularly to the protein FKBP (FK binding protein) which is distinct from the protein that binds cyclosporine. However both drug–protein complexes associate in a similar way with calcineurin and inhibits its serine/threonine phosphatase activity, although the immunosuppressive potency of tacrolimus is approximately 100 fold higher than that of cyclosporine.

After oral administration the bioavailability varies widely with a maximum of some 60%. Tacrolimus can also be administered intravenously. Its concentration–time curve is biphasic. It is metabolized in the liver and is eliminated with a half-life varying from some 12 hours in patients to 20 hours in healthy subjects.

Tacrolimus is used in situations where cyclosporine has been shown to be ineffective or cannot be used because of toxicity or otherwise. It is also used in a topical preparation in the treatment of severe atopic dermatitis, severe refractory uveitis after bone marrow transplants and in vitiligo.

Frequent adverse effects are nausea and vomiting. More serious reactions include nephrotoxicity, neurotoxicity manifesting itself as headache, tremor and insomnia. Rising blood pressure and hyperkalemia, hypomagnesemia and hyperglycemia may occur.

Sirolimus (rapamycin) inhibits T-cell activation by inhibiting intracellular signal transmission by

binding to the mammalian target of rapamycin (mTOR), a kinase important for the progression of the cell cycle. It is used for the prevention of acute rejections of kidney transplants. In the blood it is bound to erythrocytes. It is metabolized in the gut and in the liver by CYP3A4 to inactive metabolites. Side effects may include mouth sores, nausea, diarrhea, tremors, dizziness, high blood pressure, high cholesterol and triglycerides, unusual heartbeat and certain types of cancers (e.g. skin cancer).

Everolimus is a derivative of rapamycin (sirolimus), and works similarly to rapamycin as an mTOR inhibitor. It is used as an immunosuppressant to prevent rejection of organ transplants.

II.b. Glucocorticosteroids (See Chapter 24, Section II.b)

Corticosteroids suppress both humoral and cellular immunity. Single doses produce a redistribution of lymphocytes with a concentration dependent decrease of CD4 and CD8 positive cells. This *in vivo* lymphopenic effect correlates with the *in vitro* inhibition of stimulated T-cell proliferation. Furthermore, corticosteroids are able to inhibit the expression of genes coding for IL-1, IL-2, IL-6, interferon α, and tumor necrosis factor, TNF-α. Chronic administration decreases the size and also the cellularity of lymphoid tissues like lymph nodes, spleen, and thymus. Corticosteroids have more effect on the primary immune response and are less effective against previously sensitized immune responses. Their suppressive effects are more pronounced for T-cell immune responses than for the humoral immune response.

The immunosuppressive effects of corticosteroids are employed in organ transplantation programs in combination with other immunosuppressive modalities, for the management of a variety of autoimmune diseases and to suppress allergic reactions.

Adverse reactions of corticosteroids are frequent with the long-term immunosuppressive regimens which are often needed and include an increased risk of infections, Cushing-like symptoms, hypertension, hyperglycemia, osteoporosis, growth retardation in children and mental reactions such as dysphoria, psychosis and depression.

II.c. Cytotoxic Drugs

Cytotoxic agents which are used both for the treatment of cancer as for their immunosuppressive activity include cyclophosphamide, methotrexate, chlorambucil, vincristine, vinblastine and dactinomycin. These agents are discussed in more detail in Chapter 27. Generally for immunosuppression lower, daily administered doses are given for a prolonged period of time while for cancer chemotherapy often high, intermittently administered doses are employed to kill rapidly proliferating tumor cells.

Cytotoxic agents which are exclusively used to achieve immunosuppression are azathioprine and mycophenolate mofetil, although their over all mechanism of action is similar to that of the antitumor drugs, i.e. inhibition of lymphocyte proliferation after antigen exposure.

Azathioprine is a pro-drug as it is converted by interaction, mainly in red blood cells, with nucleophils like glutathione to its active form 6-mercaptopurine after which 6-mercaptopurine nucleotides are generated that inhibit purine synthesis and can lead to DNA damage by intercalation. Although the activity of 6-mercaptopurine is well understood there are indications that azathioprine itself contributes to an enhanced immunosuppressive activity.

Azathioprine can be administered both orally and intravenously. It is well absorbed orally and after its rapid conversion to 6-mercaptopurine it is inactivated by xanthine oxidase which converts 6-mercaptopurine to 6-thiouric acid. This final metabolite is then excreted in the urine. In combination with the xanthine oxidase inhibitor allopurinol dose adjustments of azathioprine are needed. Renal disease also raises 6-mercaptopurine concentrations and can make dose adjustments necessary. Azathioprine is still used in organ transplantation programs and for the management of several autoimmune diseases. Its adverse effects include nausea, vomiting, diarrhea and, more seriously, bone marrow suppression and hepatotoxicity. Azathioprine is not thought to cause fetal malformation.

Mycophenolate mofetil is used together with cyclosporine and corticosteroids for the prophylaxis of acute organ rejection in patients undergoing allogeneic renal, or hepatic transplants. Compared with azathioprine it is more lymphocyte-specific and is associated with less bone marrow suppression, fewer opportunistic infections and lower incidence of acute rejection. More recently, the salt mycophenolate sodium has also been introduced. Mycophenolate mofetil is rapidly hydrolyzed to mycophenolic acid, its active metabolite. Mycophenolic acid is a reversible noncompetitive inhibitor of inosine monophosphate dehydrogenase, an important enzyme for the *de novo* synthesis of purines. As lymphocytes have little or no salvage pathway for purine

synthesis they are more sensitive to mycophenolic acid than other cells. Mycophenolate mofetil is well absorbed after oral administration with a bioavailability of more than 90%. Mycophenolic acid is highly protein bound. It is glucuronidated in the liver and then excreted in the urine. Its elimination half-life is approximately 18 hours. In renal failure mycophenolic acid glucuronide can displace mycophenolic acid from its plasma protein binding sites, thus increasing the clearance of mycophenolic acid. Gastrointestinal complaints are frequent. Blood dyscrasias may occur. Other adverse effects can involve the central nervous system resulting in complaints such as anxiety and depression. Cardiac arrhythmias and heart failure have been reported.

II.d. Immunoglobulins

Rh(D) immune globulin is a solution of human IgG against the Rh(D) antigen on erythrocytes. It is prepared from plasma with high antibody titers against the Rh(D) antigen of hepatitis B and HIV negative donors. The indication of Rh(D) immune globulin is the prevention of erythroblastosis fetalis, the hemolytic anemia of newborn. To prevent anti-Rh antibody formation in the mother it should be given, by intramuscular injection, to Rh-negative mothers within 72 hours after their Rh-positive child is born. In some patients it may trigger an allergic reaction.

Anti-lymphocyte globulin (ALG) has been prepared as an highly purified solution of γ-globulins with antilymphocyte activity by immunizing horses with human lymphocytes. It activates complement-mediated destruction of lymphocytes and thus decreases cellular immunity with only a limited effect on humoral immunity. Anti-lymphocyte globulin suppresses delayed type hypersensitivity reactions. It is used for the prevention and treatment of rejection episodes of transplanted organs. It also has some indication for the management of idiopathic aplastic anemia. Adverse effects include pain at the site of injection, erythema, serum sickness and rarely anaphylactic shock and thrombocytopenia.

Anti-thymocyte globulin (ATG) is a purified immunoglobulin from horse, rabbit, sheep, or goat serum after immunization with human thymocytes. The administration of anti-thymocyte globulin results in a depletion of T-cells as a result of complement dependent lysis and opsonization by the macrophage–monocyte system. The depletion of CD4 positive cells is long lasting and results in an inversion of the CD4/CD8 ratio. There are hardly any effects on B-lymphocytes and on monocytes. Anti-thymocyte globulin is mainly used to treat allograft rejection. There are batch to batch differences in the efficacy of these polyclonal antisera and they carry the risk for serious allergic reactions. They will more and more be replaced by monoclonal antibodies. ATG like ALG is associated with cytokine release syndrome in the short term and an increased risk of post-transplant lymphoproliferative disorder in the long term. Anti-IL-2Rα receptor antibodies such as basiliximab and daclizumab are increasingly being used in place of ALG and ATG.

Muromonab is a mouse monoclonal antibody against the CD3 receptor of T-lymphocytes. Its activity is based on inhibition of interactions between antigen-presenting cells and T-cells. By preventing antigen presentation it suppresses T-cell activation and proliferation. The indication for muromonab is the treatment of acute graft rejection after kidney, liver and hart transplantations. Its adverse effects consist of those symptoms that are initiated by the release of cytokines and lymphokines as a result of the reaction of muromonab with CD3 positive T-lymphocytes. These symptoms may vary from a mild flu-like syndrome to serious cardiac, pulmonale and neurological reactions.

Basiliximab is a chimeric mouse–human monoclonal antibody to the IL-2Rα receptor of T cells and daclizumab (Zenapax) is a humanized monoclonal antibody against the same receptor. They prevent binding of interleukin-2 to the CD25 antigen on activated T-lymphocytes thus inhibiting T-lymphocyte proliferation. Like the similar drug basiliximab, daclizumab reduces the incidence and severity of acute rejection in kidney transplantation without increasing the incidence of opportunistic infections.

Infliximab is a monoclonal antibody against TNF-α (see Chapter 26, Section III.d.1). It has been approved for the treatment of psoriasis, Crohn's disease, ankylosing spondylitis, psoriatic arthritis, rheumatoid arthritis and ulcerative colitis. Similar immunosuppressants are etanercept, and adalimumab.

III. IMMUNOSTIMULANTS

Immunostimulants are potentially of benefit in immunodeficiency disorders such as acquired immunodeficiency syndrome (AIDS), in chronic infectious diseases, and in some selected malignancies, especially those that involve the lymphatic system.

Bacillus Calmette-Guerin (BCG) and its active component, muramyl dipeptide, have been shown to have aspecific immunostimulant activity. It is mainly used for the local treatment of bladder cancer. It binds to fibronectine in the bladder epithelium. Hypersensitivity reactions and immune complex disease are its major adverse reactions.

Immunoglobulin obtained from pooled plasma obtained from hepatitis B and HIV negative donors is used as an aspecific immunostimulant in immunodeficiency diseases, idiopathic thrombocytopenia, autoimmune hemolytic anemias, Kawasaki syndrome and to prevent infections in immune compromised patients with leukemia or multiple myeloma. Adverse effects include potentially severe hypersensitivity reactions.

Thymosin is an immunomodulatory peptide produced by the thymus gland and other cells. Thymosin alfa 1, a 28-amino acid peptide, is one member of the family of thymosins that collectively appear to influence a variety of regulatory and counter-regulatory functions in terms of T-cell maturation and antigen recognition, stimulation of native interferons and cytokines such as interleukin-2, and activity of natural killer cell-mediated cytotoxicity. In some countries it is approved as an adjuvant for influenza vaccine or as a treatment for chronic hepatitis B and, in combination with interferon for hepatitis C. Thymosin alfa 1 has been used with some success to treat children with the severe form of DiGeorge Syndrome.

Interferon alfa (interferons are discussed more detail in Chapter 25, Section IV.d and in Chapter 27, Section V) is a species specific natural occurring compound. Its proliferation is stimulated during viral infections. Human recombinant interferon alfa has immunostimulating effects such as the activation of macrophages, T-lymphocytes, and natural killer cells. Its indications include haircell leukemia, chronic myeloid leukemia and non-Hodgkin lymphomas, condyloma accuminatum, Kaposi sarcoma related to AIDS and chronic hepatitis B and C. Its most frequently occurring adverse reaction is a flu-like syndrome which can be serious with malaise, fever, neurological symptoms from nervousness to convulsions and coma, blood dyscrasias, cardiotoxicity and also nephrotoxicity.

The beta-interferons, interferon beta-1a and interferon beta-1b, have both immunemodulating effects. Interferon beta-1b is produced with recombinant DNA technology. *In vitro* interferon beta-1b is able to stimulate CD8 positive suppressor cells and thus suppresses T-cell activity. Also *in vivo* T-cell activity is suppressed as is the expression of the major histocompatibility complex and antigen presentation. Interferon beta-1a is obtained from genetically manipulated rodent cell lines. It has antiviral and immunemodulating activity. It suppresses the expression of gamma-interferon and stimulates the suppressor activity of peripheral mononuclear cells. Both beta-interferons are only indicated for the relapsing-remitting form of multiple sclerosis. However the evidence for clinical efficacy in this disease is under debate.

Interferon gamma is an activator of macrophages. Its anti-viral activity is limited compared to that of interferon alfa. Human recombinant interferon gamma restores, at least in part, macrophage cytotoxicity and with that decreases the incidence of infections in patients with chronic granulomatous diseases. Its adverse effects consist mainly of flu-like syndrome skin rashes may occur.

Aldesleukin is with recombinant technology prepared interleukin-2 (IL-2). IL-2 binds to the IL-2 receptor and so stimulates proliferation of T-helper cells and cytotoxic T-cells. It also activates macrophages and stimulates B-cell activity. It is used in metastasized renal carcinoma. Life threatening cardiotoxicity may occur. Other adverse effects include bone marrow depression and neurotoxicity with manifestations varying from somnolence to delirium.

Immunocyanin is a stable modification of keyhole limpet hemocyanin, a non-heme, oxygen-carrying copper protein found in arthropods and mollusca. It is an aspecific activator of both cellular and humoral reactions. Immunocyanin is used for the local treatment of bladder cancer. Its systemic adverse effects are usually limited to some mild fever.

Isoprinosine is an immunostimulant drug that increases natural killer cell cytotoxicity as well as to increase the activity of T-cells and monocytes. The drug has some clinical activity against viral encephalitis such as subacute sclerosing panencephalitis and severe manifestations of immunodeficiencies. Because the purine (inosine) moiety of isoprinosine is rapidly catabolized to uric acid it should be used with care in patients with a history of gout.

The anthelmintic agent levamisole increases delayed hypersensitivity and T-cell mediated immunity. It has been used as adjuvant therapy for colorectal cancer. A recent Cochrane review concluded that

levamisole is more effective than prednisone alone in reducing the risk of relapse of nephrotic syndrome in children. It frequently shows neurotoxic adverse reactions varying from nervousness, depression and insomnia to convulsions and coma. Bone marrow depression may occur.

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Chapter 29

Vitamins

Chris J. van Boxtel

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I. INTRODUCTION

Vitamins are small organic molecules which in small amounts are obligatory nutrients and used by the body as co-factors in a multitude of metabolic processes. They play a role in hormone production, are necessary for blood cell formation and for producing nervous-system constituents, and they are ingredients for the formation of genetic material. There are no chemical relationships between the various vitamins and mostly also their most physiological actions are not related.

Their solubility either in fat or water is the major criterion for the classification of the 13 chemicals, or groups of chemicals, identified as vitamins. The eight B vitamins and vitamin C are water soluble. Except for some B vitamins, the possibilities for their storage are very limited and they have to be consumed almost on a daily basis. Vitamins A, D, E and K are fat-soluble and are thus found in fat-containing foods. As these vitamins are at least to some extend stored in body fat, daily consumption is not needed. Some general information on the water soluble and fat-soluble vitamins are summarized in Tables 1 and 2, respectively.

In the form in which they are consumed, many vitamins are not biologically active. For several water-soluble vitamins such as thiamine, riboflavin, nicotinic acid, pyridoxine, activation includes phosphorylation or, as is the case with riboflavin and nicotinic acid, coupling to purine or pyridine nucleotides is required. In their major known actions, water-soluble vitamins participate as cofactors for specific enzymes, whereas at least two fat-soluble vitamins, the vitamins A and D, behave more like hormones and interact with specific intracellular receptors in their target tissues.

Vitamins must be derived from the diet because either they cannot be synthesized *de novo* in human beings or their rate of synthesis, e.g. the production of nicotinic acid from tryptophan, is inadequate for the maintenance of health. Only vitamin D can be manufactured by the body at a sufficient rate.

Recommended dietary allowances for vitamins have proved to be useful guidelines however it has to be appreciated that these guidelines are not more than estimates made from experiments on only a limited number of subjects. These recommended dietary allowances also need periodic reevaluation. While vitamin deficiencies due to inadequate intakes are encountered in developing countries, few cases are seen in the Western world apart from patients with an increased risk for deficiencies such as diabetics or alcoholics. On the contrary, the widely held belief that vitamins promote better health is deceptive and may lead to overdose disorders.

On the other hand, in recent years there has been an increasing role for the use of certain vitamins in the prevention and management of specific diseases. The use of nicotinic acid in hyperlipidemia is an old but still a good example for such use.

II. WATER-SOLUBLE VITAMINS (SEE TABLE 1)

II.a. B Vitamins

The group of B vitamins consists of thiamine or aneurine (vitamin B_1), riboflavin (vitamin B_2), nico-

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Table 1. Water-soluble vitamins

Vitamin	Active compound	Sources	Recommended daily allowances
B_1	Thiamine	Green peas, spinach, aleurone layer of unpolished rice, organ meats, beef, pork	Depending on total caloric intake <1 yr: 0.2 mg 1–13 yr: 0.3–0.8 mg ⩾13 yr: 1.1 mg pregnancy: 1.4 mg lactating women: 1.7 mg
B_2	Riboflavin	Milk, eggs, organ meats, leafy vegetables, yeast, brown bread; synthesis by intestinal bacteria	<1 yr: 0.4 mg 1–13 yr: 0.5–1.0 mg ⩾14 yr man: 1.5 mg ⩾14 yr woman: 1.1 mg pregnancy: 1.4 mg lactating women: 1.7 mg
B_3	Nicotinic acid	Cereal, light meat, beef, tuna peanuts beans; from nicotinic acid, nicotinamide is formed in the liver	<1 yr: 2 NE 1–13 yr: from 4 to 11 NE >13 yr man: 17 NE >13 yr woman: 13 NE pregnancy: 18 NE lactating women: 17 NE
B_5	Pantothenic acid	Is widespread; probably a minor part is synthesized by the body itself	0–3 yr: 2 mg 4–13 yr: 3–4 mg >13 yr: 5 mg pregnancy: 5 mg lactating women: 7 mg
B_6	Pyridoxine	Meat, liver, kidney, raw cereals, wheat germ, soybeans	<1 yr: 0.25 mg 1–16 yr: 0.7–1.4 mg ⩾16 yr: 1.0–1.6 mg pregnancy: 1.7 mg lactating women: 1.7 mg
B_7	Biotin	Soybeans and other legumes, egg yolks, nuts, and organ meats; it is also produced naturally in the body by intestinal bacteria	<1 yr: 5–6 µg 1–19 yr: from 8 to 25 µg ⩾19 yr: 30 µg pregnancy: 30 µg lactating women: 35 µg
B_{11}	Folate (see Chapter 41, Section II)	Liver, cereals, legumes, spinach, asparagus, beans	<1 yr: 40–65 µg 1–19 yr: from 60 to 275 µg ⩾19 yr: 200–400 µg pregnancy: 600–800 µg lactating women: 400–600 µg
B_{12}	Cyanocobalamin (see Chapter 41, Section II)	Protein bound in the form of methyl- and 5-deoxy adenosylcobalamin in clams, fish meat, liver, eggs, milk and cheese	<1 yr: 0.5–0.6 µg 1–16 yr: 0.6 up to 2.2 µg ⩾16 yr: 2.2–2.6 µg pregnancy (2nd and 3rd trimester): 2.9 µg lactating women: 3.5 µg
C	Ascorbic acid	Potatoes, leafy vegetables, fruits (especially rose hips, black berries, kiwi, strawberries)	<1 yr: 35 mg 1–19 yr: 40 up to 70 mg ⩾19 yr: 70 mg pregnancy: 90 mg lactating women: 110 mg

NE: niacin equivalent: 1 mg NE = 60 mg of tryptophan = 1 mg niacin.

Table 2. Fat-soluble vitamins

Vitamin	Active compound	Sources	Recommended daily allowances
A_1	Retinol	Retinolesters: cod liver oil, liver, fortified breakfast cereals, egg, butter, milk	<1 yr: 400–450 RE = 1330–1500 IU 1–19 yr: 400–1000 RE = 1330–3330 IU ⩾19 yr: 800–1000 RE = 2665–3330 IU
A_2	Didehydroretinol	carotenes: carrots, tomatoes	pregnancy: 1000 RE = 3330 IU lactating women: 1250 RE = 4165 IU
D_2	Ergocalciferol	Synthesized in the skin upon exposure to ultraviolet-B radiation (cholecalciferol)	0–3 yr: 5–10 µg, dep. exposure to sunlight 4–50 yr: 2.5–5 µg, idem 51–70 yr: 5–10 µg, idem
D_3	Cholecalciferol	Mackerel, sardines, salmon and some foods fortified with vitamin D	⩾71 yr: 12.5–15 µg, idem pregnancy (2nd and 3rd trimester) lactation: 7.5–10 µg, idem
E	Group active derivatives of tocol and tocotrienol; most active is RRR-α-tocoferol = (d)-α-tocoferol	Vegetable oils and cereals, vegetables, fruit	Depending on the amount of polyunsaturated fatty acids (PUFA) in the diet: <1/2 yr: 2.9 α-TE 1/2–1 yr: 3.6 α-TE 1–19 yr: 5.5 up to 13.3 α-TE >19 yr: 13 down to 8.3 α-TE pregnancy: 0.6 α-TE extra lactating women: 2.7 α-TE extra
K_1	Phylloquinone	In chloroplast of green plants and in vegetable oils (phylloquinone)	Newborns are much more dependent on the amount of vitamin K in food than healthy adults because the intestinal flora has not yet been fully developed; (see Chapter 41, Section VIII)
K_2	Menaquinone	Synthesis by gram positieve intestinal bacteria (menaquinone)	

IU: international unit; RE: retinol equivalent (1 RE = 1.0 µg crystalline retinol = 3.33 IU); α-TE: α-tocoferolequivalent (1 α-TE = 1.49 IU).

tinic acid or niacin (vitamin B_3), pantothenic acid (vitamin B_5), pyridoxine (vitamin B_6), biotin (vitamin B_7), folic acid (vitamin B_{11}) and cyanocobalamin (vitamin B_{12}).

Historically choline, inositol and carnitine have been considered to be part of the vitamin B complex. However, for the general population there has been no demonstration of a dietary need for these agents and also for none of them has there been a therapeutic role established. Vitamins of the B family are found in many food ingredients like in yeast, in meat, in dairy products and also in eggs and grain cereals and separate vitamin B deficiencies are unlikely to occur. Excessive intake of these vitamins is eliminated in the urine because of the fact that they are water-soluble.

Thiamine (vitamin B_1) is phosphorylated by ATP to thiamine pyrophosphate. This is a coenzyme for, among others, alpha-ketoglutarate dehydrogenase, transketolase and pyruvate dehydrogenase. Thiamine pyrophosphate is involved in fatty acid metabolism and in the metabolism of carbohydrates and amino acids. Indirectly it also plays a role in nucleic acid biochemistry. In the body nicotinamide, another B vitamin, is via niacin from the amino acid tryptophan and this formation is promoted by thiamine.

Inadequate nutrition and conditions which are complicated by malabsorption may lead to thiamine deficiency. Beriberi, a diet-deficiency disease, is especially prevalent in those parts of the East where the diet consists mainly of polished rice. The disease is characterized by neuritis but may also lead to serious heart failure. Recovery is prompt when adequate amounts of vitamin B_1 are restored to the diet. Severe deficiency as can occur in alcoholics may lead to Wernicke's encephalopathy, often accompanied by Korsakoff's syndrome. Care should be taken with intravenous substitution with thiamine in these cases to prevent serious complications like vascular collapse with hypotension, respiratory distress or angioedema.

Riboflavin (vitamin B_2) is found in liver, milk, meat, green vegetables, cereals and mushrooms. It is active in the form of two coenzymes, flavin mononucleotide and flavin adenine dinucleotide. As a coenzyme for proton transfer in the respiratory chain it is indispensable for energy-release from carbohydrates, lipids and proteins. Riboflavin deficiency only occurs in combination with deficiencies of other members of the vitamin B family. The symptoms of such deficiency consist of angular stomatitis, lesions of the cornea, dermatoses and normochromic normocytic anaemia.

As already mentioned above, apart from its formation from tryptophan niacin or nicotinic acid (vitamin B_3) is also found in many food ingredients, especially in fresh meat, eggs, and milk. Deficiency may cause pellagra which is characterized by gastrointestinal, skin and nervous system abnormalities. Niacin is converted in the body to the coenzymes nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADPH). Both are cofactors for oxidation/reduction reactions which are crucial for tissue respiration. Nicotinic acid occurs in these two nucleotides in the form of its amide, nicotinamide. Nicotinamide is also sometimes termed vitamin B_3 although it does not fulfill the criterion for a vitamin that there has to be a dietary need. Nicotinic acid itself and not nicotinamide has peripheral vasodilatory and lipid-lowering effects when given in pharmacological doses (see Chapter 20). Nicotinic acid and nicotinamide are identical in their function as vitamins and they are both used for prophylaxis and treatment of pellagra.

Pantothenic acid (vitamin B_5) is both present in many nutrientcients and it is also produced by intestinal bacteria. Deficiency is therefore thought to be unlikely. Its active form, 4-phosphopantetheine, is an element of both coenzyme-A and acyl-carrier protein and thus participates in fatty acid synthesis and in the posttranslational modification of proteins. Acetylcoenzyme-A is important for the synthesis of the neurotransmitter acetylcholine.

Pantothenic acid deficiency manifests itself by symptoms of neuromuscular degeneration and adrenocortical insufficiency.

Pyridoxine (vitamin B_6) is essential for protein metabolism and plays an important role in hemoglobin production. Pyridoxamine and pyridoxal also possess vitamin B_6 activity. Sources of pyridoxine are grains, cereals, bread, liver, avocado's, spinach, green beans, and bananas. Pyridoxine deficiency as a result of an deficient diet is usually part of multiple vitamin deficiencies. Symptoms of deficiency include dermatological problems and anemia. Pyridoxine deficiency may lead to convulsions through lowered concentrations of gamma-aminobutyric acid. Pyridoxine, pyridoxamine and pyridoxal are converted in the body by pyridoxal kinase to pyridoxyl phosphate, the active form. Isoniazid (see Chapter 25) is a potent inhibitor of pyridoxal kinase and it has its antivitamin B_6 effect by inhibiting the formation of the coenzyme form of the vitamin. This coenzyme forms stable, yet transient Schiff-base complexes with amines and is involved in all phases of amino acid metabolism. It also is a coenzyme for glycogen phosphorylase which breaks glycogen down to glucose. For the formation of nicotinamide from tryptophan pyridoxal phosphate is needed and for the extra desaturation of unsaturated fatty acids pyridoxal phosphate is also a cofactor.

Pyridoxine is indicated in vitamin B deficiency, for the treatment of some pyridoxine responsive anemia's and for isoniazid-induced neuropathy. It may relieve symptoms of pellagra when niacin fails. Long-term administration of large doses may produce neurotoxicity manifesting itself in progressive peripheral sensory neuropathy.

Biotin (vitamin B_7) is widespread in foods and is also synthesized by intestinal bacteria. It is a coenzyme for the carboxylation of pyruvate, acetylcoenzyme-A (CoA), propionyl CoA, and β-methylcrotonyl CoA and is involved in fatty acid formation and in energy release from carbohydrates. In humans deficiencies only occur in patients with an abnormal gut flora and manifests itself as exfoliative dermatitis and alopecia.

Folic acid or vitamin B_{11} is a coenzyme needed for protein synthesis, among others hemoglobin. Especially organ meats but also green vegetables and legumes, nuts and grains are all important sources for folic acid. In foods which are stored at room temperature or during the process of cooking folic acid decomposes and is lost. Folic acid is one of these not strictly fat soluble vitamins that can be stored in the liver and therefore does not have to be consumed daily. However, adequate folate intake during the periconceptional period helps protect against a number of congenital malformations including neural tube defects. The Recommended Dietary Allowance

(RDA) for folate equivalents for pregnant women is 600–800 micrograms.

Cyanocobalamin, or vitamin B_{12}, is in small amounts required for red blood cell production and for the formation of nucleoproteins and proteins. It is also needed for the proper functioning of the nervous system. Folic acid supplements can correct the anemia associated with vitamin B_{12} deficiency. Unfortunately, folic acid will not correct changes in the nervous system that result from vitamin B_{12} deficiency. Vitamin B_{12} is only found in animal sources such as liver and other organs. Some vitamin B_{12} is obtained from fish, eggs and milk. Folic acid and cyanocobalamin have been discussed in more detail in Chapter 22.

II.b. Vitamin C (See Table 1)

Ascorbic acid or vitamin C is found in fruits, especially citrus fruits, and in fresh vegetables. Man is one of the few mammals unable to manufacture vitamin C in the liver. It is essential for the formation of collagen as it is a cofactor for the conversion of proline and lysine residues to hydroxyproline and hydroxylysine. It is also a cofactor for carnitine synthesis, for the conversion of folic acid to folinic acid and for the hydroxylation of dopamine to form norepinephrine. Being a lactone with two hydroxyl groups which can be oxidized to two keto groups forming dehydroascorbic acid, ascorbic acid is also an anti-oxidant. By reducing ferric iron to the ferrous state in the stomach, ascorbic acid promotes iron absorption.

Oral absorption of ascorbic acid is via an energy-dependent process that is saturable and dose-dependent. Ascorbic acid is stored in the body. Excessive amounts of consumed vitamin C, i.e. if daily intake surpasses 100 mg, are rapidly excreted in the urine.

Deficiency may occur in infants if no fruits or vegetables are added to their milk formulas. In alcoholics, and in elderly subjects who consume inadequate diets vitamin C deficiencies are frequent. Severe ascorbic acid deficiency is characterized by the syndrome known as scurvy. Its manifestations are generally based on a loss of collagen. Symptoms include hemorrhages, loosening of teeth. In children cellular changes in the long bones occur.

Vitamin C is used for the treatment of ascorbic acid deficiency. Claims that high doses of up to 1 g daily had efficacy in shortening the duration of the common cold and could lessen its manifestations could not be substantiated. However, excessive doses may carry the risks for bladder and kidney stones.

III. FAT-SOLUBLE VITAMINS (SEE TABLE 2)

III.a. Vitamin A

Retinol or vitamin A_1, a primary alcohol, is present in esterified form in the tissues of animals and saltwater fish, mainly in the liver. Vitamin A_2 is a closely related compound, 3,4-didehydroretinol. In retinoic acid, i.e. vitamin A acid, the alcohol group has been oxidized. Because of possible cis-trans configurations around the double bonds in the side chain geometric isomers of retinol exist. Of all known derivatives, all-trans-retinol and its aldehyde, retinal, exhibit the greatest biological potency *in vivo*. Tretinoin, all-trans-retinoic acid, can be isomerized in the body to 13-cis-retinoic acid or isotretinoin. A large number of analogues of retinoic acid have been synthesized, including etretinate, the prodrug of the active compound acitretin. The term retinoids refers to the chemical entity retinol together with all closely related analogues which need not have retinol-like, i.e. vitamin A activity.

In the body retinol can also be made from the vitamin precursor carotene. Vegetables like carrots, broccoli, spinach and sweet potatoes are rich sources of carotene. Conversion to retinol can take place in the intestine after which retinyl esters are formed by esterifying retinol to long chain fats. These are then absorbed into chylomicrons. Some of the absorbed vitamin A is transported by chylomicrons to extrahepatic tissues but most goes to the liver where the vitamin is stored as retinyl palmitate in stellate cells. Vitamin A is released from the liver coupled to the retinol-binding protein in plasma.

Vitamin A is essential for proper functioning of the retina, for the integrity of epithelial tissue, for growth and bone development and for reproduction. For vision the active vitamin appears to be retinal as the chromophore of both rods and cones is 11-cis-retinal which, in combination with the protein opsin, forms the photoreceptor rhodopsin. Retinoic acid is the active form associated with growth, differentiation, and transformation. Both all-trans and 9-cis retinoic acid act as a steroid hormone to affect cellular differentiation, especially for morphogenesis, reproduction and for immune responses. At

least two classes of retinoic acid receptors have been identified. The RAR receptors, with three iso-forms, bind both all-trans and 9-cis forms while the RXR receptors only bind the 9-cis form. The β-isoform of the RAR receptor is involved with teratogenic effects under influence of an excess of all-trans vitamin A.

Vitamin A deficiency can result from insufficient dietary intake, from malabsorption and it has been recognized that also malfunction of RAR-receptors can lead to symptoms of vitamin A deficiency. These symptoms include skin lesions, night blindness, corneal ulcerations and conjunctivitis and poor bone remodeling. Vitamin A deficiency associated with malnutrition is wide spread in large parts of the world and may be fatal in infants and young children suffering from kwashiorkor or marasmus.

There are many retinol containing preparations to treat vitamin deficiency states. Retinoids are also used to treat dermatological diseases like acne, psoriasis, Darier's disease, and ichthyosis. Tretinoin, all-trans-retinoic acid, is a topical preparation while isotretinoin or 13-cis-retinoic acid, and etretinate are available for oral administration.

High daily doses of retinoids can lead to hypervitaminosis A manifesting itself as dermal toxicity such as erythematous dermatitis, bone pains, neurological symptoms and hepatosplenomegaly. A recent study shows a correlation between low bone mineral density and too high intake of vitamin A.

III.b. Vitamin D

Cholecalciferol (D_3) and its active form 1,25-dihydroxycholecalciferol are only to a certain extend vitamins because they can be synthesized by the human body. However deficiencies resulting in rickets in children and osteomalacia in adults do exist. Cholecalciferol can be synthesized by humans in the skin upon exposure to ultraviolet-B (UVB) radiation from sunlight, or it can be obtained from the diet. Plants synthesize ergosterol, which is converted to vitamin D_2 (ergocalciferol) by ultraviolet light. Vitamin D_2 may be less active in humans. Vitamin D promotes uptake of calcium and phosphate in the intestine and it stimulates osteoclasts to break down hydroxyapatite and release calcium into blood. Vitamin D is discussed in more detail in Chapter 24, Section V.a.

III.c. Vitamin E

Vitamin E or α-tocopherol is a lipophilic antioxidant which animals cannot synthesize. However vitamin E is found in liver and it is also present in vegetable oils, in green vegetables and in wheat. Its only established function in man is as an anti-oxidant. It will protect poly-unsaturated fats, cholesterol, and rods and cones from free radical damage. The antioxidant properties of vitamin E act in concert with selenium, which complexes with three amino acids to form the free radical scavenger glutathione.

Tocopherol is present in adequate amounts in the normal diet and vitamin E deficiency is not known in otherwise healthy children or adults. In man vitamin E also lacks efficacy in the treatment of those diseases that resemble vitamin E deficiency in animals.

Vitamin E may be indicated in some rare forms of anemia such as macrocytic, megaloblastic anemia observed in children with severe malnutrition and the hemolytic anemia seen in premature infants on a diet rich in polyunsaturated fatty acids. Also anemia's in malabsorption syndromes have shown to be responsive to vitamin E treatment. Finally, hemolysis in patients with the acanthocytosis syndrome, a rare genetic disorder where there is a lack of plasma β-lipoprotein and consequently no circulating alpha tocopherol, responds to vitamin E treatment. In neonates requiring oxygen therapy vitamin E has been used for its antioxidant properties to prevent the development retrolental fibroplasia. It should be noted that "high dose" vitamin E supplements are associated with an increased risk in all-cause mortality.

III.d. Vitamin K

The K vitamins include vitamin K_1, phylloquinone or phytonadione, and vitamin K_2 which is a group of compounds, the menaquinones. Menadione, vitamin K_3, is a precursor of menaquinone-4. Vitamin K is present in alfalfa and fish livers. Other dietary sources include green vegetables, soybean oil and eggs. A normal diet together with the bacterial synthesis of vitamin K in the gut are usually sufficient to prevent deficiencies in healthy adults.

In normal individuals phytonadione and the menaquinones have no activity while in vitamin K deficiency the vitamin promotes the hepatic biosynthesis of factor II (prothrombin), factor VII, factor IX and factor X. Vitamin K functions as an essential cofactor for the enzymatic activation of precursors of these vitamin K dependent clotting factors. The quinone structure of the active form of vitamin K, i.e. reduced vitamin K or hydroquinone,

is reversibly oxidized to its 2,3-epoxide in forming gamma-glutamylcarboxylate residues from glutamate residues on the precursor protein. Only the gamma-glutamylcarboxylate allows the protein to bind calcium which is necessary for clot formation. The epoxide is reduced again to the active hydroquinone form of vitamin K by a coumarin-sensitive epoxide reductase.

The human requirement for vitamin K appears to be very small but mild clotting disorders may result from digestive disturbances with consequent insufficient absorption of vitamin K.

Hypoprothrombinemia may occur in malabsorption syndromes and also the use of broad-spectrum antibiotics may produce a hypoprothrombinemia that responds readily to small doses of vitamin K. In premature infants and in infants with hemorrhagic disease of the newborn the use of vitamin K may be indicated. However, the main indication for the use of vitamin K is to antagonize the anticoagulant activity of coumarins. Oral absorption of phytonadione and the menaquinones is by the lymph while menadione and its water-soluble derivatives are absorbed directly. The absorption of phytonadione is energy-dependent and saturable. Intravenous administration of phytonadione has produced flushing, dyspnea, chest pains, and cardiovascular collapse.

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Chapter 30

Dermatologicals and Miscellaneous Agents

Chris J. van Boxtel

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I. DERMATOLOGICAL AGENTS

I.a. Introduction

Although it is the purpose of Section II of this book to give the reader an overview of our pharmacotherapeutic armamentarium, the coverage is not and cannot be intended to be all-inclusive.

Albeit that many of the agents used in dermatology will be prescribed only by dermatologists, we felt that the pharmacotherapeutic management of skin diseases should not be totally excluded from this text. We will not elaborate on the unique aspects of dermatological pharmacology such as the choice of dermatological vehicles, skin penetration, the use of special formulations to decrease absorption through the skin and the barrier function of the skin in general. However, several dermatological medications are worth to be mentioned. Firstly, because they are used on a large scale by a variety of disciplines and secondly, because with some there is a precarious balance between benefit and risk. If a drug is mentioned in the WHO Model Formulary 2006 this could also be an argument to have it listed here. For the selection of the agents that are briefly presented in this chapter those were the major criteria.

I.b. Topical Antibacterial Agents

Systemic antimicrobials are indicated for the treatment of sever or wide-spread infections of the skin, for infections which are accompanied with systemic symptoms and for dermatological infections that did not respond to topical treatment. Also for deeply localized infections like erysipelas and cellulitis and for the management of acne and rosacea the systemic use of antibiotics is indicated. The use of topical antibiotics is only justified for the treatment of minor cases of impetigo and infected eczema. Topical antibiotic agents can also be used for patients with mild forms of acne or rosacea. As it is advocated that the topical use of antibiotics which are also used for systemic infections should be limited to avoid the emergence of resistance and of sensitization of the patients, several antibiotics were developed that are only used topically.

I.b.1. Antibiotics

Antibiotics which are used in topical formulations include the aminoglycosides framycetine, neomycin and also gentamicin. However their use in dermatology is not recommended. Framycetine frequently gives rise to sensitization and resistance with cross-reactivity and cross-resistance extended to other aminoglycosides. Neomycin has the same disadvantages. Although generally poorly absorbed, even small amounts of absorbed neomycin carry the risk of oto- and nephrotoxicity. Gentamicin when applied to the skin can lead to detectable plasma concentrations with subsequent risks for toxicity.

Bacitracin and gramicidin are polypeptide antibiotics with activity against gram-positive organisms and against most anaerobic cocci. Systemic toxicity for bacitracin is rare because of poor absorption through the skin. Gramicidin is used only topically

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because of its systemic toxicity. It is often used in combinations e.g. with neomycin or polymyxin to broaden its spectrum.

Mupirocin is not related to any of the systemically used antibiotics. It is an inhibitor of bacterial protein synthesis and is especially active against gram-positive aerobic bacteria, e.g. methicillin-resistant *S. aureus* and group A beta-hemolytic streptococci. Absorption through the skin is minimal. Intranasal application may be associated with irritation of mucous membranes.

Polymyxin B sulfate, a polypeptide antibiotic, is effective against gram-negative organisms. Hypersensitivity to topically applied polymyxin is rare. To reduce the likelihood of neurotoxicity and nephrotoxicity the total daily dose applied to the denuded skin or to open wounds should not exceed 200 mg.

Topical tetracyclines are sometimes used to treat acne and minor superficial pyogenic infections of the skin. Patients hypersensitive to one member of this class of antibiotics may also be hypersensitive to other tetracyclines. Photosensitization may occur.

Clindamycin shows *in vitro* activity against *Propionibacterium acnes* and topically applied clindamycin is effective for the treatment of acne. Approximately 10% of an applied dose is absorbed. In spite of this absorption pseudo-membranous colitis with bloody diarrhea is seldom seen.

Fusidic acid is an antibiotic that belongs to a group of its own, the fusidanes. It has a steroid-like structure which might be responsible for the steroid-like high penetration. The anti-microbial activity of fusidic acid is specifically aimed at the most common skin pathogens, including *Staphylococcus aureus*. No cross-resistance or cross-allergy has been seen with other antibiotics. It is used in dermatology for the treatment of mild to moderately severe skin and soft-tissue infections, e.g. impetigo, folliculitis, erythrasma, furunculosis, abscesses and infected traumatic wounds.

I.b.2. Other Antibacterials

Silver sulfadiazine, a sulfonamide, is used for the management of infected burns. The occurrence of sulfonamide hypersensitivity is a serious risk though and this agent should be reserved for selected cases. Its activity is probably based on the bactericidal action of silver which is released but absorbed only to a negligible extend. The sulfonamide is well absorbed and appreciable blood levels are reached when large areas are treated.

Metronidazole is effective in the treatment of acne rosacea although for this indication its mechanism of action is not clearly understood. Long-term topical use for this indication is not recommended. This advice is founded on experiments in animals showing a carcinogenic effect by oral administration of metronidazole. There is inadequate evidence of the safety of metronidazole in human pregnancy. Metronidazole is classified in Lactation Risk Category L3 (moderately safe).

I.c. Topical Antifungal Agents

I.c.1. Antibiotics

Topical formulations of nystatin and of amphotericin B are useful in the management of *Candida albicans* infections of the skin. Both antibiotics are ineffective against dermatophytes. The use of nystatin is limited to topical treatment of cutaneous and mucosal *Candida* infections because of its narrow spectrum and its negligible absorption from the gastrointestinal tract. Hypersensitivity reactions are rare. It is not known whether topical nystatin can cause fetal harm when used by a pregnant woman. Amphotericin B has broader antifungal activity but its topical use is restricted to *Candida*. Topical use of amphotericin B has shown minimal absorption through the skin and is well tolerated. Limited human surveillance data do not indicate any harm to mother or fetus, but relative safety is still unknown.

Griseofulvin is an antifungal antibiotic used for treating common dermatophyte infections. It is inactive against yeasts. It is available in some countries as a solution which can be applied to the affected areas. However griseofulvin is mostly used systemically.

I.c.2. Azole Derivatives

Topical azole derivatives include the imidazoles bifonazole, clotrimazole, econazole, ketoconazole, miconazole, oxiconazole, lanoconazole, flutrimazole and sertaconazole. These drugs show activity against the dermatophytes *Epidermophyton*, *Microsporum* and *Trichophyton*. They are also effective against the yeasts *Candida albicans* and *Pityrosporum orbiculare*. Local side effects include pruritus, erythema and local irritation. Allergic dermatitis is rare.

I.c.3. Other Antifungals

Benzoic acid with salicylic acid is useful as an antifungal agent against various types of dermatophytoses. The combination also has keratolytic properties. Salicylic acid may cause mild irritation of the skin. If applied to large areas of the body, amounts sufficient to cause toxicity may be absorbed.

Methylrosanilinum chloride (Gentian violet) is a desinfectant with antifungal activity against yeasts. As a aqueous solution it is used topically to treat candida infections. Adverse effects include severe irritation, temporary staining of skin, permanent staining of fabrics. Animal carcinogenicity has been described (restricted use in some countries).

Ciclopirox olamine is a hydroxypyridone antifungal that is structurally unrelated to other antifungal agents. It is a broad-spectrum antimycotic agent with inhibitory activity against dermatophytes and yeasts such as candida species and *Pityrosporum orbiculare*. Although some absorption may occur adverse reactions are rare. Local pruritus may occur.

Naftifine is highly active against dermatophytes but less active against yeasts. Its mechanism of action is based on selective inhibition of squalene epoxidase, a key enzyme for the synthesis of ergosterol. Side effects include local irritation and erythema. Contact with mucous membranes should be avoided.

Terbinafine is closely related to naftifine and has similar activity. It is used for the topical treatment of dermatophyte infections. It can give local irritation and erythema and care should be taken to avoid contact with eyes and mucous membranes.

Tolnaftate is topically effective against various dermatophyte infections. It has also activity against *Pityrosporum orbiculare* but not against candida species. Local irritation and contact sensitization are rare adverse effects.

Selenium sulfide is a complementary drug for use in rare disorders or in exceptional circumstances. It has activity in pityriasis versicolor (lotion) and in seborrhoeic dermatitis. Adverse effects include local irritation and hair discoloration or loss. Absorption may result in systemic toxicity including tremors, weakness, lethargy, pain in lower abdomen and occasional vomiting.

I.d. Antivirals

Aciclovir, a synthetic purine nucleoside analogue derived from guanine, has *in vitro* inhibitory activity against members of the herpes virus family. Aciclovir is phosphorylated preferentially by herpes simplex virus-coded thymidine kinase and following further phosphorylation aciclovir triphosphate interferes with herpes virus DNA polymerase and viral DNA replication. Aciclovir topical cream is indicated in the management of initial genital herpes and in limited non-life threatening mucocutaneous herpes simplex virus infections in immunocompromised patients.

Topical aciclovir has limited effectivity in the treatment of recurrent herpes genitalis or herpes febrilis infections in non-immunocompromised patients, although topical aciclovir may cause some reduction in the duration of viral shedding. Topical aciclovir has no role in the treatment of herpes zoster.

Penciclovir is an other nucleoside analogue with a similar mechanism of action as aciclovir. Also with penciclovir the efficacy of topical use is marginal at best.

Idoxuridine is a halogenated pyrimidine derivative. Any efficacy of topical application of idoxuridine for the treatment of cutaneous and mucocutaneous herpes simplex lesions is dubious. An improvement of therapeutic efficacy of idoxuridine entrapped in liposomes in treatment of HSV-1 and HSV-2 patients has been reported.

Foscarnet is an inorganic pyrophosphate analogue which causes selective inhibition of viral DNA polymerase and reverse transcriptase. Topical foscarnet cream has appeared to be a safe and effective treatment for aciclovir-unresponsive mucocutaneous herpes simplex virus infection in AIDS patients.

I.e. Ectoparaciticides

The pediculicides include permethrin, malathion, lindane and combinations of pyrethrum extract or bioalletrin with piperonylbutoxide. Permethrin, lindane and benzyl benzoate are also effective scabicides.

Permethrin is neurotoxic to the parasites it affects. Up to 2% of topically applied permethrin is absorbed. Adverse reactions include local burning and pruritus. Sensitization may occur.

Lindane is the gamma isomer of hexachlorocyclohexane. Almost 10% of the topically applied dose is absorbed, stored in fatty tissues including the brain and then only very slowly excreted. Serious concerns about the neurotoxicity and hematotoxicity of this agent, especially in infants, children and pregnant women exist. Local irritation is frequent and

contact with mucous membranes and the eyes must be avoided. Permethrin cream was found to be significantly more effective in the treatment of scabies in comparison with lindane.

Malathion is an organophosphate cholinesterase inhibitor. Up to 8% of the topically applied dose may be absorbed. Malathion is used as a treatment for head lice, body lice and scabies. It effectively kills both the eggs and the adult lice. Malathion is an insecticide of relatively low human toxicity. However if malathion is used in an indoor environment, as it breaks down into malaoxon, it can be seriously and chronically poisonous. The safety of malathion in pregnancy and in lactating women and in children has not been established.

Bioallethrin is a synthetic pyrethrin insecticide. Piperonylbutoxide, a weak insecticide itself, has synergistic activity. The same holds true for the combination of pyrethrum extract with piperonylbutoxide. These combinations have the same efficacy as permethrin. Local irritation occurs frequently effect and contact with mucous membranes and the eyes must be avoided.

Benzyl benzoate has some pediculicide activity but is especially an effective scabicide. Irritation of the skin and allergic reactions are frequent. This agent is considered safe in pregnancy.

I.f. Retinoids

Tretinoin or retinoic acid is the acid form of vitamin A. Actually it is the all-trans isomer of retinoic acid. It is an effective topical agent for acne vulgaris. Its mechanism of action is believed to be associated with increased epidermal cell turnover. Some 10% of the topically applied dose is absorbed, metabolized by the liver and excreted in the urine and bile. To be effective tretinoin should be applied in a concentration that results in mild irritation and erythema. Patients should be advised to avoid or minimize sun exposure and use a protective sun screen as animal studies have raised some concern about possible carcinogenic effects under the influence of ultraviolet radiation. There are no indications that topical tretinoin is associated with an increased risk for birth defects.

Isotretinoin, or 13-cis-retinoic acid, and etretinate are available for oral administration. Isotretinoin is a synthetic retinoid that is used for sever cystic acne, recalcitrant to standard therapies. Its mechanism of action is not well understood but involves the inhibition of sebaceous gland size and function. Isotretinoin is well absorbed. In plasma it is extensively bound to albumin. It is metabolized in the liver mainly to 4-oxo-isotretinoin. Its elimination half-life is 10–20 hours. The adverse effects resemble hypervitaminosis A with dryness and itching of the skin. Abnormalities of plasma triglycerides and high density lipoprotein frequently occur. Less common side effects are headache, corneal opacities and muscle and joint pains. Skeletal hyperostosis may occur with premature closure of epiphyses in children. Teratogenicity is a significant risk in patients taking isotretinoin. Adequate contraception is obligatory for women of childbearing potential.

Acitretin is the major acid metabolite of etretinate and it is available for systemic use in severe forms of psoriasis which proved resistant to other treatments. In many countries etretinate was removed from the market due to the high risk of birth defects. Acitretin, in contrast to etretinate, does not accumulate in tissues and has an elimination half-life of only 2 days instead of 100 days. However, it has been found that acitretin can be metabolized to etretinate *in vivo* thus lessening the possible advantages of acitretin over etretinate with respect to their teratogenic activity. The formation of etretinate from acitretin appeared to be augmented by alcohol consumption. The advise is now that women must avoid becoming pregnant for at least 3 years after discontinuing acitretin.

I.g. Vitamin D Derivatives

Calcipotriol is a vitamin D_3 derivative which is used as a topical agent in the treatment of psoriasis. Although not completely elucidated its mechanism of action seems to be based on inhibition of the proliferation and stimulation of the differentiation of epidermal keratinocytes. Adverse effects include irritation of the skin but also urticarial reactions. Calcipotriol has 100 fold less vitamin D activity as its active vitamin D_3 metabolite calcitriol. However, calcipotriol in overdose can cause symptoms of hypercalcemia.

Tacalcitol is a synthetic vitamin D_3 analogue that is an effective drug for the topical treatment of psoriasis. Tacalcitol exerts its biological activity by preventing the proliferation of keratinocytes. It is well tolerated. Side effects, such as local irritation, pruriginous or burning sensations, were reported in only a small percentage of the subjects who were treated. Tacalcitol should be used with caution during pregnancy. There is no adequate information regarding its safety during breast-feeding.

I.h. Topical Corticosteroids

Numerous glucocorticosteroids for topical application are available. Essentially they all suppress the symptoms of inflammatory and hypersensitivity reactions and their mechanism of action is similar. Their indications include seborrhoeic and atopic dermatitis, phototoxic reactions, psoriasis, chronic discoid lupus, hypertrophic lichen planus and alopecia areata. However it has to be kept in mind that the use of corticosteroids for these conditions in most cases only gives symptomatic relieve and that the problem tends to recur on cessation of therapy. Traditionally topical corticosteroid formulations are grouped according to approximate relative efficacy. This efficacy is determined by both the potency of the agent and the concentration in which the corticosteroid is used.

Examples of group I, i.e. weak or low efficacy topical steroids, are hydrocortisone acetate in various concentrations, methylprednisolone 1.0% and prednisolone 0.5%. Group II, the moderately potent steroids, includes alclometasone dipropionate 0.05%, hydrocortisone butyrate 0.1%, triamcinolone acetonide 0.025% and fluocinolone acetonide 0.01%. Group III, the potent steroids, contains among others betamethasone valerate 0.1%, betamethasone dipropionate 0.05%, budesonide 0.025%, desoximetasone 0.05%, fluticasone propionate 0.05%, amcinonide 0.1%, fluocinonide 0.05% and mometasone furoate 0.1%. Group IV comprises the very potent agents such as clobetasol propionate 0.05% and halobetasol propionate 0.05%.

Increasing the concentration increases the penetration, but not to the same degree. Solubility of the corticosteroid in the vehicle is an other determinant of absorption and efficacy. So different formulations of the same corticosteroid can end up in a different efficacy classification. Efficacy can be further augmented by using the corticosteroid under occlusion. Occlusion with plastic enhances penetration and also absorption. However, with increased absorption also the risk of systemic side-effects increases. Systemic absorption will suppress the pituitary-adrenal axis and may cause Cushing's syndrome and a plethora of other adverse events (see Chapter 24, Section II.b). Even small amounts absorbed may already cause growth retardation in children.

Atrophy of the epidermis is a frequently occurring local adverse effect. A decrease of dermal collagen results in atrophic striae, loss of elasticity and telangiectasias. Bruising and purpura may occur as a result of increased fragility of skin vessels. And finally, contact hypersensitivity reactions to topically applied steroids are not rare events.

I.i. Other Dermatologicals

Aluminum acetate is a topical agent used as an antiseptic including suppurating superficial wounds and tropical ulcers, and the lesions produced by pemphigus and impetigo.

Benzoyl peroxide is a keratolytic drug. It has bacteriostatic activity against *Propionibacterium acnes.* Initial irritation is common. Rarely, contact sensitivity occurs. Potassium permanganate is used for the same indications.

Dithranol is an anthracene derivative for the topical treatment of moderately severe psoriasis. It is an irritant and contact with eyes and healthy skin should be avoided.

Fluorouracil is a pyrimidine analogue (see Chapter 27, Section II.b.3). Topical application may be used for malignant and premalignant skin conditions, including actinic keratosis. Adverse effects include local inflammatory and allergic reactions. Photosensitivity reactions during and for up to 2 months after treatment may become manifest.

Podophyllin is a resinous powder obtained from the American Mayapple. Podophyllin is used to remove genital warts. As it is a strong irritant the use on large areas and mucous membranes should be avoided. Systemic effects resulting from cutaneous absorption including gastrointestinal complaints, transient blood discrasias, renal failure and delayed neurotoxicity may occur. It is contraindicated in pregnant and lactating women.

Pramocaine is a topical anesthetic used as an antipruritic. The use on large areas and mucous membranes should be avoided. Topical lidocaine in combination with levomenthol is used for the same indications. Levomenthol has mild local anaesthetic, cooling and decongestant properties.

Becaplermin is a recombinant human "platelet derived growth factor". It is used to promote the granulation of diabetic, primarily neuropathic, chronic ulcers. Despite the low absorption and short elimination half-life, use during pregnancy and lactation is advised against.

Imiquimod is approved for the local treatment of external genital and perianal warts in adults. The agent has immunomodulating effects and it also stimulates antiviral activity.

II. MISCELLANEOUS AGENTS

II.a. Introduction

There are many medicinal agents that we did not deal with in the previous 13 chapters and several possible reasons could have played a role. In the light of the abundance of comparable drugs and me-too products it will very often have been the case, and inevitably so, that a particular compound was not mentioned because other representatives from the same class were chosen as examples. An other possible reason is that we did not incorporate in our text the group, class or subclass to which a particular medicament belongs, like for example the mineral preparations for substitution therapy or the group of antidotes and the compounds that are used for diagnostic purposes only. Often such decisions were made because we felt that too small a segment of the medical profession would ever be confronted with these agents to any significant extend or that no overt pharmacological principle was involved. However, for a few drugs an exception is warranted here. The third reason why certain remedies were thus far not mentioned is because almost all the agents used for a particular group of diseases, like the sympathomimetics, parasympathicolytics (Chapter 18) and corticosteroids (Chapter 24) for respiratory diseases, are mentioned elsewhere. It would therefore not serve any purpose to have a separate chapter to cover these agents in the context of lung disease. However, in consequence theophylline, the leukotriene antagonists and the anti IgE antibody omalizumab were left out. The fourth reason why some drugs were not discussed earlier could have been that the drug in question could not unequivocally be classified. Among the relatively small number of compounds that were omitted for this reason there are some that are worth mentioning, sometimes because they form a new pharmacological approach or might even be the first pharmacotherapeutic modality to treat a symptom or a disease.

The so-called biologicals have received from us some special attention in these paragraphs of Chapter 30 as we feel that their appearance on the global market in the past decennium might signify a milestone in the history of pharmaceutical medicine.

II.b. Agents to Treat Substance Abuse (See also Chapter 16)

Acamprosate (calcium acetylhomotaurinate) is a synthetic compound with a similar chemical structure to that of gamma-aminobutyric acid. It is the first agent specifically designed to maintain abstinence in alcohol dependency. Its mechanism of action is believed to be via inhibition of neuronal hyperexcitability by antagonism of excitatory amino acid activity and reduction of calcium ion fluxes. The efficacy of acamprosate was shown to be dose dependent. There is no evidence of abuse potential with acamprosate. Absorption is rapid but limited after oral administration and when acamprosate is concomitantly administered with food, the amount absorbed is decreased. Acamprosate is not protein bound. The elimination of acamprosate occurs as unchanged acetyl-homotaurine in urine, the other half might be eliminated by biliary excretion. During repeated oral administration steady-state is reached only after 5–7 days. Acamprosate is generally well tolerated, its most common adverse events being gastrointestinal, especially diarrhoea, or dermatological. They are mostly mild and transient.

Disulfiram (tetraethylthiuram) is used as an pharmacological adjunct in the treatment of alcoholism. Alcohol is metabolized by alcohol dehydrogenase to its major metabolite acetaldehyde, which is further oxidized by aldehyde dehydrogenase. Disulfiram is an aldehyde dehydrogenase inhibitor and alcohol consumption in the presence of disulfiram results in acetaldehyde accumulation with symptoms of flushing, severe headache, nausea and vomiting, hypotension and confusion. Disulfiram is well absorbed after oral administration. It is metabolized in the liver with an elimination half-life of some 24 hours. Tiredness, headache and sleepiness are the most common of its less serious adverse effects. Disulfiram can be neurotoxic resulting in peripheral neuropathy and optic neuritis. Psychosis and confusional states may also occur. Although rarely, disulfiram can cause hepatitis, which is sometimes fatal.

Bupropion and also varenicline are mentioned in Chapter 21, Section I.c.4. Bupropion is a norepinephrine and dopamine reuptake inhibitor deveoped as an antidepressant. It is now used on a large scale as a smoking cessation aid. Varenicline is the first nicotinic receptor partial agonist approved to treat smoking addiction.

Nicotine is available for nicotine addicted subjects as gums, dermal patches, lozenges and nasal sprays to help people quit smoking. All these formulations appear to be equally efficacious, approximately doubling the quit rate compared with placebo. However the abstinence rate at one year is often still not higher than 5%. Administration as a

patch can result in contact dermatitis. Nicotine gum can give mild gastrointestinal complaints.

Mecamylamine is a nicotinic antagonist and thus may block the rewarding effect of nicotine. Data from two small studies suggest that the combination of nicotine and mecamylamine may be superior to nicotine alone.

II.c. Agents Used for Weight Correction

Orlistat, a semisynthetic derivative of lipstatin, is a potent and selective inhibitor of pancreatic lipases. It was designed to treat obesity. Orlistat prevents approximately 25% of dietary fat from being absorbed. Very little of the drug itself is absorbed. Its adverse effects are therefore restricted to those related to fat malabsorption, with potential losses of fat-soluble vitamins. It has a relatively small effect on body mass, but enough to realise in one study a 37% reduction in the incidence of type 2 diabetes.

Sibutramine is a centrally-acting serotonin-norepinephrine reuptake inhibitor with some structual similarities to amphetamines. It was developed for the treatment of obesity. Peak plasma levels are reached after 1 hour. It is metabolised by CYP3A4 with an elimination half-life of approximately 1 hour. It is modestly effective in promoting weight loss. Although concerns were raised about its cardiovasculair safety, a recent study in overweight/obese subjects with an increased risk of cardiovascular disease concluded that sibutramine was efficacious, tolerable and safe in this high-risk population.

Rimonabant is an inverse agonist for the cannabinoid receptor CB1. In 2006 rimonabant was approved in the European Union as an anti-obesity drug. The use of rimonabant after one year produces a modest weight loss of approximately 5%. However there are serious concerns over suicidality, depression and other related side effects associated with use of the drug. In Europe, rimonabant is now contraindicated for patients with severe depression.

Anabolic steroids have been promoted as a means to foster protein synthesis and inhibit catabolism. Possibilities for considerable weight gain have been implied. In practice however these effects are disappointing, certainly in relation to the toxicity of these agents. In HIV-infected patients the administration of anabolic steroids appeared to result in a small increase in both lean body mass and body weight. The androgenic properties that all anabolic steroids have in common stand in the way of their therapeutic use.

Of antihistamines like cyproheptadine, which also have antiserotoninerge properties, it was suggested on the basis of some clinical observations that they could bring forward an increased appetite and related increases in body weight. However, controlled comparative investigations in respect of these effects are missing.

II.d. Enzyme Replacement Therapy

Agalsidase alpha (Replagal) and agalsidase beta (Fabrazyme) are in human cell lines produced, recombinant forms of the enzyme alpha-galactosidase-A. Fabry disease is characterized by a deficiency of this enzyme. Currently Fabry disease is being treated at the cellular level through enzyme replacement therapy using agalsidase alpha and agalsidase beta. These enzymes are eliminated by hydrolisis with a half-life of 80–120 minutes. Infusion related complaints such as fever, chills, flushing, headache, chest pain, pain in the (under) abdomen, nausea, dyspnea and fatigue are frequently occurring side effects.

Alglucosidase alpha is recombinant human acid alpha-glucosidase. In Pompe disease, glycogen storage disease type II, there is a deficiency of alpha-1,4-glucosidase (or acid maltase). In 2006 alglucosidase alpha (Myozyme) was approved as the first treatment for infants with Pompe disease. The benefits of this treatment modality in the late-onset form of Pompe disease have not been established. Alglucosidase alpha is administered by intravenous infusion. The plasma elimination half-life is approximately 2.5 hours. Adverse reactions like fever, hives and rashes are frequently seen. Life-threatening anaphylactic reactions, including anaphylactic shock may occur.

Galsulfase (Naglazyme), a recombinant form of human N-acetylgalactosamine 4-sulfatase, was approved in 2005 for the treatment of mucopolysaccharidosis VI (MPS VI) or Maroteaux–Lamy syndrome. In the Maroteaux–Lamy syndrome there is a deficiency of a lysosomal hydrolase that catalyzes glycosaminoglycans leading to an the accumulation of the substrate and widespread cellular, tissue, and organ dysfunction. After intravenous infusion galsulfase is eliminated by peptide hydrolysis with an elimination half-life of 23 hours. The most common adverse events are headache, fever, arthralgia, vomiting, upper respiratory infections, abdominal pain and diarrhea. Angioneurotic edema, hypotension, and respiratory distress were reported.

Idursulfase (Elaprase) is a drug used to treat mucopolysaccharidosis II or Hunter syndrome. It is a lysosomal storage disease caused by iduronate-2-sulfatase deficiency. Idursulfase is a purified form of iduronate-2-sulfatase produced by recombinant DNA technology in a human cell line. The drug provides clinically important benefits to Hunter syndrome patients. After intravenous infusion Idursulfase is eliminated by peptide hydrolysis with an elimination half-life of 45 minutes. The most common adverse events are hypersensitivity reactions, pyrexia, headache and arthralgia.

Laronidase (Aldurazyme) is recombinant-L-iduronidase. In mucopolysaccharidosis I (Hurler syndrome) there is a deficiency of the lysosomal enzyme α-L-iduronidase. Laronidase is employed for the non-neurological manifestations of Hurler syndrome. After intravenous infusion laronidase is eliminated with a half-life of 1.5–3.6 hours. Infusion related side effects are seen frequently. Hypersensitivity reactions may occur.

Imiglucerase, recombinant β-glucocerebrosidase, is effective for the treatment of type 1 Gaucher's disease. Imiglucerase is gradually replacing the human placental derived alglucerase. Lysosomal β-glucocerebrosidase catalyses the hydrolysis of the membrane lipid glucoserebroside into glucose and ceramide. In Gaucher's disease there is a deficiency of this enzyme resulting in glucoserebroside accumulation in macrophages in liver, spleen, lymph nodes and bone marrow. Imiglucerase is administered by intravenous infusion and disappears rapidly from plasma with an elimination half-life of some 5–10 minutes after the infusion is terminated. Allergic reactions to heamacel, a gelatin based plasma substitute which is a component of imiglucerase, have been described.

II.e. Selected Respiratory Agents

Theophylline, a dimethylxanthine, causes bronchodilation, possibly by inhibiting the enzyme phosphodiesterase in smooth muscle of the bronchioli. An other proposed mechanism of action is that of adenosine receptor antagonism. It has positive chronotropic and inotropic, CNS stimulant and weak diuretic properties. In obstructive lung disease sustained release tablets are to be preferred. Theophylline has a narrow therapeutic index. Therapeutic plasma concentrations are between 7–15 mg/l. Theophylline undergoes N-demethylation via CYP1A2 in the liver and is eliminated in the urine as metabolites and 10% unchanged. The elimination half-life shows large interindividual variability. It can cause nausea, diarrhea, increase in heart rate, CNS excitation and sometimes lethal arrhythmias.

The leukotriene antagonists montelukast and zafirlukast block the actions of cysteinyl leukotrienes at the cysteinyl leukotriene receptor 1 (CysLT1) on target cells such as bronchial smooth muscle. They are able to improve asthma symptoms, reduce asthma exacerbations and reduce secundary markers of inflammation in peripheral blood and in bronchoalveolar lavage fluid. Montelukast is administred orally. It is rapidly absorbed with a bioavailability of around 65%. It is extensively metabolized and eliminated with a half-life of around 7 hours. Side effects include gastrointestinal disturbances, hypersensitivity reactions, sleep disorders and increased bleeding tendency. Zafirlukast has a similar profile as montelukast. After oral administration it is metabolised and eliminated with a half-life of around 10 hours. Headache, dizziness, fever and gastrointestinal complaints are the main side effects. Neuromuscular and skeletal complaints such as back pain, myalgia and weakness may occur. Adequate information about safety of montelukast or zafirlukast during pregnancy or in lactating women is not available.

Zileuton, also a leukotriene modifier, blocks 5-lipoxygenase and thereby inhibits leukotriene synthesis. It is a hydroxyurea derivative. It is used for prophylaxis and chronic treatment of asthma in patients 12 years of age and older. Zileuton is rapidly absorbed and has a high protein binding of 93%. It is metabolized in the liver and eliminated with a half-life of 2.5 hours. Headache is a frequently occurring side effect as are liver enzyme elevations. Other adverse reactions include gastrointestinal disturbances, dizziness, fever, insomnia, malaise, nervousness and somnolence. Hypersensitivity reactions are rare. Animal studies seem to indicate adverse effects during pregnancy. The degree of excretion in breast milk is unknown.

Omalizumab is a recombinant DNA-derived humanized IgG monoclonal antibody that selectively binds to human immunoglobulin E (IgE) and inhibits the binding of IgE to high-affinity IgE receptors. It is used mainly in allergy-related asthma therapy. Adding omalizumab injections to an existing treatment program using inhaled steroids has been clinically proven to help reduce the number of asthma attacks. The drug is administered subcutaneously in 1–3 injections every 2 or 4 weeks. Injection-site reactions are frequent. The use of omalizumab seems

to be associated with provoking upper respiratory tract infection. Anaphylaxis has occurred after the first but also after repeated omalizumab injections.

II.f. Unclassified Agents

Sildenafil is an oral therapy for erectile dysfunction (see also Chapter 20, Section XII.b). Its mechanism of action is based on selective inhibition of phosphodiesterase type 5 with relaxation of corpus cavernosum smooth muscle. Sildenafil is rapidly absorbed. First pass metabolism to an active metabolite by cytochrome P450 enzymes, mainly CYP3A4, reduces its oral bioavailability with 25–60%. Its elimination half-life is 3–5 hours. Lower doses are recommended in patients receiving cytochrome P450 enzyme CYP3A4 inhibitors, such as ketoconazole, erythromycin or cimetidine. Common adverse events associated with sildenafil are transient and mild or moderate and included headache, flushing, dyspepsia, nasal congestion and abnormal vision. Marked hypotension may occur during concurrent administration of sildenafil and organic nitrates, a combination which is contraindicated. Some serious cardiovascular events, some of them fatal, have been seen in patients with other known risk factors.

Betaine or trimethylglycine (TMG) is an amino acid. Betaine is used to treat high homocysteine levels. Betaine donates a methyl group to convert homocysteine to methionine in a reaction catalysed by betaine homocysteine methyltransferase. In a proportion of patients with homocystinuria who have not responded adequately on conventional treatment with diet and vitamins the agent is able to induce an additional reduction of homocysteine levels. Reduction of the homocysteine levels improves the prognosis of patients with homocystinuria, especially at an early stage. There is rapid oral absorption with peak plasma levels being reached after 1.5 hours. Betaine is mainly eliminated by metabolism with an elimination half-life of 14.5 hours. Betaine if taken in high dosages can cause nausea, increased body temperature, restlessness, insomnia and muscle tension headache.

Carglumic acid (N-Carbamoyl-L-glutamic acid) is an agent that is indicated for the rare disorder hyperammonaemia due to the illness N-acetylglutamate synthetase deficiency. In individual cases, this treatment modality proved to be of value. Carglumic acid is an analogue of N-acetylglutamate, the natural activator of carbamoylfosfate synthetase. Carglumic acid realizes a decrease in ammonia levels in blood and an increase of urea in blood and urine. A normalization of the plasma levels of ammonia is usually achieved within 24 hours. After oral dosing some 30% is absorbed with peak plasma levels after 3 hours. Carglumic acid is partly metabolized. It is eliminated with a half-life of some 5.5 hours. Tolerability is good. Carglumic acid is contraindicated for lactating women.

Cysteamine (β-mercapto-ethylamine) is used for the treatment of nephropathic cystinosis. Cysteamine converts within lysosomes cystine into cysteine and cysteine–cysteamine mixed disulfide, both of which can exit the lysosome thus removing the extra cystine. After oral administration peak plasma levels are reached at about 1.4 hours post dose. It is eliminated as a sulfate in the urine with a half-life of 4–5 hours. The most frequent adverse reactions seen involve the gastrointestinal and central nervous systems. Side effects include abdominal pain, diarrhea, drowsiness, fever, loss of appetite, nausea or vomiting and skin rash. Confusion, dizziness and headache may occur.

Miglustat is an inhibitor of glucosylceramide synthase, an enzyme that is responsible for the first step in the synthesis of most glycosphingolipids. This inhibition reduces the accumulation of glucosylceramide in patients with type I Gaucher's disease. Although it is the only oral drug available for the treatment of Gaucher's disease, miglustat is at the moment only used for patients who cannot be treated with enzyme replacement therapy. After oral administration peak levels are reached at 2.5 hours after dosing. The drug is eliminated in the urine with an elimination half-life of 6–7 hours. Gastrointestinal complaints are the most frequently occurring side effects. Cases of peripheral neuropathy have been reported in patients treated with miglustat.

Nitisinone is a reversibile inhibitor of 4-hydroxyphenylpyruvate oxidase, an enzyme that plays a crucial role in the tyrosine catabolic pathway. Nitisinone prevents the accumulation of the toxic metabolites fumaryl acetoacetate, succinyl acetoacetate and succinyl acetone. Nitisinone is used for the treatment of hereditary tyrosinemia type 1. After oral administration bioavailability is 90% and peak levels are reached at 2.5 hours after dosing. The drug is eliminated mainly in the urine but some CYP3A4-mediated metabolism seems to occur. The elimination half-life is 45 hours. Blood dyscrasias are frequently occurring side effects as are eye problems like conjunctivitis, corneal opacity and keratitis. Exfoliative dermatitis, erythematous rash and pruritus

may occur. Nitisinone should not be used during pregnancy unless clearly necessary and mothers receiving nitisinone should not breast-feed.

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Section III

Treatment of Health Problems

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Chapter 31

Symptomatic Treatment

Iwan Darmansjah, Inger Hagqvist

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I. INTRODUCTION

In 1959, H.K. Beecher, author of *The Measurement of Subjective Responses* wrote: "Notwithstanding the fact that the limelight in therapeutics has for some time been focused on the great advances made in chemotherapy, it is nonetheless true that much of medicine is still concerned with the treatment of symptoms". This statement is true and holds on until this date.

Prior to the 1940s almost all pharmacotherapy conducted by physicians is merely the alleviation of symptoms of disease and causal treatment consisted mostly of surgical interventions. It is only that after the development of antiparasitic agents and antiinfectives, like salvarsan and later penicillin, that causal treatment was known and that the understanding was induced that if possible, a disease should be treated at its root (causal treatment) in favor of symptomatically. This created the insight that causal treatment bears more weight compared to symptomatic treatment.

Although in general, causal treatment is more beneficial to the patient, this form of treatment is not always available for all diseases. Today, it is even rare for a variety of diseases like carcinoma, hypertension and other cardiovascular diseases, influenza, migraine, arthritis, bronchial asthma, and many more. Even with powerful medicines like corticosteroids and specially targeted drugs, the above diseases are not being handled causally.

Apart from disease entities, one recognizes a variety of symptoms that makes up a disease, like pain, fever, convulsions, cough, rhinitis, nausea, meteorism, diarrhea, headache, dyspnea, anorexia, insomnia, constipation, etc. All these symptoms could make up a symptom complex or syndrome, or may stand alone by themselves without being part of a disease entity. The term of symptomatic drug treatment usually refers to its use for the alleviation of symptoms, whether as a part of a syndrome or standing alone.

Symptomatic treatment still is an important treatment modality, and should be regarded as equally important as causal treatment. When one neglects symptoms or treat them inappropriately it may result in aggravation of the situation. On the other hand, treatment of all symptoms a patient may have, especially excessive treatment, will increase the risk of adverse reactions, which eventually could be dangerous. The guidance given in this chapter will discuss the drugs of choice for the use in symptoms seen

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in general and specialist practices to alleviate suffering, as well as in hospitalized patients. Although the above mentioned symptoms are regarded as trivial by many of the medical profession, inadequate management could elicit a severe chain reaction and cause unnecessary suffering of the patient, including hospitalization. Most of these cases are in fact preventable with appropriate symptomatic management.

II. COMPLAINTS AND SYMPTOMS

Usually the complaints a patient has makes the patient decide to consult a doctor. There are other motives of course, such as a medical check up or going to a laboratory for a test without a doctor's prior consultation to indicate the items for testing. However, very few things can be elucidated in laboratory check-ups without the guidance of a well-conducted anamnesis by a doctor. Every practicing physician has experienced how difficult it is to translate a patient's complaint(s) into the medical symptomatology. Understanding patient's complaints in the context of medical symptomatology is very much needed because the treatment that a physician will choose for his patient is not applicable for complaints, which are not in the medical vocabulary. The use of several languages or dialects produces a variety of imprecise meanings of words and terms. The type of complaint is determined by the individual and therefore subjectivity is great and variable, dependent of several factors, such as: educational and cultural background, language used, intelligence, religion or belief, age, sex, etc.

Headache for instance has several connotations for many people. It may be interpreted as the real meaning of the term, but often this may be lightheadedness or dizziness, vertigo, or even migraine. This should of course be solved through proper history taking so that it is clear what the patient means. Failure to do this will evidently result in missing the target of the symptom. Perhaps, here lays the ART of prescribing, but when a diagnosis is firmly established and the complaint of the patient is understood in formal medical terms, one would need SCIENCE to choose the right medication. Evidence-based therapy and drugs of choice should be applied, and redundant therapy minimized, hereby eliminating polypharmacy.

Important: The patient's symptoms and problems must always be put into the appropriate context, and causal treatment should be given whenever possible. Some of the symptomatic treatments described in the following should therefore mainly be seen as a complement to causal treatment. In many conditions of a more trivial and transient character patients also need to use medicines and wants a doctor's advice on what is the best therapy for the alleviation of their symptoms.

III. PAIN

Acute pain is a warning signal and it is necessary to take a medical history and make the appropriate investigations to make a diagnosis and to give causal treatment. In pain of a more chronic nature an analysis of the origin of the pain and its character must be made in order to give the correct treatment (Table 1).

III.a. Symptomatic Treatment of Pain[1]

Drug treatment is one of the most important principles in the management of pain. The WHO has described in its 'pain relief ladder' a practical approach to the choice of analgesics in symptomatic treatment of cancer pain. The 'ladder' is based on a pharmacological approach rather than based on the physiology of pain.

In caring for an individual, a treatment based on broad analytical thinking about the cause and nature of the pain has the best chance of success. However, the 'ladder' may serve as an educational and, to some extent, practical guide in weighing factors such as analgesic potency, mechanism of action and risk of adverse reactions.

The principles are initiation of analgesia for mild to moderate pain with mild peripherally acting analgesics and thereafter the addition of centrally acting mild analgesics. If this approach is inadequate or pain is initially severe, more powerful centrally acting analgesics can be used in increasing doses and/or with the addition of peripherally acting analgesics. A mechanical application of the principles of the pain ladder may however lead to treatment error, and the choice of analgesics must always

[1] Text from Läkemedelsboken 2007/2008; Chapter Smärta och palliativ vård, author Jan Hasselström; p. 699 – only the text box; p. 707 (starting with the heading Symtomatisk farmakologisk behandling)–713 (up to and including the paragraph headed Ögat (under the main heading Lokalanestetika); Tables 1 (3), 2 (4), (3) 5 and 4 (6). Reproduced by permission of Apoteket AB.

Table 1. Main types of pain

Nociceptive pain	The pain is mediated via pain receptors (nociceptors) from the damaged tissue. The pain signal is transported via A-delta-fibres or C-fibres to the central nervous system
Neuropathic pain	The pain signal occurs in the nervous system due to damage or mis-function in the nerve itself or in the central nervous system
Psychogenic pain	Pain caused by psychic mechanisms
Pain of unknown origin	Pain without obvious or suspect damage or disease, possibly with weak strengthening of peripheral pain signalling after a healed damage

take into account the origin of the pain and the available documentation regarding the individual's pain.

The division into peripherally and centrally acting analgesics is now being challenged, but has not yet been replaced by a better alternative. The so-called centrally acting opioids have been shown in several cases to have important peripheral effects through, for example, opioid receptors in synovia and in the gastrointestinal tract. Several of the so-called peripherally acting substances, i.e. paracetamol and the NSAIDs have been shown in experimental systems to have central effects by inhibiting the excitatory amino acid systems which are important in the regulation of central pain transmission. From a practical point of view the central/peripheral division holds though, in that it recommends a combination of analgesics with complementary modes of action.

In establishing a maintenance treatment with analgesics and in the assessment of effect–duration, the half-life ($t_{1/2}$) of a medicine often gives some guidance. If a dose is given before the drug is eliminated from the body, a steady-state concentration will be attained by regularly added doses. Such a balance between administration and elimination occurs within 4–5 times the $t_{1/2}$ after the first dose or at a dose change (see Chapter 11). The effect of an analgesic, and its adverse reactions, in relation to the given dose, cannot be evaluated fully until such a balance has been achieved.

III.b. Specific Comments on Analgesic Use

III.b.1. Paracetamol

Paracetamol is an effective analgesic without obvious clinical anti-inflammatory effect. It has low toxicity if it is used appropriately. Paracetamol is a first choice treatment for mild to moderate pain and can be given for all types of nociceptive pain. It has been shown to have effects comparable to several other analgesics for e.g. non-inflammatory arthrosis pain. Single doses of more than 1 gram have no additive effect and a total dose of 4 grams daily should not be exceeded.

Paracetamol can cause serious liver damage with life threatening necrosis in single doses of >10 grams, although an exact toxic dose has not been defined. Acetylcysteine is used as an antidote for paracetamol intoxication. The chance of successful treatment is increased if the antidote is given as shortly as possible after paracetamol intake. Alcoholics and patients that are treated with enzyme inducing drugs, e.g. carbamazepine, phenytoin or rifampicin, may be at risk of developing liver damage at normal therapeutic doses, so these patient groups should be treated with caution.

III.b.2. Non-steroidal Anti-inflammatory Drugs (NSAIDs) (See Tables 2 and 3)

Research over the last years and the debate around the most recent NSAIDs, the cyclo-oxygenase-2-(COX-2-) selective inhibitors (coxibs), have contributed to an increased understanding of the effects and potential adverse effects of the whole substance group. The early findings from 1999 when it was shown the coxibs could give a certain reduction in gastrointestinal damage, particularly in susceptible individuals, have been generally accepted. An expected protective effect reaches at most a 50% reduction in the frequency of serious gastrointestinal events.

The addition of proton pump inhibitors (PPIs) to treatment with conventional NSAIDs is probably the most cost-effective alternative for the prevention of gastrointestinal events. Addition of misoprostol is also a well-documented prophylactic routine.

Table 2. Medicines used in nociceptive pain conditions – paracetamol and NSAID

Substance	Mechanism of action	Half-life (h)	Time to steady-state concentration (h)	Clinical comments
Peripherally (?) acting – effective in nociceptive pain				
Paracetamol	Unclear. Centrally via excitatory amino acid systems?	1.5–3	6–15	Baseline drug in nociceptive pain. Analgesic effect comparable to several NSAID has been shown for non-inflammatory arthrosis
Short-acting NSAIDs – effective in nociceptive pain of inflammatory origin				
Acetylsalicylic acid (ASA)	Non-reversible COX inhibition	0.25 (3–4 for active metabolite)	15–20	Acts pain relieving via the metabolite salicylic acid. Thrombocyte inhibition mainly via ASA. Not recommended as first choice due to risk of G-I adverse reactions
Diclofenac	Reversible COX inhibition	1–2	5–10	Useful, tried and tested first choice among NSAIDs. Available also in gel form and as a plaster
Ibuprofen	Reversible COX inhibition	~2	~10	Useful, tried and tested first choice among NSAIDs. Available also in gel form and as a plaster
Ketoprofen	Reversible COX inhibition	~2	~10	Useful, tried and tested first choice among NSAIDs. Local treatment with the gel form is an alternative, particularly in patients at risk
Medium acting NSAIDs – effective in nociceptive pain of inflammatory origin				
Indometacin	Reversible COX inhibition	4–12	20–48	Tried and tested NSAIDs. *Not* recommended as first choice due to risk of e.g. GI adverse reactions
Naproxen	Reversible COX inhibition	10–17	2–3.5 days	Useful, tried and tested first choice among NSAIDs
Long-acting[a] NSAIDs – effective in nociceptive pain of inflammatory origin				
Nabumetone	Reversible COX inhibition	18–25 (refers to active metabolite)	4–7 days	Alternative with low toxicity, long-acting
Coxibs (COX-2 inhibitors; NSAIDs with COX-1-sparing effect)				
Celecoxib	Reversible COX-2 inhibition with COX-1-sparing effect	8–12 (refers to active metabolite)	~5	NSAID with low toxicity and medium effect duration

[a]Slow release formulations are available for tried and tested substances, e.g. ketoprofen and naproxen, if increased duration of effect is needed.

Of practical importance is the problem of prescribing to the elderly, and to those with comorbid conditions e.g. greater risk of serious gastroduodenal reactions, high risk of exacerbating cardiac failure and development of renal failure in patients dependent on prostaglandins to maintain glomerular perfusion, dehydration, concomitant use of ACE inhibitors and diuretics. It is of importance to use the lowest effective dose and use it intermittently if possible.

Unfortunately, the cyclo-oxygenase-2-(COX-2-) selective inhibitors have been shown to carry an increased risk of thromboembolic events in long-term use, which limits their usefulness. For other NSAIDs

Table 3. Organ systems where NSAID (including COX-2 inhibitors) may cause adverse reactions, and suggestions of clinical measures to reduce the risks

Organ	Risk factors	Recommended clinical measures
GI	Age > 65 Previous ulcer Steroid treatment Treatment with more than one NSAID	Scrutinize the indication, inform about the risks and choose another analgesic. Consider ulcer prophylaxis with proton pump inhibitors or misoprostol, or alternatively choose a COX-2 inhibitor
Heart	Heart failure or other serious heart disease	Scrutinize the indication – choose other analgesic if possible. Start with a low dose
Vessels, heart	Hypertension Ischaemic heart disease	Extra blood pressure checks. NSAIDs including COX-2 inhibitors may increase the risk of ischaemic disease and stroke
Kidneys	Kidney disease	Scrutinize the indication – choose another analgesic if possible. Start with a low dose
Lungs	Asthma	Do not use NSAIDs in patients with ASA hypersensitivity or pronounced allergic asthma. Do not use parenteral formulations in asthmatics
CNS	Elderly patients	Use low dose and avoid indometacin
Uterus and pregnancy	The whole pregnancy period	Avoid NSAIDs in the last trimester. Use NSAIDs in first and second trimester only after careful consideration of possible risks (early miscarriages and malformations, respectively). Misoprostol is contraindicated throughout pregnancy

there is currently no firm evidence to allow for the assessment of a possible excess risk in this area although some studies suggest there is also a small increase in risk for at least some of this group.

III.b.3. Some Comments on Potent Centrally Acting Analgesics (See Tables 4 and 5)

Potent opioids act through opioid receptors in the central nervous system where they inhibit the transport of pain impulses. They are mostly used for treatment of malignant cancer pain and for post-operative pain. Severe, long-term non-malignant pain, e.g. in *ischaemic* leg ulcers, sometimes necessitates the use of opioids. The risk of treatment discontinuation due to adverse reactions is high.

The adverse reactions include slowing of gastrointestinal propulsion with the ensuing risk of constipation, which can be prevented with lactulose or lactitol. Opioid treatment can also cause nausea and sometimes vomiting. There is also a dependence problem and a risk of respiratory depression. The latter may be a practical problem in anaesthetic practice or in overdose, but rarely in the case of treatment with slowly increased oral doses. The nausea is caused by a direct stimulation of dopamine receptors in the 'chemoreceptor trigger zone' and is blocked by treatment with dopamine antagonists, e.g. metoclopramide and neuroleptics. However, treatment with histamine antagonists can be tried as a first option. Opioids also influence several central nervous functions and may cause mood changes and cognitive disturbances and, rarely, confusion.

III.b.3.1. Tolerance and equi-analgesic dose. Sometimes there is a reason for changing the opioid in an individual patient. In these circumstances the recommendation has been to switch between opioids according to particular so-called equi-analgesic dose measures. These are often based on single dose studies and therefore have limited applicability in patients who have been treated for a longer time.

Some patients undergoing long-term opioid treatment develop a tolerance with loss of analgesic efficacy. The mechanisms behind this effect are likely to be multi-faceted and partly determined by individual factors. There is widespread and documented experience that the tolerance developed in a particular individual is not developed in parallel for different opioids. Different sources therefore recommend

Table 4. Medicines for nociceptive pain conditions – opioids

Substance	Half-life (h)	Time to steady-state concentration (h)	Clinical comments
Mild opioids – effective in nociceptive pain			
Dextropropoxyphene	9–13	~2.5 days	Active toxic metabolite which in the elderly and in patients with decreased kidney function may build up (concentrate?) and cause confusion. Risk of pronounced respiratory depression together with alcohol intake. Low risk of abuse
Codeine	2–3	15	Acts by conversion to morphine. Around 7% of the population with slow hydroxylation phenotype do not convert codeine into morphine. Low risk of abuse
Tramadol	6	30	Weak effect
Potent opioids – effective in nociceptive pain			
Morphine	3–4	12–20	Baseline drug. The dose is adjusted when changing from parenteral formulation to oral, with a 3-fold increase due to low bioavailability. The amount needed shows large variations between individuals. Particular sensitivity in the elderly and in patients with kidney disease. Risk of abuse
Ketobemidone	3–4	12–20	No major differences compared with morphine. Possibly higher risk of cognitive adverse reactions, against the background of different mechanism of action. Alternative in reduced kidney function. Risk of abuse
Methadone	15–70	2–12 days	Long effect duration in repeated doses. Should be dosed considering the long half-life. Risk of abuse
Buprenorphine	4–6	20–30	Partial agonist. Can act as antagonist in concomitant treatment with other opioid. Also available as plaster without definite advantages as concerns the method of administration. Probably lower risk of dependence
Oxycodone	3–5	12–25	More expensive alternative to morphine, without any definite advantages. Not first choice treatment. Risk of abuse
Fentanyl	Plaster formulation determines time to steady state		Used as plaster according to special instructions
Hydromorphone		12–20	More expensive alternative to morphine, without any definite advantages. Risk of abuse

so-called opioid rotation as a possible measure to reduce the problem of clinical tolerance. There is however no basis for a recommendation of this practice as a general principle.

One should be cautious in the choice of dosage if opioid tolerance has occurred and a switch is planned. If there is pronounced tolerance the new opioid should normally be initiated at the recommended starting dose, otherwise there is a definite risk of opioid adverse effects.

III.b.4. Combination Drug Treatment

There is insufficient documentation regarding the use of different analgesics in combination. In a recent evaluation by the Swedish Council on Technol-

Table 5. Medicines for neuropathic pain conditions – antidepressants and antiepileptics

Substance	Mechanism of action	Half-life (h)	Time to steady-state concentration (h)	Clinical comments
Antidepressant drugs – effective in neuropathic pain				
Amitriptyline	Mixed noradrenaline- and serotonin-reuptake inhibitor	19	4–5 days	Careful dose increase. Elderly can manage with 10 mg 3 times/day. Can be given as one dose for the night. Best documented
Nortriptyline	Mixed noradrenaline- and serotonin-reuptake inhibitor	28	5–6 days	Doses > 75 mg per day are rarely needed. Effect can be measured after 5–6 days. Less well documented in neuropathic pain
Duloxetine	Mixed noradrenaline- and serotoninreuptake inhibitor	12		Expensive new drug with effect in neuropathic pain, without any definite advantages
Anti-epileptic drugs – effective in neuropathic pain				
Carbamazepine	Membrane stabilising	35 (16–24 in long-term treatment)	4–5 days	Slow escalation of dose reduces the risk of adverse reactions. Effective only in neuralgiform pain. Avoid concomitant use of dextropropoxyphene due to interactions
Gabapentin	Unclear	5–7	1–2 days	Slow escalation of dose reduces the risk of adverse reactions. Renal elimination – observe possible need for dose reduction in elderly. Evidence of effect in zoster pain and in neuropathic pain. Not first choice
Progabalin	Unclear	6–12	1–2 days	Expensive new drug without any definite advantages compared with older established therapy

ogy Assessment in Health Care (SBU) of treatment options, the observation is made that the addition of an NSAID or weak opioid to paracetamol treatment often results in improved pain alleviation. The reverse, adding paracetamol to NSAID or opioid treatment does not however seem to have a noticeable effect, though there is support for a combination of an NSAID + a weak opioid or tramadol in arthritis pain. This points towards generally avoiding fixed combinations as a standard choice in order to allow individual drug dose adjustments and reduce the risk of adverse reactions and interactions.

It is doubtful if combination drugs with centrally acting muscle relaxant substances can be given a general recommendation. Carisoprodol is metabolized to the dependence producing substance meprobamate, and should therefore be avoided.

Caffeine is included in several fixed combinations. It potentiates the effect of other analgesics and also has an analgesic effect of its own (see Goldstein, 2001). In migraine, the caffeine stimulates gastric emptying and allows a faster absorption of other analgesics e.g. aspirin. Combination drugs containing caffeine thus have a place.

III.b.5. Local Anaesthetics

The use of local anaesthetics outside specialized surgical or anaesthetical practice is usually limited to infiltration anaesthesia, different surface anaesthetic methods, and (nerve) block of fingers and toes. Lo-

cal anaesthetics may also be used for the purpose of identifying the location of a source of pain.

The risk of adverse reactions is low, and includes mainly vaso-vagal reactions, which can partly be prevented by the patient lying down in connection with the application. The vaso-vagal reaction is characterized by a fall in blood pressure, bradycardia, pallor and, rarely, loss of consciousness and convulsions. Infiltration of larger amounts of anaesthetics, e.g. in a fracture hematoma, increases the risk of systemic toxic reactions with paraesthesias, metal taste and visual disturbances. The infiltration should be stopped when there are such symptoms, which could precede the more serious reactions (loss of consciousness and convulsions).

Allergic reactions to modern local anaesthetics are very rare. A possible allergy can be investigated in consultation with an allergist, should reactions like falling blood pressure, bronchospasm, edema or urticaria occur.

Systemic reactions to added adrenaline (norepinephrine) are unusual, but can occur and are usually expressed as temporary blood pressure increase, palpitations and anxiety. These reactions rarely require any other treatment than calming explanations. Adrenaline containing local anaesthetics should only be given with particular caution to individuals with increased susceptibility to adrenaline effects – e.g. patients treated with noradrenaline reuptake inhibitors or patients with certain heart diseases.

III.b.6. Infiltration Anaesthesia

Infiltration anaesthesia is applied fan-shaped, with as few needle punctures as possible, in close proximity of the wound or the skin area to be treated. An aspiration should always take place to avoid intravascular injection. Suitable alternatives are lidocaine (lignocaine) or prilocaine for injection 5–10 mg/ml, with or without adrenaline. When making an incision of an abscess it is sometimes difficult to use a local anaesthetic if there is a pronounced inflammatory reaction, since the effect of the anaesthetic is reduced due to an increased acidity level. While adrenaline reduces bleeding and delays dispersion of the anaesthetic, local anaesthetic/adrenaline combinations are contraindicated for local anaesthesia of digits, on the face or where the skin survival is at risk.

III.b.7. Nerve Block (Conduction) Anaesthesia

Nerve block anaesthesia in general practice mostly concerns finger or toe blocks. Lidocaine or prilocaine, 10 mg/ml *without* adrenaline (norepinephrine), is used and is injected on each side of the finger or toe, in two portions by the four nerve branches. Injection of larger volumes than 1–2 ml/side carries a risk of ischaemia because of the firm tissue. The transport through the nerve sheath takes a few minutes, and for a satisfactory result one should wait 5–10 minutes before the planned intervention starts.

III.b.8. Surface Anaesthesia

III.b.8.1. Skin. Surface anaesthesia of the skin can be produced with help of a cream containing a eutectic mixture of local anaesthetics (EMLA), which is a water/oil emulsion of equal parts of prilocaine and lidocaine with particularly good penetration capacity. EMLA is applied under occlusion, around 40–60 minutes before the planned intervention. This is an effective way of producing anaesthesia before needle punctures and minor, painful, procedures. The method is excellent, particularly in paediatrics, to reduce fear and pain.

EMLA cream can also be used in treatment of post-herpetic pain. When using EMLA on larger surfaces, e.g. in revision of pressure wounds, there is an increased risk of systemic toxic effects. The dose of EMLA should be adjusted according to the surface covered, type of intervention and depending on the skin being intact or not, or if a mucous membrane also is included.

III.b.8.2. Mucous membranes. In interventions or examinations of the mouth cavity and throat an aerosol solution of lidocaine, 10 mg/dose, is used. The method is often uncomplicated, but the patient should be warned of the risk of problems with swallowing, and abstain from eating and drinking until the feeling of numbness has disappeared.

In painful infectious conditions and irritations of the mouth, throat and oesophagus viscous lidocaine may be helpful.

Before bladder catheterization lidocaine or prilocaine gel 2% is used. In male catheterization around 20 ml gel is needed. The gel is administered slowly with a needle, in two portions. It is important to know that an increased resistance often happens after half the portion has been administered, due to

increased sphincter tonus. When this happens one should wait a few minutes and, when the anaesthetic effect sets in, the remainder can be administered to fill the whole urethra. The same method is used in women, but with about half the dose, around 10 ml.

III.b.8.3. Eye. When removing foreign bodies from the eye a short acting surface anaesthesia can be produced by lidocaine 40 mg/ml, oxybuprocaine 4 mg/ml or tetracaine (amethocaine) 5 mg/ml. Welding flash burns or corneal injuries can be treated with cinchocaine cream.

The patient should protect the eye when it is anaesthetized since there is a risk of injury if small fragments enter the eye or if the patient scratches the eye.

III.c. Headache

Headache is one of the most frequent complaints which mankind suffers from. Most commonly the headache starts from one of the pain sensitive structures of the skull, but diseases originating outside the skull are also important causes of headache. Diseases of the eye, sinuses, jaw, teeth and neck often cause headache, but also visceral tissue may give rise to headache. The headache may be secondary to many diseases, e.g. anaemia and hypertension. Drug induced headache is not uncommon, either as an adverse reaction, e.g. to calcium antagonists and SSRIs, or as part of more complex problems in chronic headache.

If precipitating factors can be identified these should obviously be eliminated as far as possible before drug treatment is used. Examples are tension, stress, lack of sleep, alcohol, smoking, large intake of coffee and tea, irregular meals, bad work posture and problems with eyesight. Hormonal fluctuations and common colds also often cause headache.

Tension headache which is the most common form of headache can be divided into an episodic and a more chronic form. In both cases the patient needs help in identifying and changing the causative factors. In chronic tension headache drugs should be given with caution in order not to risk a worsening of the condition by high intake of analgesics. Tricyclic antidepressants may be tried in chronic headache and sometimes have a good effect in spite of the absence of depressive illness. In more episodic cases, first choice treatments are paracetamol, acetylsalicylic acid and short acting NSAIDs like ibuprofen.

IV. FEVER

The body temperature is regulated via the hypothalamus. A fever is a body temperature of more than 38.2°C, measured rectally. Premenstrual women have higher body temperature and children develop fever easier than adults. The body temperature is lowest in the early morning hours and highest in the afternoon, and increases during exercise.

Fever is common in, and often a sign of, infection irrespective of its cause. Other diseases, which cause fever, are tumours, non-infectious inflammations, endocrine disorders and thrombo-embolic disease. Drugs can cause fever, e.g. angiotension-II-antagonists, ACE inhibitors and phenytoin.

The reason for the fever must always be investigated and treated as the first option. The fever should be treated if it in itself contributes to the feeling of illness or influences the patient's general condition, but antipyretics can also disguise deterioration and should be used with caution.

A febrile person should stay in a cool place and not be covered in thick blankets/quilts. The body can be dapped with water to cool it down. It is very important to drink plenty of liquid to replace fluid loss due to evaporation. Physical strain should be avoided during fever and preferably until a few days after the fever has disappeared.

Recommended antipyretics are paracetamol, acetylsalicylic acid and short acting NSAIDs to adults. Children under the age of 18 should not be treated with acetylsalicylic acid due to an increased risk of Reye's syndrome in viral infections.

V. LIGHT-HEADEDNESS

This term is for many patients not clearly distinguishable from vertigo, which is a vestibular impairment, or dizziness such as occurring in low blood pressure, hypoglycemia, or even headache. Light-headedness is often combined with vegetative disorders such as nausea and vomiting and the ability to maintain balance is impaired. The light-headedness may be of peripheral otogenic origin or central, and an investigation including ear- and neurological-status is a must to make the correct diagnosis.

Antiemetics such as meclozine and prochlorperazine may alleviate light-headedness. In benign postural light-headedness the best treatment is mobilisation and some physical manoeuvres. Do not forget

that light-headedness is a common adverse drug reaction!

When light-headedness is precipitated by the presence of a low blood pressure usually no drug treatment is needed. Physiologically, low blood pressure by itself does not cause complaints. Being tired, by insomnia or by gastrointestinal disturbances may cause the symptoms. These causes should then be corrected. To increase blood pressure with sympathomimetic drugs may be dangerous with constriction of the arterial blood vessels, resulting in a diminished vascularisation and perfusion of organs, especially the kidney. The use of corticosteroids for this condition is contra-indicated.

VI. CONSTIPATION

Constipation may be caused by slow intestinal transition, pelvic floor dysfunction, bowel dysfunction like irritable Bowel syndrome and tumours, but can also be secondary to other diseases and life conditions. Many medicines cause constipation, for example opiates, calcium channel blockers and drugs with anticholinergic effects, e.g. antidepressants.

Drugs are not a first choice treatment for constipation. The patient should eat food with high fibre content and drink enough liquid. Consistent food habits and regular bowel movements counteract constipation and physical exercise is also important for intestinal function.

If drugs are used, the first choice should be a bulk laxative, e.g. isphagula or sterculia gum. Non-absorbent carbohydrates with osmotic activity also work well but often cause flatulence. Salinic laxatives like polyethylene glycol and magnesium oxide are very effective but often cause stomach upsets like flatulence and abdominal pain. Tegaserod, a 5-HT_4 partial agonist, appears to improve the frequency of bowel movements in those with chronic constipation (see Evans et al., 2007).

Irritants (like bisacodyl, senna glucosides) should be used restrictively.

VII. NAUSEA AND VOMITING

Nausea and vomiting often are a non-specific symptoms of many conditions and diseases. Misinformation obtained from an inadequate anamnesis may lead to erroneous treatments. Nausea and vomiting are often treated with all kinds of medicaments without any existing evidence of efficacy, these may not alleviate nausea but even make it worse.

Vomiting accompanying gastro-enteritis, especially in the pediatric patient, is a special problem because it is prevalent in developing countries and may aggravate dehydration resulting in death. Oral rehydration fluid should be given when vomiting or diarrhoea is severe to prevent dehydration; it should be given in small sips with an interval of a few minutes to allow the fluid to be absorbed. Large amounts of fluid given at once may cause further vomiting.

Nausea and vomiting in early pregnancy should be managed in the first place by reassurance, attention to emotional factors, and general measures such as a cup of tea and biscuit, and light and frequent meals with adequate fibre intake. In resistant cases, drug therapy may be necessary.

As first choice treatment a well-established antihistamine such as meclozine is recommended. Promethazine is another antihistamine which reduces nausea, but sedation is a not always desired adverse effect. Metoclopramide increases intestinal motility and could be used short term also early in pregnancy. A neuroleptic such as prochlorperazine reduces nausea but should only be used for short-term treatment due to the risk of extrapyramidal adverse reactions. Serotonin receptor antagonists can be used in post-operative nausea and during treatment with cytostatics.

VIII. METEORISM

Meteorism may be caused by several factors, such as post-anaesthesia, dyspepsia, constipation, gas-producing food, anticholinergic drugs and papaverine, omitting meals or even late eating habits. Chronic meteorism may be associated with the absence of masticating teeth, resulting in the swallowing of gas. Anticholinergics in combination with an analgesic are often used to treat meteorism; this will result in exaggeration of the situation, because it will diminish peristalsis and increase gas retention in the intestines.

Meteorism may be minimized by chewing the food well and also by physical exercise. Putting a patient on soft food is deleterious, so is a strict diet. If anything, certain foods should be temporarily avoided, like milk, chili, and too much vegetables or fruit.

Treatment of constipation and other disorders of the gastro-intestinal tract may reduce flatulence problems. Medicines that increase peristalsis should not be used because of the risk of adverse reactions.

Dimetylpolysiloxane disperses gas bubbles in vitro and although its clinical effectiveness is not impressive in adequate doses it can be tried.

IX. PRURITUS

A number of conditions can give rise to pruritus and, irrespective of its cause, it is often affected by psychological factors.

Pruritus is often one of the symptoms in skin diseases, e.g. in eczema, urticaria and in scabies infection.

Pruritus is also common in disease which is not primarily dermatological: many endocrine diseases can produce pruritus; cholestasis is another cause, like kidney- and blood-diseases. Infections and malignant tumours can also give rise to pruritus.

Many drug reactions cause pruritus, mainly in connection with skin eruptions, e.g. urticaria in penicillin-V allergy. Morphine is an example of a drug which may produce pruritus without other skin involvement.

Pruritus is a common symptom in dry and dehydrated skin, in the elderly, but also as a result of excessive hygiene.

The treatment should be causal, but symptomatic treatment is also important. Heat and dehydration should be counteracted as far as possible. Skin softeners without perfume and irritant ingredients should be used frequently to treat dry skin. A sedating antihistamine often alleviates the pruritus, especially at night. Local steroids have no place in treatment unless there are inflammatory skin changes.

X. RHINITIS

The precipitating factors for rhinitis must be established first. Dust, smoke, molds and other allergens are examples, and the use of air conditioners in bed-rooms and cars can also be the cause when a runny nose condition becomes prolonged. After establishing the probable cause(s), three distinct categories can be distinguished: allergic rhinitis, vasomotor rhinitis, and acute rhinitis such as in influenza or common cold.

Patients with rhinits as a part of a common cold should be advised to sleep in an upright position and rinse the nose and throat with isotonic salt solutions several times a day.

Nasal formulations of modern sympathicomimetics like oxymetazoline and xylometazoline are effective. Rebound nasal congestion after withdrawal of sympathicomimetic-containing nose sprays or drops is a common phenomenon and *patients should be advised to use these medicaments no longer than 3–5 days.* Older per oral drugs like ephedrine and pseudo-ephedrine have no place in the therapy of rhinitis due to the risk of serious adverse reactions which are not in proportion to the indication.

Nasal corticosteroids are effective in vasomotor rhinitis, but because of the duration of the disorder, certain caution is advised to avoid systemic effects and local adverse reactions after long-term use. Ipratropium bromide spray works well if the dominating problem is runny nose.

In allergic rhinitis the first choice treatment is a non sedating antihistamine, per oral or nasal. Local treatment with sodium cromoglicate often works well, sometimes in combination with antihistamines. In severe nasal congestion a local steroid is usually needed to alleviate the symptoms.

Systemic corticosteroids, although perhaps effective when an allergic factor plays a dominant role, is not recommended for routine use, because of the chronic nature of the disease and hence prolonged use of the drug.

XI. COUGH

Cough is a protection- and cleansing-mechanism in irritation of the airways and should therefore not be suppressed unless necessary.

The cough may be caused by infections of different origins, from ordinary trivial viral upper respiratory infections to serious bacterial pneumonias including tuberculosis.

Diseases affecting the airways such as asthma, chronic obstructive pulmonary disease, emphysema, bronchiectasis, tumours all cause cough. Circulatory disease may also provoke cough, e.g. heart insufficiency. Sometimes cough is a symptom in gastro-oesophageal reflux, and drugs such as ACE inhibitors can cause cough.

The importance of reducing smoking cannot be emphasized enough. This is partly to reduce the risk

of serious heart- and lung-disease, but smokers also more often fall victim to, and are more seriously affected by, airways infections, including common colds. Thus smokers should stop smoking and everyone should avoid smoky environments.

Cough may be dry or productive. A centrally acting cough suppressant can be tried in dry cough: first choice treatment is noscapine which is safer and has less adverse reactions than codeine and ethyl morhpine.

In cough occurring mainly at night, an antihistamine with a sedating effect, e.g. diphenhydramine, can be tried as an adjuvant. A more upright posture at night helps.

In productive cough mucolytics such as bromhexine and acetylcysteine might work although there is no strong evidence for their effectiveness. Inhalation steroids may sometimes be effective even in non-asthmatics in cases of protracted cough in connection with airways infections.

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Chapter 32

Emergency Medicine

Jamie J. Coleman, Kumud K. Kafle, Robin E. Ferner

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I. INTRODUCTION

An emergency is a situation that requires immediate attention to avert a serious outcome.

Evidence of efficacy is, in one sense, easier to obtain for drugs used to treat emergencies – the results are obvious in a short time. In another sense, it is much harder to obtain, because clinical trials are difficult in critically ill patients who need urgent treatment. For this reason, there are very few good clinical trials in emergency medicine.

We consider only those acute emergencies that are not covered in some detail elsewhere.

II. ACUTE TOXIC CONFUSION AND OTHER PSYCHIATRIC EMERGENCIES

Patients in acute toxic confusional states can become agitated or violent; subdued or frightened; or anywhere along this spectrum. Most commonly they are most strikingly disoriented and confused. Patients can be violent towards themselves or others. Paranoid delusions are common. The condition tends to be worse at night and in strange environments, such as hospital. Acute toxic confusion commonly accompanies infection, hypoxia, drug-withdrawal syndromes, recovery from drug overdose, or other physical disorders.

Delirium is a clinical diagnosis, based on the recent and abrupt appearance of clouded consciousness, with disorientation in time, and then in place and person. The patient can appear perplexed at first, gradually becoming frankly paranoid and aggressive, often with visual hallucinations. In elderly patients without clear localizing signs, acute toxic confusion is most often related to urinary tract infection.

II.a. Management

The aim is to treat the underlying disorder, while preventing harm to the patient or others. Specific treatment includes withdrawing drugs that could be contributing, correcting biochemical disturbance, taking appropriate microbial cultures and giving antibacterial treatment, and administering thiamine if alcohol abuse or malnutrition may be causal.

The Cochrane Collaboration reviewed interventions for delirium in patients with chronic cognitive impairment and concluded: “Delirium, though a frequent problem in the hospitalised elderly patient, is still managed empirically and there is no conclusive evidence in the literature to change practice at this time”.

Psychiatric patients who are acutely violent can be very difficult to manage safely. Carers may have to summon help, waiting to approach the patient until enough people are available to proceed safely. Where a person is so violent as to present a threat

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to himself/herself or to others, then the only option may be restraint and the administration of a tranquillizer or sedative.

Intramuscular injections can be given without siting an intravenous cannula, a difficult procedure in a struggling or uncooperative patient. It is necessary to use adequate restraint and exposure of the injection site so that relevant anatomical landmarks can be identified. Patients should be monitored after they have been sedated, as respiratory or cardiovascular complications can ensue, or the violent behaviour re-emerge.

Intramuscular haloperidol is a suitable drug for tranquillizing violent patients, but it can be difficult to determine the correct dosage, and there is the risk of an acute dystonic reaction, particularly in younger patients. The British National Formulary recommends intramuscular injections of from 2 to 10 mg, subsequent doses being given after 4–8 hours; but in exceptional cases, initial doses of up to 30 mg may be necessary.

Haloperidol is less likely to cause hypotension than chlorpromazine, which has α-adrenoceptor antagonist effects. Both can cause cardiac arrhythmias if used in high dosage or in patients with pre-existing heart disease, or as an idiosyncratic reaction. There have been numerous reports of sudden and unexplained deaths, probably due to cardiac arrhythmia, in patients given chlorpromazine and other neuroleptics. The risk of serious arrhythmia is higher in the obese, and possibly in those of African ancestry.

Patients in whom haloperidol is contraindicated can be treated by intramuscular injection of benzodiazepines, but these can cause respiratory depression or respiratory arrest if given in too high a dose, are contra-indicated in patients with pre-existing respiratory depression, and have no specific anti-psychotic effect.

The intramuscular dosage of diazepam solution for injection is 5–10 mg, repeated if necessary after 4 hours. A rectal solution also exists. If respiratory depression occurs, it can be reversed with the antagonist flumazenil.

II.b. Prevention

There is no evidence from randomized trials that general strategies to prevent delirium are successful. Benzodiazepines are significantly better than placebo in preventing delirium and seizures due to alcohol withdrawal, and long-acting benzodiazepines (such as diazepam) are more effective than short-acting agents. Phenothiazines are no better than placebo at forestalling delirium, and may increase the risk of seizures.

III. ANAPHYLAXIS

Anaphylaxis is the life-threatening clinical syndrome of histamine release, capillary leakage, and cardiovascular collapse caused by a Type I (immediate) hypersensitivity reaction, or by activation of the system that causes such reactions. It is usually of sudden onset, and the cause can be: a medicine (penicillin or vaccines, for example); a food (such as shellfish or nuts); an insect sting (from bees or wasps, usually); or some other environmental allergen (latex from rubber gloves or condoms can cause it). The specific binding of an allergen to IgE on mast cells causes degranulation of the cells, with release of a group of inflammatory mediators including histamine, bradykinin and leukotrienes, which are responsible for the symptoms and signs, many of which are induced by the increase in capillary leakage, which allows leakage of fluid out of the circulation (to cause cardiovascular collapse) and into tissues (to cause oedema).

The main clinical features are:

- cardiovascular
  - hypotension
  - palpitation
  - collapse
- respiratory
  - laryngeal oedema
  - stridor
  - dyspnoea
  - bronchospasm
- cutaneous
  - erythema and flushing
  - urticaria
  - pruritis
  - angioedema, with swelling of the lips, tongue and face
- gastrointestinal
  - nausea, vomiting, and abdominal pain.

The estimated incidence in the United Kingdom is 8.4 per 100,000 person years, and it may be higher in the United States of America. Ten percent of cases are severe, and 1% are fatal. Treatment is empirical, but well established (Table 1).

Table 1. Drug treatment of anaphylaxis in adults

Epinephrine (adrenaline) 500 micrograms by intramuscular injection = 0.5 ml of a 1 mg/ml solution (1:1000)
Chlorphenamine 10 mg by intramuscular or slow intravenous injection
Hydrocortisone 200 mg by intramuscular or slow intravenous injection

III.a. Management

The crucial treatment is intramuscular epinephrine (adrenaline), and this should be given as soon as the diagnosis is made in a patient with hypotension or respiratory distress or both. Epinephrine (adrenaline) alleviates the immediate symptoms by its effects on both α- and β-adrenoceptors reversing peripheral vasodilatation, reducing oedema and suppressing further mediator release. The standard adult dosage is 500 micrograms (0.5 ml of epinephrine 1 mg/ml solution (1:1000)), given by intramuscular injection. Repeated doses of intramuscular epinephrine (adrenaline) can be given at 2–5 minute intervals until symptoms improve. The route is very important, because absorption from subcutaneous sites is too slow to be immediately effective, and administration by intravenous injection except under carefully controlled conditions carries an unnecessarily high risk of provoking ventricular arrhythmia.

It is usual to give a sedating antihistamine, for example chlorphenamine 10 mg by intramuscular or slow intravenous injection, because of the relatively short half-life of epinephrine (adrenaline), and because of the active role of histamine in anaphylaxis. In addition, the inflammatory reaction can be moderated by the administration of a corticosteroid, such as hydrocortisone 200 mg by intramuscular or slow intravenous injection. Corticosteroids may take several hours to act, but can be of some help in so-called biphasic anaphylactic reactions.

In patients who have neither hypotension nor respiratory effects, hydrocortisone and chlorphenamine usually suffice. Supportive treatment with oxygen by face-mask, and intravenous fluid for hypotension, may be helpful. Patients who have predominant or recurrent bronchospasm can receive inhaled β_2-agonists such as albuterol (salbutamol), but may still require intramuscular epinephrine (adrenaline). The major adverse effects of epinephrine (adrenaline) are of ventricular arrhythmias, particularly ventricular fibrillation, severe hypertension that can increase the risk of stroke, and myocardial ischaemia.

III.b. Prevention

Prevention of anaphylaxis requires avoidance of the allergen or pseudo-allergen responsible. Immediate treatment of emergent anaphylaxis can prevent progression to serious or irreversible collapse. In hospital, this is best achieved by making suitable drugs easily available. In the community, patients who have had severe and potentially fatal anaphylactic reactions can be provided with an epinephrine (adrenaline) autoinjector ("Epipen") or preloaded syringe for self-injection, or administration by a family member or colleague.

Some patients who have had an anaphylactic reaction wear a medical alert bracelet or necklace with an inscription endorsed by a doctor that alerts other doctors to the possible cause of any future reaction.

IV. CARDIAC ARREST

Cardiac arrest is the classical medical emergency, because hypoxic brain damage will be irreversible after more than about three minutes of circulatory failure. Cardio-pulmonary resuscitation in Europe is now codified in a scheme that has the benefits of practical experience and is easy to implement, though not entirely evidence-based. It depends on being able to: diagnose cardiac arrest by the presence of unconsciousness in a patient with absent carotid or femoral pulses and absent breathing; supply sufficient oxygen by basic resuscitation to the brain to defer irreversible damage; and reverse the cause of cardiac arrest in some patients.

A few patients who suffer a witnessed cardiac arrest respond at once to mechanical defibrillation by a praecordial thump, a forceful blow to the midsternum with the closed fist. All others should have oxygenation by mouth-to-mouth breathing, bag-and-mask ventilation, endotracheal intubation, or laryngeal airway ventilation. Oxygenated blood is then circulated by closed cardiac massage, that is, external cardiac compression in which the heart is squeezed between the sternum and thoracic spine with sufficient force to expel blood from the ventricles into the pulmonary and systemic circulations. Between compressions, the ribs and sternum relax, and blood is drawn from the veins into the heart. The provision of effective and continuing chest compressions is one of the most important factors influencing

survival. Interruptions are common and decrease the chances of recovery.

A single resuscitator can institute chest inflation by mouth-to-mouth breathing (two breaths), followed by cardiac compression (30 beats), until help arrives or the situation is clearly hopeless. When a second person is present, then one rescuer can inflate the chest (two breaths) and the other can compress the heart (thirty beats), in sequence.

Defibrillation is one of the few interventions that has been shown to improve outcome from cardiac arrest. The cardiac arrhythmias commonly associated with sudden collapse are (1) asystole and (2) rapid and ineffective depolarization due to ventricular fibrillation (VF), pulseless ventricular tachycardia (VT), or supraventricular tachycardia with 1:1 ventricular response (as can occur with pre-excitation syndromes). The best strategy is to treat collapsed patients who have a broad-complex tachycardia at once by external Direct Current (DC) defibrillation.

When the cardiac electrical activity is maintained, but there is no mechanical output (pulseless electrical activity, electromechanical dissociation), then hypovolaemia, tension pneumothorax, pulmonary embolism, cardiac tamponade, and various forms of metabolic or pharmacological disturbance may be responsible. In asystole or pulseless electrical activity (with an underlying rate of less than 60 beats per minute) a single intravenous bolus of 3 mg atropine is recommended.

Epinephrine (adrenaline) should be given every 3–5 min whilst the patient remains in cardiac arrest, immediately if the patient has an initially non-shockable rhythm (asystole or pulseless electrical activity) but delayed until before the third shock for shockable rhythms. Continued administration of epinephrine (adrenaline), cardiac massage, and DC shock may be required for several cycles.

Amiodarone 300 mg as an intravenous bolus increases survival in VF or pulseless VT that does not respond to three DC shocks.

The patients who have the best chance of surviving cardiac arrest are those with primary ventricular fibrillation after myocardial infarction; patients with electromechanical dissociation or asystole fare worst. Even in those in the most favourable group, with witnessed ventricular fibrillation in hospital, the best that can be hoped for is a survival rate till discharge of about 20%.

V. METABOLIC EMERGENCIES

V.a. Hypoglycaemia

Hypoglycaemia is present when the blood glucose concentration falls below normal. In practice most subjects will have evidence of neuroglycopenia, that is to say, impaired central nervous system function, as a consequence of a low blood glucose concentration when it is below 2.2 mM/l. There may be symptoms of headache or blurred vision ("spots before the eyes"); behavioural disturbance, with drowsiness, irrationality, or aggression; autonomic symptoms of sweating, palpitations, tremor, and hunger, as a result of increased counter-regulatory production of catecholamines; and, at blood glucose concentrations below 1 mM/l, loss of consciousness and seizures.

The commonest cause of hypoglycaemia is administration of therapeutic doses of insulin or sulphonylureas in patients treated for diabetes. Non-diabetic people may also take or be given hypoglycaemic agents. Hypoglycaemia can occur spontaneously in insulinomas, hypoadrenalism, and other uncommon circumstances.

Diagnosis of hypoglycaemia requires that blood glucose concentration be measured before treatment. If the cause is uncertain, samples can be taken to measure the concentrations of insulin, insulin antibodies, and pancreatic C-peptide before the administration of glucose.

V.b. Management

The treatment of uncomplicated hypoglycaemia is to administer sufficient glucose by mouth or intravenously to restore blood glucose concentration to normal values.

In patients who are hypoglycaemic but not unconscious, and in those revived by injections, sugary drinks (but not 'diet' drinks), chocolate bars, sugar cubes, glucose tablets, and raisins have all been used to increase carbohydrate intake. A rapidly-dissolving preparation containing glucose can be inserted between the gum and the cheek, allowing some absorption of glucose even in those who are not fully conscious. Rectal administration of glucose has no therapeutic effect.

The recommended initial treatment for unconscious patients is to infuse 20 g of glucose, as 100 ml glucose 20% solution (200 g/l) over about 15 min. In childhood, it may be better to use glucose 10%

solution in a dosage of 2 ml/kg, infused over three minutes.

In most cases, neurological symptoms and signs rapidly regress. However, in some patients, the dose of glucose is insufficient to restore blood glucose concentration, and in others, neurological deficit remains after the correction of blood glucose concentration.

If blood glucose concentration remains low, then further glucose can be administered as an intravenous injection, followed if necessary by continuous intravenous infusion of glucose 10% solution. Alternatively, glucose 20% solution can be infused through a central vein. Blood glucose concentration is measured frequently, and the rate of infusion adjusted to maintain blood glucose concentration between 3 and 7 mM/l. Adjunctive or alternative strategies include the administration of glucagon and hydrocortisone. Glucagon, a counter-regulatory hormone that stimulates gluconeogenesis from hepatic glycogen, can be given intramuscularly by an unskilled bystander, and so can be used in the absence of medical aid to treat patients who are unconscious.

In many countries glucagon is available in packs containing a syringe pre-filled with sterile water for intramuscular injection and a vial containing glucagon 1 mg, to be prepared just prior to injection. Glucagon is ineffective in those patients whose hypoglycaemia is accompanied by depletion of hepatic glycogen stores, but is particularly effective in pancreatectomized patients. It takes 10–20 min to work. When the patient is conscious, he or she can take a snack or meal to avoid recurrent hypoglycaemia.

In rare circumstances, including overdosage of sulphonylurea tablets, administration of glucose causes a transient increase in blood glucose concentration, which is sufficient to provoke a further outpouring of insulin by the pancreas, and severe rebound hypoglycaemia. Such cases are very difficult to manage. The treatment of choice is injection of the somatostatin analogue ocreotide, which inhibits further pancreatic insulin. A few patients fail to regain consciousness after normal blood glucose concentration has been maintained for some time. There is evidence that such patients have cerebral oedema, perhaps as a result of excitotoxin release in response to hypoglycaemia. Mannitol and dexamethasone may reduce cerebral oedema.

V.c. Hyperkalaemia

Hyperkalaemia is present when the plasma (or serum) potassium concentration is above the upper limit of normal. Severe hyperkalaemia is usually accompanied by electrocardiographic changes. It can cause cardiac standstill, so requires immediate treatment. The causes include renal failure; drugs such as potassium-sparing diuretics, or angiotensin-converting enzyme inhibitors; cell lysis (e.g. rhabdomyolysis); and endocrine disorders (e.g. hypoadrenalism).

Intracellular potassium concentration is about 35 times higher than extracellular potassium concentration, so small degrees of haemolysis in blood samples can produce spurious hyperkalaemia. It is therefore important to make sure that a biochemical result is obtained on a second, fresh, sample, or that the patient has the electrocardiographic signs expected in hyperkalaemia. These progress sequentially from tall, peaked, T-waves, to prolongation of the PR interval, broadening of the QRS complexes, which eventually degenerate to a "sine-wave", ventricular arrhythmia, and asystole.

V.d. Management

The therapeutic strategy in severe hyperkalaemia is to protect the heart from arrhythmia by increasing extracellular calcium concentration; reduce the extracellular potassium concentration by driving potassium into cells with insulin (and glucose), or with β_2-agonists, or both; and remove potassium ions from extracellular fluid by dialysis or ion-exchange. Calcium ion concentration in extracellular fluid can be increased rapidly by slow intravenous injection of calcium gluconate 1 gram (10 ml of 100 g/l (10%) solution). Calcium chloride can also be used: a 10% solution contains about three times as much calcium on a molar basis as calcium gluconate 10% solution.

Insulin and glucose together increase the activity of the cellular membrane sodium–potassium pump, and so increase the flow of potassium from extracellular to intracellular fluid. Five grams of glucose should be given with every 1 unit of insulin to prevent hypoglycaemia. A common regime would be to give 50 ml of glucose 50% solution with 5 units of insulin, but hypo- and hyper-glycaemia are still possible, and blood glucose concentration should be monitored frequently during and for some hours after infusion.

Parenteral β_2-agonists such as albuterol (salbutamol) increase the activity of the membrane sodium-potassium ATPase, and so increase potassium entry into cells. Nebulized or infused albuterol (salbutamol) significantly lowers serum potassium concentration over 5 hours. A suitable initial dose of nebulized albuterol is 5 mg in adults. It can provoke tremor and tachyarrhythmia, and it is desirable to monitor cardiac rhythm during nebulization. The combination of nebulized albuterol (salbutamol) with infusion of insulin + glucose is more effective than the infusion alone.

The serum potassium concentration can be effectively reduced by dialysis, and this is often indicated in patients presenting with renal failure and acute hyperkaleamia. However, dialysis may take some time to institute, especially if the patient has to be transferred to a specialist centre. Calcium polystyrene sulphonate is often used, but there is little evidence of efficacy and its use is not entirely without risk.

VI. STATUS EPILEPTICUS

Status epilepticus is the state of continuous seizures, or seizures which recur without a period of complete recovery in between, lasting long enough to cause irreversible neuronal damage. An operational definition has been proposed by Lowenstein and Alldredge (1998): "either continuous seizures lasting at least five minutes or two or more discrete seizures between which there is incomplete recovery of consciousness". It constitutes a medical emergency. The majority of patients with the condition will have generalized tonic-clonic ('grand mal') seizures. Occasionally, there will be impaired consciousness and electroencephalographic evidence of continuous seizure activity without tonic-clonic jerking.

Treatment can be divided into four phases. The first priority is to ensure that the airway is patent, and the patient is breathing satisfactorily. This is often difficult when the patient's jaw is tightly clenched, but administration of oxygen via a face-mask and measurement of oxygen saturation by a finger probe can be helpful. It is also necessary to secure intravenous access early for most effective treatments to be given.

Treatment to stop seizures is the next stage. Benzodiazepines can prevent the development of full status, and are the first-line drugs in the treatment of early status. They will stop seizures in about 80% of patients if administered within the first 30 min. The choice of benzodiazepine includes: diazepam by intravenous injection over 2 min, 5–20 mg in adults; and lorazepam by intravenous injection over 2 min, 2–4 mg in adults. Lorazepam may be more effective. Parenteral benzodiazepines can cause respiratory depression and respiratory arrest. This means that they should preferably be given only in circumstances where there is adequate provision for resuscitation. It is desirable to have access to the benzodiazepine antidote flumazenil. In patients without venous access, diazepam can be given rectally, or midazolam can be given as a buccal preparation.

The possible causes of status epilepticus include hypoglycaemia and Wernicke's encephalopathy, and so, in patients where the cause is unknown, specific treatment for those conditions is given, unless hypoglycaemia has been excluded by finger-prick blood glucose testing. The treatment for hypoglycaemia is discussed above, and should be given if there is doubt about glucose status.

Where patients are at risk of Wernicke's encephalopathy – for example, because of chronic alcohol abuse, hyperemesis gravidarum, or malnutrition – they should be given thiamine. In many countries no intravenous preparation of thiamine alone is available, and the compound preparations that are available are prone to cause anaphylactoid reactions, so they should be given by slow infusion, and with adequate facilities for resuscitation. A high potency preparation (Pabrinex®) that contains thiamine 250 mg in 10 ml with ascorbic acid, nicotinamide, pyridoxine and riboflavin, can be given by intravenous infusion over 10 min.

There is no direct evidence to support the practice of giving this 'blunderbuss' treatment to any patient with status epilepticus of undetermined cause. We suggest that the need for glucose be dictated, where possible, by estimation of blood glucose concentration, and the need for thiamine be assessed clinically taking into account the risk factors mentioned. If seizures continue in spite of the first-line treatment already described, then there is an urgent need to stop the seizures. A consensus still favours intravenous phenytoin, or the derivative fosphenytoin, although this can only be done safely with electrocardiographic monitoring because of the pro-arrhythmic effect of phenytoin augmented by hypoxia. Parenteral preparations of phenytoin can also cause hypotension, ataxia, nystagmus, drowsiness, and coma. The recommended regime is, in subjects who have not received phenytoin as part of

their prior treatment: a loading dose of phenytoin 15 mg/kg body-weight by intravenous infusion at a rate no faster than 50 mg/min; followed by a maintenance dose of phenytoin 100 milligrams every 6–8 hours, with assessment of therapeutic and adverse effects and measurement of drug plasma concentration to guide further treatment. The absorption of phenytoin after intramuscular injection is poor and erratic, and this route should not be used.

Phenobarbital (phenobarbitone) and sodium valproate are alternatives in patients who cannot be given or have not responded to treatment with phenytoin. The recommended dosage is: a loading dose of phenobarbital injection, 10 mg/kg body-weight up to a maximum of 1 gram, diluted 1 in 10 with sterile water for injection and infused at a rate no faster than 100 mg/min.

Phenobarbital is a very sedative barbiturate, with a long elimination half-life. It can cause drowsiness, coma, and respiratory depression. It is therefore safe to use it only where adequate facilities are available for mechanical ventilation if that is required. Sodium valproate infusion has been shown to be effective in children with status in a small uncontrolled study.

Refractory status epilepticus that has failed to respond to one of these treatments, and has continued for more than 20–30 min, requires urgent action. The accepted strategy is to paralyze and ventilate the patient and administer an antiepileptic drug in sufficient dosage to suppress EEG evidence of seizure activity. The barbiturate anaesthetic thiopental (thiopentone), the benzodiazepine midazolam, and the anaesthetic propofol have all been used. What little comparative evidence there is remains inconclusive. Such treatment can only be carried out with facilities for artificial ventilation and intensive care, and effects can only be monitored by EEG recording.

Once the status has resolved, there is still a need to establish its aetiology if this remains unclear, and plan longer-term treatment.

VII. EMERGENCY MANAGEMENT OF POISONINGS

VII.a. Organophosphorus Pesticide Poisoning

Organophosphorus insecticides are readily absorbed from skin, mucous membranes, and gut. They inhibit cholinesterases, and patients present with an acute cholinergic syndrome. Symptoms depend in part on the route of exposure. They commonly start with ocular pain, conjunctival congestion, increased respiratory secretions, tightness in the chest, wheezing, salivation, nausea, vomiting, and abdominal cramps. Later, severe sweating, pallor, and muscle twitching develop. Signs include miosis and bradycardia. With severe poisoning, the patient may quickly lose consciousness, and flaccid paralysis, respiratory and circulatory failure and pulmonary oedema occur. The possibility of organophosphorus poisoning should be considered in patients with coma and pin-point pupils.

About 2–4 days after apparent recovery from the acute poisoning, an ‘intermediate syndrome’ of muscle paralysis can occur, requiring prolonged ventilation before strength returns. A minority of organophosphorus compounds can cause a delayed, chronic, peripheral neuropathy (organophosphorus-induced delayed neuropathy – OPIDN), first manifest some weeks after acute poisoning.

VII.a.1. Management

Management consists of preventing further exposure to the poison by removing contaminated clothing, and washing contaminated skin. Since concentrated organophosphorus agents are extremely toxic, those treating the patient should ensure that they are themselves adequately protected from contamination. Supportive care is directed towards airway management including suctioning of secretions and vomitus, oxygenation, and if necessary, intubation and artificial ventilation. Gastrointestinal decontamination is probably not warranted, since it is unlikely to affect the outcome.

Specific treatment starts with the administration of atropine sulphate, a competitive antagonist of acetylcholine at muscarinic receptors. Sufficient atropine should be given to control hypersecretion and produce tachycardia and pupillary dilation. Very large doses of atropine are required: atropine sulphate 2–4 mg should be given intravenously every few minutes during the first hour, and then by continuous infusion. Patients may require up to 500 mg intravenously during the first day, and treatment may be needed for days.

Atropine does not counter muscle weakness and respiratory failure. To overcome this, pralidoxime (P2AM), a cholinesterase reactivator, is used in many countries, in an initial dose of 30 mg/kg intravenously followed by 8 mg/kg/h until clinical recovery. Oximes have to be given before the irreversible ‘aging’ of the enzyme–organophosphorus

complex takes place. Controlled trials have failed to show benefit from pralidoxime, and it may even increase harm. Overall, it is unclear whether oximes are harmful or beneficial in the management of acute organophosphorus poisoning.

VII.b. Methanol and Ethylene Glycol

Methanol and ethylene glycol are contaminants of illicit ethanol, and can be taken as ethanol substitutes. Both agents cause severe metabolic acidosis with a high anion gap.

Methanol is metabolized to formaldehyde and formic acid, which injure the retinal cells and optic nerves, and lead to severe acidosis. Treatment delay increases morbidity. Thus, early recognition and management are crucial. Clinical features emerge up to 36 hours after ingestion. Nausea, vomiting, abdominal pain, headache, dizziness, paraesthesia, blurred vision, and diminished visual activity may occur, and coma supervenes. Dilated, unreactive, pupils predict permanent blindness.

Ethylene glycol is rapidly metabolised to glycolaldehyde, then glycolic acid, glyoxylic acid and finally to oxalic acid. The metabolites are toxic to kidneys, brain and heart.

Clinical manifestations occur in three phases. In the neurological stage, the patient appears intoxicated, with slurred speech, ataxia, stupor, and hallucinations, and may be comatose, with respiratory depression. The cardiopulmonary stage is delayed by 12–24 hours, when hypotension, tachycardia, muscle tenderness and congestive cardiac failure are seen. After 1–3 days the renal stage supervenes, with loin pain, crystalluria, oliguria and renal failure, as a result of calcium oxalate crystal deposition in the renal tract. Sequestration of calcium can cause profound hypocalcaemia, tetany, and cardiac arrhythmia.

VII.c. Management

Management of methanol and ethylene glycol poisoning is similar. Symptomatic support of respiration and circulation is augmented by correction of metabolic acidosis with intravenous bicarbonate infusion, and control of seizures with diazepam. Ethanol inhibits the metabolism of methanol and ethylene glycol to the toxic metabolites, and can give time for further treatment. The goal is to maintain blood ethanol concentrations between 100 and 150 mg per decilitre, sufficient to saturate alcohol dehydrogenase. The dose of ethanol should be adjusted to achieve these concentrations. Ethanol may be given orally or IV. The IV route provides fairly consistent concentrations but may cause thrombophlebitis. Ethanol has unpredictable kinetics and causes central nervous system depression. There is, in small children, the added risk of hypoglycaemia.

Recently a more promising antidote, fomepizole (4-methylpyrazole) has been used in ethylene glycol poisoning. This agent is given IV as a 15 mg/kg body-weight loading dose followed by 10 mg/kg every 12 hours, and continued until the patient is asymptomatic with normal blood pH and with concentrations of ethylene glycol below 20 mg/100 ml. Though fomepizole may eliminate the need for haemodialysis and lacks the central nervous system effects of ethanol, it is very costly, even in developed countries. Further data are needed to confirm its usefulness.

For patients who have ingested more than 30 ml of (pure) methanol or ethylene glycol, dialysis is recommended, and haemodialysis is more effective than peritoneal dialysis. Dialysis both removes the alcohols and their metabolites, and corrects the renal and metabolic disturbances and so is the preferred treatment in severe poisoning. The maintenance dose of ethanol required may be tripled during haemodialysis as ethanol is also removed. Early treatment is indicated if ethylene glycol concentrations are above 20 mg/100 ml (200 mg/l), if the arterial pH is below 7.3, if serum bicarbonate concentrations are less than 20 mM/l, and when there are oxalate crystals in the urine.

All patients with methanol toxicity should be given folic acid 50 milligrams intravenously every 4 hours to increase the metabolism of formic acid. In ethylene glycol ingestion, folate, thiamine and pyridoxine should all be administered, to enhance the metabolism of the poison to non-toxic products, and minimize oxalic acid production. Calcium supplements are required for symptomatic hypocalcaemia.

VII.d. Kerosene (Paraffin Oil)

Kerosene is a mixture of aliphatic and aromatic hydrocarbons, naphthenes (cycloalkanes) and other organic compounds. Systemic absorption from the lungs or stomach can cause central nervous system depression. The oil has a low surface tension and low viscosity so that small quantities can spread over a large surface area. This can affect the lungs, and

the risk of chemical pneumonitis is high after ingestion of kerosene and other light petroleum fractions. Pulmonary symptoms can vary from cough and dyspnoea to symptoms of bronchopneumonia, pulmonary oedema, respiratory distress and cyanosis if aspiration has occurred. In severe poisoning, death may result.

VII.e. Management

Gastric lavage is contraindicated because of the serious danger of aspiration and the relatively benign gastrointestinal effects. Patients with respiratory difficulties require oxygen and sometimes mechanical ventilation. Pulmonary oedema, if it occurs, should be treated with diuretics (furosemide 25–100 mg intravenously) or by mechanical ventilation. Antibiotic treatment is unnecessary unless bacterial pneumonia, a rare sequel to kerosene pneumonitis, develops. Mortality is less than 1%.

VII.f. Acetaminophen (Paracetamol)

Acetaminophen (paracetamol) poisoning is common in Western countries and is increasing elsewhere. Single doses as low as 7.5 g in adults or 150 mg/kg in a child can cause severe toxicity. Very occasionally, lower doses cause harm. Mortality, from hepatic or occasionally renal failure, is related to blood concentration and the time between ingestion and the initiation of antidotal treatment. Even severely poisoned patients may be asymptomatic, although nausea and vomiting are fairly common.

Acute liver failure, beginning within one or two days of overdosage, can lead to encephalopathy, haemorrhage, oedema and death. Prolongation of prothrombin time is proportional to the degree of liver injury and is the best guide to severity of liver injury. Peak toxicity is seen 3–4 days after the overdose is taken.

VII.g. Management

Activated charcoal may be given as first aid if the patient presents within an hour of ingestion. Antidotal treatment is almost universally effective if administered within 6 hours of overdose. The serum paracetamol concentration measured between 4 and 16 hours determines whether antidotal treatment with acetylcysteine is required, but if a significant overdose has been taken and no result is available by 6 hours after overdose, antidote should be given. Treatment can be discontinued if results subsequently establish a serum concentration indicating a low risk of hepatic damage.

The risk of hepatic damage and hence the need for acetylcysteine can be determined by using a nomogram that is a graph of log paracetamol concentration versus time. Patients without additional risk-factors need treatment if the blood paracetamol concentration lies above a line on this nomogram that joins 200 mg/l at 4 h and 25 mg/l at 16 h. Patients who are malnourished, alcoholic, have HIV, or take enzyme-inducing drugs such as carbamazepine, phenytoin, and rifampicin, are at high risk for liver damage. They need treatment if the blood paracetamol concentration lies above a line joining 100 mg/l at 4 h and 12.5 mg/l at 16 h.

Patients for whom specific treatment is indicated are given intravenous acetylcysteine 150 mg/kg body weight in 200 ml glucose 5% solution over 15 min; then 50 mg/kg in 500 ml glucose 5% solution over 4 h; then 100 mg/kg in one litre glucose 5% solution over 16 h. Patients who present after 16 hours may also benefit from acetylcysteine and this has been demonstrated in those with hepatic encephalopathy. An alternative and cheaper drug is oral methionine, but its absorption is unreliable in patients who are vomiting, and it is not useful if patients present later than 12 hours after ingestion.

VII.h. Aspirin

Nowadays severe aspirin poisoning is rare. The pharmacokinetic behaviour of aspirin is complex. Absorption after overdose can be delayed by the formation of a 'bezoar' (a mass of tablets stuck together) in the stomach, and by delayed gastric emptying. Absorbed aspirin is hydrolysed to salicylic acid, conjugated with glycine and glucuronic acid, and eliminated. However, these are saturable pathways so that elimination is prolonged in overdosage. If metabolic pathways are saturated then elimination through renal excretion becomes important. Renal elimination is sensitive to changes in urinary pH, but not to urinary flow rate.

Two competing effects are seen in overdosage: aspirin stimulates the respiratory centre, increasing depth and rate of respiration, and resulting in respiratory alkalosis. However, (acetyl)salicylic acid can itself cause a high anion gap metabolic acidosis, so that respiratory alkalosis followed by metabolic acidosis strongly suggests aspirin poisoning. Nausea, vomiting, sweating, hyperpnoea and epigastric

pain are common. Tinnitus is common even in mild overdose. In more severe cases, 'air hunger' due to metabolic acidosis, dehydration, gastrointestinal bleeding, oliguria, renal failure, and hyperpyrexia can occur. Confusion is a sign of very severe overdosage, and coma is only seen in potentially fatal cases, unless another agent has been taken in addition.

The severity of poisoning correlates poorly with plasma salicylate concentration. Six hours after ingestion salicylate levels of 300–500 mg/l may suggest mild toxicity, 500–750 mg/l moderate toxicity, and over 750 mg/l severe toxicity.

VII.i. Management

Activated charcoal adsorbs salicylate effectively, and has been given in repeated oral doses (50 g 4 hourly) to enhance clearance, although its effect on outcome is unknown. Fluid and electrolyte replacement are important and special care should be taken to maintain normal potassium concentrations. Patients with signs of poisoning, especially when plasma salicylate concentration exceeds 500 mg/l, should receive specific elimination therapy.

A higher proportion of salicylate is ionized in alkaline urine, and ionized salicylate is not reabsorbed. Urine can be made alkaline to pH 8–8.5 by giving sodium bicarbonate 100 mM in glucose 5% solution 1 litre at 100–200 ml/h. Overhydration can provoke pulmonary oedema, especially in seriously poisoned patients.

The most effective treatment is haemodialysis, which allows the removal of salicylate and the correction of acid-base, fluid, and electrolyte disturbances, and is the preferred treatment for severe or complicated salicylate poisoning.

VII.j. Tricyclic Antidepressants

Poisoning with tricyclic antidepressants such as imipramine, amitriptyline, and dosulepin is dangerous. Symptoms appear within 30–60 minutes and reach a peak in 4–12 hours. Anticholinergic features, with dry mouth, dilated pupils, urinary retention and absent bowel sounds are common. In more severe poisoning, hallucinations, hyperreflexia, tachycardia, hypotension and varying degrees of loss of consciousness occur. Major toxic effects are hypotension, ventricular arrhythmias, metabolic acidosis, coma, and seizures. The patient can progress abruptly from minor symptoms to major toxicity.

VII.k. Management

Supportive care is important, especially in unconscious patients. If the airway is protected (gag reflex or cuffed endotracheal tube present), then activated charcoal can be given. Repeated doses of oral activated charcoal increase the rate of elimination of several tricyclic antidepressants, but may not influence outcome.

The most dangerous complication of tricyclic poisoning is cardiac arrhythmia. Any patient with ventricular arrhythmia, an undiagnosed broad-complex tachycardia, widening of the QRS complex (greater than 120 ms), or a prolonged QT interval (above 420 ms) should be given sodium bicarbonate 50 mM by infusion (e.g. 100 ml sodium bicarbonate 4.2% solution) over about 15–20 minutes. Both the sodium ions and the alkalinization of blood contribute to the effectiveness. Direct current cardioversion may sometimes be required. Antiarrhythmic drugs may worsen tricyclic-induced arrhythmia, and should not be given. Sustained seizures should be treated with diazepam.

VII.l. Benozodiazepines

The benzodiazepines such as diazepam, oxazepam, and temazepam are common causes of acute poisoning, but rarely cause serious toxicity by themselves, even in enormous doses. They can potentiate central nervous system depression from other drugs, including alcohol.

Clinical features of weakness, ataxia, drowsiness, and short-term memory loss can be seen within 30–60 minutes. Coma and respiratory depression are rare but can occur with the ultrashort-acting agents like triazolam and midazolam. Diagnosis is made from the patient history.

VII.m. Management

Most cases of pure benzodiazepine overdose recover within 24–48 hours with simple supportive treatment. Gastrointestinal decontamination is probably not warranted, since it is unlikely to affect the outcome.

The specific antidote flumazenil is probably only justified in patients with severe (for example, parenteral) poisoning and co-existent disease (for example, chronic obstructive airways disease), where it may avert the need for mechanical ventilation. Flumazenil 200 μg intravenously over about 15 s, repeated every 60 s up to a total dose of 1 mg can

be given. It should be avoided in patients who have taken both benzodiazepines and tricyclics, because it can then provoke seizures.

VII.n. Snake Bite Poisoning

Poisoning from snake bite is an important medical emergency in many African, South American and Asian countries. Although the exact figures are not available, a conservative estimate from India is that about 100 deaths from snake bite occur per day. There are many species of snakes in the world but only about 300 are poisonous. Most sea snakes are poisonous whereas most land snakes are non-poisonous. Most land snakebites occur in the villages, fields, or forests and are away from medical aid. Even though standard textbooks write about identifying the snake, this is often impractical. Hence the accepted pattern in many centres in countries where snakebites are frequent is to start the treatment as soon as the patient is brought to the hospital.

The clinical features depend upon the type of snake bite. There are three main patterns: neurotoxic, as with elapidae such as cobras and kraits; vasculotoxic with alteration in blood coagulation as with vipers; and myotoxic as with sea snakes; although they are all often complicated by local tissue damage. The severity of poisoning will depend on the amount and potency of venom injected and the patient's general health.

In elapid envenomation, the patient complains of pain and numbness at the site of the bite, paralysis of muscles around the bite, lassitude, and drowsiness. These are followed by clouding of consciousness, dimness of vision, breathing difficulty, and cranial nerve paralysis with ptosis, dysarthria, dysphagia and dribbling of saliva. The patient passes into coma, respiration ceases and convulsions appear. In krait bite, symptoms occur later, and cramp-like abdominal pains are common.

In viperine envenomation, local burning pain at the site and painful oedema accompanied by lymphangitis occur. Petechiae, epistaxis, gastrointestinal and intracranial haemorrhage are seen. The clotting time is very much prolonged and patient may present with symptoms of acute renal failure or disseminated intravascular coagulopathy (DIC). In severe cases, vomiting, faecal and urinary incontinence, and hypotension lead to acute circulatory collapse and death.

VII.o. Management

First aid is to reassure the patient and arrange transfer to hospital as quickly and passively as possible. It is recommended that a bitten limb be immobilised by a pad and bandage, and there is experimental evidence for this approach although 'traditional' first aid treatments are useless and often dangerous.

Patients with systemic symptoms should be considered for treatment with antivenoms. Clinicians are not in agreement as to the exact criteria, and few randomized controlled trials have been conducted.

Where the snake has been identified and specific antivenom is available, then this should be used. However, since treatment is urgent, and identification of snakes is difficult, in many Asian countries polyvalent antivenom is used. The Indian anti-snake venom (ASV), manufactured by Serum Institute India, Pune, and Haffkine Bio Pharmaceutical Corporation, Mumbai, consists of hyperimmune horse serum against four common snakes – cobra, common krait, Russell's viper and saw-scale viper.

It is recommended for vasculotoxic and neurotoxic snake poisoning. It is marketed in a lyophilised form which needs to be reconstituted with distilled water before use. ASV is always in short supply, difficult to procure and very costly. Low doses of ASV may be as effective as high doses, with shorter hospital stays, and reduced cost.

Since ASV is known to produce hypersensitivity reactions, a test dose should be given. Patients are given supportive treatment with tetanus vaccine 0.5 ml IM, chlorphenamine 10 mg IV, and hydrocortisone 100 mg IV before ASV is given. In addition, epinephrine (adrenaline) solution (1 mg/ml) should be available for administration in case anaphylaxis occurs. Two vials of ASV diluted in 100 ml glucose 5% solution are given over one hour. The neurological and haematological parameters are assessed. If abnormal, a further vial of AVS in 100 ml glucose 5% solution is administered over the next 4 hours. This is repeated four hourly until neurological and haematological parameters are normal, and then 1 vial in 500 ml glucose 5% solution is administered over the next 24 hours.

More sophisticated antivenoms, containing antibody binding fragments, are less immunogenic than whole antibody antivenoms, and seem safe and effective.

VII.p. Opiate Poisoning

Poisoning with opiates such as morphine, pethidine, and heroin is increasingly common as opiate abuse becomes more widespread. The drugs are often injected or inhaled. The cardinal clinical features are coma, pin-point pupils and respiratory depression, which strongly suggest opiate poisoning.

VII.q. Management

Management consists of supportive care to maintain oxygenation, and the specific antidote naloxone. Intubation and artificial ventilation may be needed. Naloxone is given if the patient is in coma or the respiratory rate is 12 breaths per minute or less. Naloxone is given in dose of 0.4–2 mg intravenously or intramuscularly every 2–3 minutes until the maximum dose of 10 mg has been administered or the patient begins breathing spontaneously at a satisfactory rate. In patients who have required large or repeated doses of naloxone, continuous infusion avoids resedation. Two-thirds of the initial dose of naloxone is infused per hour (in glucose 5% solution or sodium chloride 0.9% solution) and the patient should be monitored for clinical response. Patients should be closely monitored for six hours after treatment has been stopped, since features of opiate poisoning can re-emerge.

VIII. ENVIRONMENTAL ILLNESSES

VIII.a. Altitude Illness

The three main types of altitude illness, characterised initially by nausea, headache, sleep disturbance and stomach upset, are: acute mountain sickness (AMS); high altitude pulmonary oedema (HAPE) and high altitude cerebral oedema (HACE). They occur after rapid ascent to altitudes greater than 2,500 m (about 8,000 feet) in unacclimatised people. In unacclimatised mountaineers, the prevalence of AMS at 4,559 metres (15,000 feet) is approximately 50% and HAPE 4%. Risk depends on individual susceptibility, rate of ascent and pre-exposure to high altitude. AMS is not a pre-requisite for HAPE.

VIII.b. Management

Altitude illness is likely to be prevented by limiting rate of ascent above 2,500–3,000 m/day. Acetazolamide, dexamethasone, and nifedipine are all used for prophylaxis.

If altitude illness occurs, then optimum treatment is to descend at once. High altitude cerebral oedema is a medical emergency with an appreciable mortality. If immediate descent is impossible, then dexamethasone, oxygen therapy, and re-pressurization using a portable hyperbaric bag (e.g. Gamow bag) may be life-saving. Nifedipine 10–20 mg orally, and supplemental oxygen are useful in treating HAPE.

A small controlled trial suggests that the phosphodiesterase inhibitor tadalafil was effective in preventing HAPE but not AMS; dexamethasone reduces the risk of both HAPE and AMS.

VIII.c. Heat Illness

In normal humans, body temperature is controlled within narrow limits, and heat gain is equal to heat loss. When the heat stress is so great that the body gains more heat than it looses, heat illness results. It is becoming more common as a result of the strenuous exertion that humans perform in high ambient temperatures. Large cohorts of patients have been seen following pilgrimages and marathons, and in conflict. Others at risk include the elderly, infants, and those living in overcrowded conditions without adequate water supplies. Genetic or constitutional factors probably also increase the vulnerability to heat illness.

Heat illness is traditionally divided into heat exhaustion and heat stroke. Heat exhaustion is the condition in which the casualty collapses from hypovolaemia due to salt and water depletion. This is probably compounded by physiological cutaneous vasodilatation, which causes shifts in blood volume from the core of the body to the skin. People who are unacclimatised to the environment are more likely to suffer heat exhaustion, especially if there is a lack of access to water. Where a person replenishes fluid losses from sweating with water alone, salt depletion predominates and this can cause insidious symptoms of exhaustion before the final collapse.

Heat stroke is the state in which heat stress induces a dangerously high core temperature that leads to tissue damage and particularly cerebral disturbance. The core temperature usually exceeds 40°C. The condition may follow heat exhaustion but the temperature rise may occur before salt or water depletion have had time to become manifest. Many organ systems may be affected by acute heat stroke including the brain, kidney, liver and muscles. Disturbance of the hypothalamic heat regulatory centre can lead to a loss of physiological responses to the

rising core temperature. Sweating and cutaneous vasodilatation may be lost, so that the casualty may paradoxically feel cold and have cool, dry skin, and often shivering. The muscular activity, however, further increases the body temperature and a vicious circle develops.

VIII.c.1. Management

The key treatment for all types of heat illness is early recognition and transfer into an environment where treatment can be given. Measuring the core body temperature will guide the urgency of management. Core temperatures of greater than 41°C can cause irreversible damage.

Rapid cooling by tepid sponging, fan-assisted evaporation and cooled intravenous fluids is the first step. Paralysis and ventilation may be necessary, especially if the patient is non-compliant as a result of cerebral dysfunction, or is shivering, indicating that thermoregulation has broken down.

Patients who present with heat exhaustion require fluid resuscitation. An attempt should be made to assess the amount of salt depletion and dehydration. This may be difficult clinically although the presence of symptoms such as muscle cramps in sodium depletion, and signs such as loss of tissue turgor may help. Laboratory measurement of sodium, urea, creatinine and haematocrit are the best guide. Pre-renal renal impairment is common. Treatment usually requires 5–10 l of oral or intravenous isotonic fluids in the first 24 hours. In severe hyponatraemia the rapid correction of sodium should be carefully monitored with frequent sodium measurements and a reduction in fluid infusion rate if necessary to reduce the risk of osmotic demyelination (central pontine myelinolysis).

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Chapter 33

A: Treatment and Prophylaxis of Infectious Diseases

Michiel A. van Agtmael, Tran Tinh Hien, Inge C. Gyssens, Henri A. Verbrugh

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I. TREATMENT

I.a. Principles of Antimicrobial Therapy

Antimicrobial drugs exert their action by being selective, this means they are toxic for bacterial cells but not or much less for human cells. Unlike other forms of pharmacotherapy, antimicrobial therapy is not only based on the characteristics of a patient and a drug but also on the characteristics of the microbe causing the infection. Interactions between the patient and the drug have to be considered, but also interactions between a micro-organism and the patient, and between the micro-organism and the drug. These complex relationships are best illustrated by the pyramid of infectious diseases (Fig. 1). This pyramid not only depicts the relationship between pathogens and the drug, but also between the drug and the natural microbial flora colonizing the host (commensal micro-organisms).

When considering antimicrobial therapy in a patient with fever, one should answer the following questions. First, is the fever caused by an infection? If affirmative, data are needed to determine the severity of the infection, the site of infection, and the causal micro-organism(s). Second, when the cause of the fever is infectious, one should ask: is treatment with antimicrobial drugs needed? Many soft tissue infections including impetigo and decubital ulcers are best treated with local antiseptics and/or wound debridement without the use of antibiotics. If the chance to cure the infection with antimicrobial drugs alone is small (e.g. in case of abscesses or of foreign body associated infections), a surgical intervention to drain the focus should be given priority over antimicrobial drug treatments. Third, if antimicrobial drugs are necessary, one should choose the drug and the dosage regimen. Three situations may arise:

- The disease is caused by a single micro-organism, and the susceptibility of that organism to antimicrobial agents is predictable, e.g. scarlet fever caused by *Streptococcus pyogenes.*
- The disease is caused by a single micro-organism, but its susceptibility to drugs is not predictable, e.g. typhoid fever or tuberculosis.
- The disease can be caused by several different micro-organisms and therefore it is difficult to predict which drug(s) can best be prescribed.

For infections frequently encountered outside hospitals, e.g. uncomplicated urinary tract infection in young women, surveillance of resistance data of the most likely pathogens (*Escherichia coli*) allows physicians to prescribe empiric therapy without performing cultures in the individual patient. However, in severely ill hospitalised patients, it is necessary to take samples for culture before starting empiric therapy. Microscopy of the Gram stained smear can help fine-tune empiric therapy at an early stage. Whether the infection is community-acquired or hospital-acquired, and whether the patient has been exposed to previous antimicrobial therapy should also be taken into account when choosing empiric therapy.

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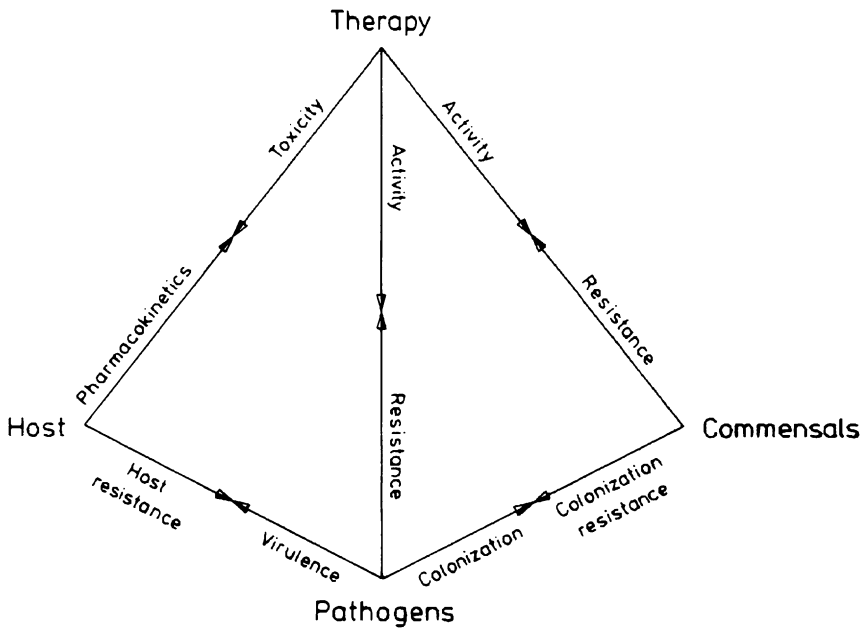


Fig. 1. The pyramid of infectious diseases.

Table 1. Guidelines for choosing an antimicrobial drug

It should:

1. Be highly active against the (suspected) causative organism
2. Reach effective concentrations at the site of infection
3. Have little toxicity (= a high therapeutic index)
4. Exert low selective pressure favoring resistant micro-organisms:
   - in the patient
   - in the environment
5. Have a formulations to be administered by parenteral and oral routes
6. Be inexpensive

A guideline for choosing an antimicrobial drug is presented in Table 1.

The choice of the drug should be made using evidence-based treatment guidelines. The guideline should specify one drug of choice for each major class of antimicrobial agents and recommend which drug to choose for each of the infections commonly encountered in that particular clinical setting. Dosage regimens are based on pharmacokinetic and pharmacodynamic characteristics of the drugs. Duration of therapy is mostly based on parameters of response, as the minimum duration of treatment has only been established for a limited number of infections.

Before discussing therapy, the interactions of the pyramid (Fig. 1) are discussed.

I.a.1. Interactions between the Pathogen and the Host

Virulence determines the capacity of an organism to establish itself on host surfaces, to invade and damage tissues and to withstand host defenses. Virulence not only determines the number of individuals who become ill after exposure to the pathogen, but also the severity of disease. In an immunocompromised host, micro-organisms with intrinsically low virulence (e.g. the normally harmless commensals) may cause disease, i.e. become pathogens. On the other hand, a highly virulent organism will not cause disease when host defenses are reinforced, e.g. through prior immunization or by improving physical barriers to contamination (protective clothing). Thus, the pathogenicity of a micro-organism of either low or high virulence can only be determined in relation to the host.

Resistance of the host to infection is determined by an intact skin surface and mucous membranes, as well as the innate and acquired immunity of the host.

In patients with impaired host defenses, however, infections usually run a more severe course. This has consequences for the selection of an antimicrobial drug, dosage regimen and duration of therapy. Studies have shown that in neutropenic patients higher doses and different dosage regimens of bactericidal agents are necessary; bacteriostatic agents will not suffice.

I.a.2. The Pathogen and the Commensal Flora

Colonisation by commensal micro-organisms is the normal status of healthy skin and mucous membranes. The capacity of the commensal microflora to limit colonisation and outgrowth of other micro-organisms has been described as colonisation resistance. Although the mechanism of this colonisation-resistance is not fully understood, (partial) loss of the commensal microflora results in increased susceptibility to new micro-organisms including potential pathogens, and, therefore, increases the risk of infection. An example is the predominance of *Lactobacillus* sp. in vaginal flora, which maintain the acid environment of the normal vagina. Elimination of these commensals by antibiotics will increases the pH and the risk of yeasts causing vaginitis. In the gastro-intestinal tract, elimination of the commensal aerobes and anaerobes by antibiotic therapy increases the risk of colonization and infection by drug resistant aerobes acquired via the oral route.

I.a.3. Interaction between Antimicrobial Drugs and Micro-organisms

Activity of antimicrobial drugs: antimicrobial drugs have the capacity to suppress growth or even to kill micro-organisms. This has led to the classification of antimicrobial drugs into bacteriostatic or bactericidal categories. The antimicrobial activity of a drug is expressed as the drug's minimal inhibitory concentration (MIC) and minimal bactericidal concentration (MBC). The MIC is usually determined *in vitro* by exposing a diluted suspension of growing bacteria (10^5 cells/ml, not visibly turbid) to serial twofold dilutions of the antimicrobial drug. The MIC is the lowest concentration of the drug expressed in milligrams per liter that prevents further growth, i.e. development of visible turbidity after overnight incubation. The MBC is always higher than the MIC and is the lowest concentration of the drug that reduces the original bacterial count by at least 99.9%. Bactericidal drugs have MBCs that are not much higher than their respective MICs, whereas bacteriostatic agents have MBCs that are much higher than their respective MICs.

I.a.3.1. Antimicrobial resistance. Resistance reflects the capacity of a micro-organism to avoid the growth inhibitory or lethal activity of a drug. Resistance can be intrinsic or acquired. Intrinsic resistance is an inherent attribute of a particular species. An example is the intrinsic resistance of anaerobic bacteria to aminoglycosides because these bacteria lack the oxygen-dependent transport system to allow aminoglycosides to enter the bacterial cell. Acquired resistance is due to a change in the genetic composition of a micro-organism, such that a drug that was formerly active against it, is not active anymore. General mechanisms of resistance are:

- The micro-organism keeps intracellular drug concentration below the toxic level, either by keeping the drug outside through a reduced permeability of its cell wall or by an active efflux mechanism that quickly pumps out drug entering the cell.
- The micro-organism inactivates drug by producing drug degrading enzymes, e.g. beta-lactamases that degrade penicillins.
- The micro-organism misses or changes the drug's target molecules, e.g. lack of or changes in certain penicillin-binding proteins in it's cell wall such that the penicillin cannot bind.
- The micro-organism overproduces the drug's target molecules such that available drug cannot bind all available target molecules.

Bacteria become resistant to antimicrobial drugs by changes in genes that are located on the bacterial chromosome or plasmid. Plasmids are extrachromosomal genetic elements commonly present in bacteria. Resistance genes are transferred vertically to all daughter cells. Resistance determinants on plasmids can also be transferred horizontally to other cells. Several types of evidence link antimicrobial drug-use to acquired microbial resistance. Resistance rates are generally higher in hospitals (high-density usage) than in the community (low-density usage). Among hospitals, studies have shown a relationship between the hospital's antimicrobial drug consumption and the frequency of microbial resistance. Within hospitals, a higher frequency of resistance is found in areas of high consumption such as Intensive Care Units. As any use of an antimicrobial agent will create a selective milieu favoring resistant micro-organisms, the liberal use of antibiotics in the community and in agriculture and animal

husbandry will increase the risk of emergence and spread of resistant micro-organisms. Overuse and inappropriate use of antimicrobial agents are, therefore, important modifiable determinants of antimicrobial drug resistance. In addition, the spread of resistant micro-organisms poses challenges to infection control where the presence and maintenance of proper hygienic barriers against the spread of resistant pathogens is a crucial determinant in hospitals as well as in the community.

I.a.4. Pharmacokinetics, i.e. Interaction between the Host and the Antibacterial Drug

To be effective *in vivo* the antimicrobial drug should reach concentrations at the site of the infection sufficient to inhibit or to kill the micro-organism(s). Therapeutic success is believed to require concentrations of antimicrobial drugs at the site of infection that at least exceed the MIC of the infecting organism. The appropriate dose and route of administration depend on an understanding of the pharmacokinetics of the drug. Pharmacokinetic parameters, together with the intrinsic antimicrobial activity of the drug, determine the effect on the infection. The growth inhibitory or bactericidal nature of the antimicrobial effect, and the rate at which this effect occurs in patients is called pharmacodynamics. Pharmacodynamic parameters or indices should be taken into account to determine the dosage regimen. Important pharmacodynamic properties have been described for certain classes of antimicrobial drugs. For example, aminoglycosides exert a concentration-dependent killing: the higher the concentration of aminoglycoside the greater the rate of kill. High peaks of aminoglycosides, e.g. gentamicin, are associated with efficacy and low troughs are associated with minimal toxicity. Therefore, aminoglycosides are administered in a once daily dosing regimen.

For infected sites that are difficult to reach, i.e. the cerebrospinal fluid, higher than usual doses should be administered, or the drug should be injected directly in the site of the infection (e.g. intrathecally). Abnormal body composition and impaired renal function may warrant dosage modification for effectiveness but also to limit toxicity.

Pharmacokinetic parameters are also important in relation to toxicity. The toxicity of antimicrobial drugs varies considerably and is usually concentration dependent. The therapeutic index is the ratio between the concentration of drug that is toxic for the patient and it's MIC for the pathogen. This index is very large for beta-lactams, since penicillins are relatively non-toxic for human cells. In contrast, the therapeutic index for aminoglycosides, is very small because these agents are toxic for human kidney tubular cellss and cells in the inner ear at concentrations not much higher than their MICs for pathogens. Therefore, monitoring of the serum concentrations of aminoglycosides is mandatory in clinical practice.

I.b. The Principle of Streamlining (from Empiric to Definitive Therapy)

Before the start of therapy, the causative micro-organism is usually not (yet) known. The range of activity of the empirically chosen antimicrobial drug or combination of drugs should be wide enough to act on all those pathogens that, on the basis of previous experience, one would predict to be able to cause the disease. However, recognition of the type of clinical infection, knowledge of the potential pathogens causing such infections, and knowledge of the resistance data by local surveillance reports on resistance will let the prescriber make well informed therapeutic choices. After the laboratory results become known, therapy should be adjusted to a simplified regimen, which becomes the definitive therapy until the infection is cured. An empiric regimen is modified:

- from combination therapy to monotherapy;
- from broad spectrum agent to narrow spectrum drug;
- from parenteral to oral treatment.

This strategy is called 'streamlining' resulting in the most effective therapy with less side effects and lower costs than the initial regimen.

Clinical improvement, especially the disappearance of fever or defervescence, is the best parameter to judge the response to therapy. However, clinical improvement can be difficult to monitor objectively in critically ill patients with multi-system disease. Also, clinical improvement can be very slow for certain infections, e.g. tuberculosis. The peripheral blood leukocyte count including the presence of early stages in leucocyte differention and the level of serum C-Reactive Protein (CRP, an acute phase protein) are parameters that can be sequentially determined to monitor improvement. For monitoring the effect of treatment of chronic infections such as endocarditis or osteomyelitis, weekly determination of the erythrocyte sedimentation rate has been proven useful.

The minimally required duration of treatment is only known for a limited number of infections. Clinical trials have shown the effectiveness of a single dose in the treatment of gonorrhoea or uncomplicated urinary tract infection in women and in surgical prophylaxis. The more precise duration of treatment has been studied for endocarditis, meningitis and staphylococcal bacteraemia. More often, guidelines for duration of treatment have been based on clinical experience with similar infections and on the parameters of response mentioned above. Failure of treatment should be recognised early. It can be due to a variety of reasons (Table 2).

Antimicrobial drugs tend to be overconsumed worldwide. Reasons for this phenomenon include the lack of knowledge about infectious diseases, i.e. the inability to distinguish between infection and other causes of fever, the uncertainty about the causative pathogen, i.e. treating viral infections with antibacterial drugs, the fear of not treating a treatable disease, and attempts to compensate for a failing surgical technique by prolonging antibiotic prophylaxis. Furthermore, patients sometimes insist that their physician prescribes an antimicrobial drug while there is no indication for it, like a common cold or viral upper respiratory tract infections. Therefore, education of the lay public may have a major impact on the quality of prescribing antimicrobial drugs. Also, drug-promoting efforts of pharmaceutical industries may not always be prudent or appropriately tailored and will have to be counterbalanced by the professional community. Furthermore, professional health care providers, especially physicians and pharmacists, may themselves be insufficiently trained or inappropriately economically motivated in their drug-prescribing activities.

Table 2. Reasons for failure of antimicrobial treatment

- The clinical or microbiological diagnosis is wrong
- The concentration of the antimicrobial drug at the site of infection is insufficient due to:
  - insufficient dose
  - poor bioavailability when given orally
  - site of infection is difficult to reach (e.g., CSF)
  - increased elimination
- Host factors reducing the *in vivo* activity of the drug:
  - abscess or empyema
  - neutropenia
  - foreign body
- Selection and growth of resistant variant/mutant of the initial pathogen during therapy
- Superinfection with a new (resistant) pathogenic species during therapy

At the time of writing over 190 systematic reviews concerning the use of antimicrobial agents and generated by various review groups, were available in the Cochrane database (www.theCochraneLibrary.com). Of course space does not permit to refer to all these particular reviews individually. However, the indications given and the treatments which are recommended rely as far as possible on evidence-based data as covered by these Cochrane Collaboration Reviews.

I.c. Diseases

I.c.1. Respiratory Tract Infections

The spectrum of respiratory tract infections (RTI) can vary from the common cold to acute or chronic bronchitis to community-acquired pneumonia to nosocomial pneumonia and aspiration pneumonia to ventilator-associated pneumonia to chronic pneumonia (in cystic fibrosis, histoplasmosis, tuberculosis, etc.). Important complications are lung abscess and pleural empyema that will often need drainage and prolonged antimicrobial treatment (>6 weeks).

An upper RTI (bronchitis, sore throat syndrome, sinusitis, otitis media) must be distinguished from a lower RTI (pneumonia) because a lower RTI always requires treatment with antibiotics and an upper RTI frequently does not. In both cases the patient will have symptoms of coughing, fever and pain on the chest. However, in pneumonia the patient is often more ill, has higher fever with chills (compatible with bacteremia) and, on auscultation, has signs of lung infiltation or pleural effusion. Crucial in the diagnosis is the chest X-ray. It is currently recommended to distinguish between mild and severe cases of pneumonia, preferably using a validated scoring system, and to adjust therapy accordingly. A sputum culture and, in a patient with high fever, two blood cultures should be taken before start of therapy.

In half the cases of acute community-acquired pneumonia a microbiological diagnosis can be made. *Streptococcus pneumoniae* is responsible for 16–60% of the cases. The second most prevalent micro-organisms are those responsible for the so called atypical pneumonia syndrome including

Mycoplasma, *Legionella* and *Chlamydia*. Hospital-acquired lower RTI are frequently caused by gram-negative bacteria. Resistant pathogens must be considered in an intensive care setting.

Risk factors in the host can give a clue for the causative pathogen e.g. Chronic Obstructive Lung Disease (COPD) – *Haemophilus*, alcoholism – *Klebsiella*, HIV – *Pneumocystis*. The immunocompromised host is also at increased risk for certain fungal (*Aspergillus*) and viral infections (cytomegalovirus or CMV). *Pseudomonas aeruginosa* is frequently involved in exacerbations of cystic fibrosis.

Risk factors in the environment include exposure to birds (*Chlamydophila psittaci* causing psittacosis), exposure to goats and sheep (*Coxiella burneti* causing Q-fever), contaminated aerosols (*Legionella pneumophila*, *Mycobacterium tuberculosis*), visits to a cave with bats (*Histoplasma capsulatum*), and living (visiting) in rural South-East Asia, Northern Australia and some parts of South America (*Burkholderia pseudomallei* causing melioidosis) are important to identify in a thorough questioning of the patient.

Is treatment with an antibiotic necessary? An important problem in the primary health care setting is treatment of mild upper RTI with antibiotics. It is well known that >90% of these upper RTI are caused by viruses and in these cases antibiotics are useless, even harmful. The benefit of antibiotics for exacerbations of chronic bronchitis is controversial.

In lower RTI it essential to choose an antimicrobial agent that achieves high concentrations in lung tissue and sputum, e.g. a beta-lactam antibiotic. When an atypical pneumonia is suspected, a macrolide or a tetracycline should be added. In a seriously ill or septic patient, parenteral therapy must be used. Severe pneumonia cases may benefit from addition of a single dose of an aminoglycoside (gentamicin) for synergy and rapid bactericidal action. There is a place in this setting for the newer quinolones (levo- or moxifloxacin) as well. In melioidosis pneumonia a ceftazidime or a carbapenem is prescribed. However, in the majority of cases pneumonia presents as clinically mild disease and in these mild cases oral treatment with amoxicillin or a tetracyline is highly effective.

On the basis of antibiotic-susceptibility tests of the isolate cultured from the inital sputum (or blood), therapy should be streamlined, preferably within 48 hours. In an uncomplicated course a switch to oral therapy should be made after a few days. If defervescence takes longer than a few days an chest X-ray should be performed to exclude empyema or lung abscess.

Worldwide *Streptococcus pneumoniae*'s susceptibility to penicillin is decreasing. In some countries up to two-thirds of the clinical isolates have reduced susceptibility to penicillin or are highly resistant to this drug. Moreover, the rate of resistance to other drugs commonly used for RTI including erythromycin, tetracycline and trimethoprim-sulfamethoxazole is higher in penicillin-resistant than penicillin-susceptible strains. Monitoring local or hospital resistance patterns of pneumococci is, therefore, needed.

If it is decided to treat an upper RTI in general 5–7 days treatment suffices. In lower RTI generally 10–14 days are recommended. Two to three weeks of treatment is advised for *Staphylococcus aureus*, *Legionella pneumophila*, *Pseudomonas aeruginosa*, *Pneumocystis jiroveci* (formerly *carinii*) and severe aspiration-pneumonia. Tuberculosis, actinomycosis, nocardiosis, aspergillosis, melioidosis and anaerobic lung abscesses require many months of treatment.

One should consider influenza- and pneumococcal-vaccination in patients with increased risk for lower RTI including patients with chronic obstructive pulmonary disease like chronic bronchitis or emphysema and cystic fibrosis patients. It should be considered for the elderly population in general. There is no role for prophylactic antibiotic therapy in patients with frequent RTI. Attempts should be made to have those patients that smoke stop doing so.

I.c.2. Gastrointestinal Tract Infections

The spectrum of gastrointestinal tract infections (GTI) cover a wide spectrum from asymptomatic *Helicobacter pylori* gastritis to self-limiting viral gastroenteritis to food poisoning to bacterial enterocolitis to antibiotic-associated *Clostridium difficile* colitis to typhoid fever with sepsis and multi-organ failure.

Worldwide 5–6 million children die each year of diarrheal diseases. Symptoms of GTI are nausea, vomiting, diarrhea (in case of *Shigella* and *Entamoeba* often bloody), abdominal pain and fever. Causal associations have been found between *Campylobacter jejuni* infections and subsequent Guillain–Barré syndrome and between enterohemorrhagic *Escherichia coli* colitis and the hemolytic uremic syndrome. In severe or complicated cases a faeces culture (and in case of high fever also two blood cultures) should be taken prior to therapy.

When the diarrhea is not viral (Noro formerly known as Norwalk virus) or protozoal (*Entamoeba*) or caused by a toxin (shell-fish poisoning) it is often caused by either *Salmonella*, *Shigella*, *Campylobacter* or *Yersinia* species. In some countries there is a high prevalence of *Vibrio cholerae* – GTI causing severe watery diarrhea. *Clostridium difficile* enterocolitis is related to prior antibiotic treatment but also observed during chemotherapy.

Decreased gastric acidity (antacids, acid-inhibitors), lack in personal hygiene, decreased intestinal motility (opiates, antiperistaltic agents), a disturbed enteric microflora and malnutrition are risk factors for a GTI. In contrast, breast-feeding reduces GTI incidence in infants.

Contaminated food and water, poor sanitation and personal hygiene, and a warm climate are clearly associated with GTI (classically the 3 Fs: Food, Fingers and Flies). Frequently people in close contact with the patient have or develop similar symptoms, underlining the contagious nature of GTI.

Is treatment with an antibiotic necessary? Firstly, most of the cases with acute diarrhea, especially in developing countries are non-specific or of viral origin. The prescription of antibiotics in such cases is ineffective and expensive waste of money. With respect to the treatment of acute non specific diarrhea the vital importance of rehydration, especially in young children, needs to be highlighted. The goal of treatment is to correct fluid volume deficits, which should be replaced on a volume-for-volume basis. Rehydration has to be provided as needed, and it has to be ensured that the patient's fluid intake is adequate. Oral rehydration solution (ORS) is used to treat dehydration caused by diarrheal diseases including cholera. Reduced osmolarity formulations are safe and more effective than standard ORS for treating non-cholera diarrhea. A systematic review available in the Cochrane database concludes that in people with cholera, reduced osmolarity ORS is associated with biochemical hyponatremia when compared with standard ORS. No adverse consequences became apparent but the numbers were small (see Murphy et al., 2004). In general, in immunocompetent patients acute bacterial gastro-enteritis or enterocolitis is self-limiting and only requires supportive therapy (fluids and electrolytes). In complicated, persistent cases or in very ill patients antibiotics are advised.

Quinolone antibiotics (ciprofloxacin) offer a considerable advantage in treating infectious diarrhea although there is increasing quinolone resistance in South-East Asia, where azithromycine has become first choice. They are effective in salmonellosis or shigellosis and they also reduce fecal shedding. There is hepatic and renal elimination of ciprofloxacin and some drug is also eliminated in the digestive tract. Most other antibiotics prolong shedding of the micro-organism and some are associated with an increased risk of relapse.

For *C. difficile* colitis oral or i.v. metronidazole is advised for at least 14 days. Shorter duration will increase the relapse-rate. Oral vancomycin is equally effective but more expensive and the frequent use of vancomycin in some countries has been associated with an increase in vancomycin-resistant enterococci and staphylococci.

Therapy should be streamlined as soon as microbiological test results become available. If defervescence takes longer than a week physical and radiological examination (ultrasound or CT-scan of the abdomen) should be performed to exclude an intra-abdominal- or liver-abscess.

The emergence of resistance among diarrhea causing pathogens is a worldwide problem with resistance patterns showing significant variation across the globe. Treatment should therefore be guided by the local or hospital resistance patterns. With the use of a restricted antibiotic regimen a reduced incidence of multi-resistant *Salmonella* isolates was recently observed in India indicating that prudence in antibiotic usage may reverse a given resistance problem.

The good bioavailability of orally administered ciprofloxacin obviates the need for the more expensive intravenous formulation. I.v. ciprofloxacin is only given to patients who have severe sepsis or severe nausea and vomiting. Ciprofloxacin's elimination is 50% hepatic and 50% renal. Therefore, dose reduction is recommended only in case creatinine clearance drops to <10 ml/min. Prevention of food-borne disease requires efforts at many levels. Monitoring safety of food processing, vector control, surveillance of outbreaks, education on personal hygiene and improving sanitation and access to safe water supplies are all necessary measures to reduce the incidence of GTI.

There is increasing evidence that eradication of *Helicobacter pylori* with combination therapy of two antibiotics (often amoxicillin with clarithromycin) with a proton pump inhibitor (e.g. pantoprazol) during one week will heal and prevent peptic ulcer disease.

I.c.3. Urinary Tract Infections

The spectrum of urinary tract infections (UTI) can vary from asymptomatic bacteriuria to cystitis to pyelonephritis to urosepsis.

Symptoms of lower UTI are frequent and present themselves often as painful urination without fever. Symptoms of upper UTI are fever and often flank pain. However, the majority of elderly patients with UTI are asymptomatic. UTI must be considered if in a midstream urine more than 10^5 bacteria/ml and more than 10 leucocytes/ml are found. A urine culture (and in patients with high fever also two blood cultures) should be taken prior to start of therapy.

Most infections are caused by gram-negative bacteria, mostly *Escherichia coli*. In recurrent UTI, after repeated courses of antimicrobial therapy, other organisms and antibiotic resistance can be expected.

Stasis of the urinary flow (e.g. caused by kidney stones, anatomic abnormalities or an enlarged prostate), female gender and diabetes mellitus are risk factors for a UTI.

Nosocomial UTI is the most common infection in hospitals and nursing homes and 80% is associated with the use of urethral catheters. An incidence of bacteriuria of 3–10%/day makes the duration of catheterization the most important risk factor for bacteriuria. Asymptomatic bacteriuria should not be treated. However, up to 30% of patients with catheter-associated bacteriuria will develop fevers or other symptoms of UTI. In long term catheterization *Providencia stuartii* and *Candida* species are the most common responsible organisms. Exchange of the catheter under therapy is advised in chronic cases.

Is treatment with an antibiotic necessary? Symptomatic patients always need treatment. Asymptomatic bacteriuria ($=10^5$ bacteria/ml in two separate urine cultures) only needs treatment in pregnancy, in children and in obstructions of the urinary tract. Obstructions in urinary flow must be treated before an antibiotic is started. There is no clear evidence that hydration or acidification of urine improves the results of antimicrobial therapy.

In lower UTI it is essential to choose an agent that achieves a high concentration in urine, e.g. nitrofurantoin or norfloxacin. In a patient with fever, an upper UTI can be expected (pyelonephritis ± bacteremia) and therefore an agent with adequate concentrations in blood and urine should be given, e.g. the second generation cephalosporin cefuroxime. When urosepsis develops (high fever, chills and hypotension) parenteral therapy must be used, adding one dose of an aminoglycoside (gentamicin) to the cephalosporin for initial broadening of the sectrum esp. for patients with nosocomial UTI or recurrent UTI. However, a meta-analysis showed that synergy and rapid bactericidal action of this combination therapy showed no reduction in mortality compared to one antibiotic.

On the basis of susceptibility tests of the isolate cultured from the initial urine (or blood), therapy should be streamlined, preferably within 48 hours. In an uncomplicated course a switch to oral therapy should be made after a few days. If defervescence takes longer than a few days repeated physical examination and radiological examination should be performed to exclude hydronephrosis, urinary stones or perinephric abscess.

Amoxicillin, ampicillin and sulfonamides are no longer reliable agents as 25–35% of *Escherichia coli* are now resistant. When bacteruria occurs under therapy, resistance must be suspected.

For lower UTI in women under 50 years of age, three days of therapy is superior than single dose therapy. In all other lower UTI 7–10 days of therapy is advised. In upper UTI 14 days is recommended. For prostatitis cotrimoxazole and fluoroquinolones reach high concentrations in the prostate but prolonged therapy (1–3 months) is necessary esp. in case of chronic prostatitis (less inflamed prostate, less penetration of the antibiotic).

Cephalosporins are the agents of choice in renal failure. They attain adequate urine concentrations despite severely impaired renal function and toxicity remains low with increased plasma levels. Quinolones are preferred over aminoglycosides due to aminoglycoside-related ototoxicity.

The frequency of relapse and the risk of renal damage determine the need for on-demand therapy or prophylactic therapy. In intercourse-related UTI in sexually active women single dose prophylactic therapy was shown to be effective. One dose of trimethoprim (± sulfamethoxazole) or nitrofurantoin is effective, inexpensive and unlikely to allow the emergence of resistant bacteria.

I.c.4. Skin, Soft Tissue, Bone and Joint Infections

Bacterial superficial skin infections including cellulitis and erysipelas, furunculosis and impetigo usually have a benign course. Infections of the subcutis often lead to necrosis of soft tissue. These infections are described in section 16 (surgical infections). Arthritis involves infection of the synovia and

intra-articular space. Osteomyelitis is defined as infection involving bone and bone marrow with bone destruction. Chronic osteomyelitis is characterised by devitalised bone and fistula formation.

Superficial skin infections are frequent and are mostly diagnosed clinically. Redness, swelling, and pain are the characteristics of both cellulitis and erysipelas. Arthritis is characterised by swelling of the joint and limitation of movement. Purulent joint fluid at puncture is diagnostic and should be cultured. Osteomyelitis is diagnosed by imaging techniques. Acute hematogenous osteomyelitis occurs mainly in children in the metaphysis of long bones. Culture of bone, and in acute cases, blood cultures, yield the causative micro-organism.

Bacterial skin infections are mostly caused by staphylococci and pyogenic streptococci (beta-haemolytic streptococci of group A). Skin infections which are vesicular at onset are often caused by herpes viruses (*Varicella, Herpes zoster*). Arthritis and osteomyelitis are mainly caused by *S. aureus*. In monoarthritis of the knee in a young adult, *N. gonorrhoeae* should be considered as a causative pathogen. Chronic (ulcerative) infections are less common and may be caused by fungi, ectoparasites (e.g. scabies), atypical mycobacteria and by *Corynebacterium diphteriae*. Gangrenous infections of the soft tissues and abscesses are often mixed infections including aerobic streptococci and anaerobic bacterial species (*Clostridia* sp., *Peptostreptococci* and *Bacteroides*). In tropical countries, chronic infections of the extremities are caused by fungi and *Actinomyces* and can lead to the clinical picture of Madura foot.

Breaches in the integrity of the skin (eczema, trauma or burns) are predisposing factors for infection. Lymphoedema represents a risk for erysipelas. Open complicated fractures are often complicated by chronic osteomyelitis. Patients with diabetes mellitus have more frequent as well as more severe infections of the skin, soft tissue and of bone. Sickle cell disease predisposes to osteomyelitis.

In developing countries many infections of the limbs result from exposure to punctures and subsequent contamination by organic material. In hospitals subcutaneous and intramuscular injections and intravenous (peripherally or centrally placed) infusions can be complicated respectively by subcutaneous or intramuscular abscesses and purulent (thrombo)phlebitis and secondary bacteraemia.

Superficial skin infections are treated without antibiotics. Local hygiene and disinfection with alcohol prevents spread of furunculosis. Local application of gentian violet in water (1%) is effective for impetigo. All pus collections must be drained by puncture or incision. Antibiotics are required only when systemic signs of infection are present or in patients with a high risk of complications (e.g. to prevent bacteraemia in a patient with prostheses or intravascular devices).

Severe cases with extended tissue necrosis or systemic illness (sepsis) require prompt high-dose parenteral therapy with a broad spectrum antibiotic, e.g., a carbapenem. Arthritis and osteomyelitis are treated initially with high-dose parenteral antistaphylococcal drugs (oxa- or flucloxacillin or in case of MRSA (Methicillin Resistant Staph. aureus alternatives like vancomycin or linezolid). Surgical debridement may be indicated, especially in the adult patient and in the more chronic types of osteomyelitis. Foreign bodies including prosthetic material will have to be removed or else it can be a focus of recrudescence. Duration of antibiotic therapy should be $\geqslant$6 weeks in osteomyelitis because the bacterial biofilm at the site of infection tends to resist the bactericidal action of antibiotics. Chronic infections sometimes require $>$12 weeks of antibiotic treatment, preferably based on a microbiological report. The combination of oral ciprofloxacin (2 $\times$ 750 mg) and rifampicin (2 $\times$ 450 mg) for prosthetic joint infections has proved successful for chronic *S. aureus* osteomyelitis. Long-term treatment with oral drugs is only possible with drugs that have a good bioavailability.

Therapy should always be streamlined if and when a microbiological report becomes available. Erysipelas caused by streptococci can be treated by penicillin. In arthritis and osteomyelitis, culture of the joint fluid or of deep tissue is recommended before the start of treatment.

Local treatment of skin and soft tissue infections with antibiotic-containing ointments or solutions should not be used because it leads to allergic reactions and rapid development of bacterial resistance. In settings where MRSA or resistant *Enterobacteriaceae* (like ESBL's gram negative bacteria with extended spectrum beta lactames) or *Pseudomonas* spp. occur, the empiric use of vancomycin and a carbapenem can be necessary. The risk of transmission of these organisms should be minimalised by hygienic and isolation measures.

Oral anti-staphylococcal penicillins or cotrimoxazole are effective against most skin pathogens. Five days of therapy (or 3 days after local signs are resolved) is usually sufficient. For arthritis 2 or 3 weeks of therapy are required. In chronic osteomyelitis, resection of dead tissue should be followed by at least six weeks to 3 months of antibiotics until the ESR returns to normal. Oral quinolones are useful for gram-negative osteomyelitis while clindamycin is effective in gram-positive and anaerobic infections.

Chlorhexidine- or iodine containing antiseptic soap is effective for the prevention of relapses of erysipelas in patients with lymphoedema. The elimination of the *S. aureus* carrier state by 5 days mupirocin nasal ointment is useful in patients and families with severe relapsing furunculosis. This should only be done after healing of the furunculosis and should be combined with a intensive program containing daily antiseptic shampoo and skin washing, bedsheets washing and evaluation of close contacts for *S. aureus* carrier state to prevent recurrence. Systemic or topical antibiotics should not be given for the prevention of skin infections. Topical silver sulfadiazine has been used successfully for the prophylaxis of superinfections of burns with *S. aureus* and *P. aeruginosa*.

I.c.5. Sexually Transmitted Disease (STD)

Many infections, including HIV/AIDS (discussed in Chapter 33B) and hepatitis B and C, are transmissible during sexual contact, those exclusively transmitted in this fashion are discussed here. It includes syphilis, chancroid, gonorrhoea, lymphogranuloma venereum and granuloma inguinale (Donovanosis), non-gonococcal urethritis/cervicitis, condylomata acuminata, genital Herpes and infectious vaginitis. Dissemination of pathogens from the genital site of infection to other parts of the body may occur.

The incidence of STDs, by their nature, closely follow changes in sexual behaviour and practices of the population as evidenced by the decline of many, but not all, STDs in the 'safe sex era' induced by the AIDS pandemic. However, STDs continue to be a major health problem worldwide. Apart from acute morbidity they also are a major cause of pelvic inflammatory disease and infertility among women of child-bearing age, and cause congenital infections among the newborn.

STDs that have manifestations at the surface of the skin or mucosa (vesicles, ulcers, fluor vaginalis, purulent urethral/cervical discharge, inguinal lymphadenopathy) are clinically evident, but require laboratory confirmation by microscopy, culture, serology or DNA-based technologies (PCR). Some STDs including Chlamydia and syphilis have a sizable asymptomatic patient cohort that can only be traced by targeted screening programs in relevant sectors of the population. Syphilis is caused by *Treponema pallidum* and is diagnosed microscopically (darkfield microscopy) and serologically. Chancroid caused by *Haemophilus ducreyi* is diagnosed by culture or PCR. Gonorrhoeae caused by *Neisseria gonorrhoeae* can be cultured or detected by PCR. Lymphogranuloma venereum (LGV) is caused by certain serotypes of *Chlamydia trachomatis* and can be diagnosed by PCR and serology. Donavanosis or granuloma inguinale caused by *Calymmatobacterium granulomatosis* is difficult to culture and is usually diagnosed microscopically on the basis of intracellular Donovan bodies in scrapings of a suspected ulcer. Non-gonococcal urethritis/cervicitis due to *Chlamydia trachomatis* (non-LGV types) can be diagnosed by direct immunofluorescence/immunoassays for specific antigen, but PCR-based assays have superior sensitivity and can be done on urine. Non-gonococcal, non-chlamydia urethritis (non-specific urethritis) is a disease with unknown etiology that is prevalent among sexually active men. Condylomata accuminata are caused by human papilloma viruses and have a characteristic presentation (highlighted by prior soaking with 3–5% acetic acid) that may be confirmed by histopathology or PCR. Genital Herpes likewise has characteristic lesions and can be confirmed by microscopy (direct immunofluorescence, Tzanck test) and by culture for *Herpes simplex* virus. The cause of infectious vaginitis, *Trichomonas vaginalis*, is established by the homogenous nature, odor, pH, and wet-mount microscopy of fluor and/or culture or by PCR (most sensitive assay!).

Because of their infectious nature STD treatment should always be combined with counseling of the patient regarding the source of their disease (partner notification and treatment) and the reduction of risk in acquiring STD's in the future. Population-based screening programs also play a major role in public health efforts to control STDs. Individual patients are usually given empiric treatment on the basis of their clinical presentation. Compliance with treatment has favoured single dose regimens and control visits whenever possible. Many patients may have

more than one STD at the same time requiring combination therapy.

Trichomonas vaginitis is treated with a single 2 g dose of metronidazole (not during 1st trimester of pregnancy); persistent/recurrent cases are given 10 days of metronidazole 3 × 1 g orally plus metronidazole 1 g vaginally, and clotrimazole 100 mg daily for 7–14 days is recommended during pregnancy. Metronidazole and alcohol should not be given together as a disulfiram-like reaction may result!

Ulcus durum/early syphilis. The primary stage of syphilis, highlighted by the genital ulcer (chancre), is contagious and is treated with benzathine benzylpenicillin G 2.4 million units i.m. weekly for three doses. In case of penicillin allergy oral doxycycline 2 × 200 mg daily for 3 weeks is given, or, when patient is also pregnant, doxycycline should replaced by erythromycin 4 × 500 mg orally. The secondary, disseminated, stage and the early (<1 year) third stage of syphilis will respond to the same regimens; treatment of the later stages of the disease as well as of organs involved are referred to other texts.

Ulcus molle/chancroid is treated with a single dose of either ceftriaxone i.m. or with azithromycin 1 g orally. Three days of oral ciprofloxacin 2 × 500 mg daily or 7 days of amoxicillin/clavulanic acid 3 × 500/125 mg orally or erythromycin 4 × 500 mg orally are alternatives.

Lymphogranuloma venereum. Three weeks of either doxycycline 2 × 100 mg daily or erythromycin 4 × 500 mg daily are the therapies of choice for this condition.

For granuloma inguinale the first choice of treatment is cotrimoxazole 2 × 960 mg orally for two weeks. Alternatives are doxycycline 2 × 100 mg orally for 2 weeks or oral azithromycin 1 g weekly for 4 doses, or 1 × 500 mg daily for 7 days.

Gonococcal urethritis/cervicitis. Due to resistance development gonococcal diseases is nowadays treated with a single dose of ceftriaxone 250 mg i.m. or with a single 500 mg dose of oral ciprofloxacin. In areas without beta-lactamase producing strains a single dose of i.m. procain benzylpenicillin 4.8 million units plus 1 g probenicid orally will cure gonococcal urethritis; alternatively, a single 3 g dose of oral amoxicillin will suffice.

Chlamydial urethritis/cervicitis is preferably treated with a single 1 g dose of azithromycin or a seven days course of doxycycline 2 × 100 mg daily; alternatively, erythomycin 4 × 500 mg daily or ofloxacin 2 × 200 mg daily, both for a week, will cure uncomplicated disease. All three classes of antibiotics are known to penetrate cellular membranes and act intracellularly, which is needed for Chlamydia being intracellular pathogens.

Although the cause of non-specific urethritis in males is unknown, several microbiological etiologies have been postulated and a trial course of antimicrobial treatment is usually given. A single dose of azithromycin 1 g or a 7 days course of 2 × 200 mg ofloxacin daily have been advocated.

There is no specific treatment for human papilloma virus infection (condylomata accuminata). Therapeutic modalities consist of chemically or physically destructive agents including the podophylllin (applied weekly as a 10% solution in benzoin) or the less toxic podophyllotoxin 0.5% (applied twice daily for three consecutive days every week for up to 4 weeks; cure rates are generally <50% and relapses are common). For older lesions various surgical techniques are advocated that are beyond the scope of this contribution.

Treatment for herpes genitalis is only indicated in serious or frequently recurring disease, in the presence of immunodepression or if psychosocial circumstances dictate this. Primary and recurrent infection is treated for 5 days with an oral derivative of aciclovir, either valaciclovir 2 × 500 mg or famciclovir 3 × 250 mg. Partial or complete aciclovir resistance may develop. Prophylactic aciclovir may be indicated if the frequency of recurrence is >6 per year. Local care of lesion (cleansing, disinfecting creams) is indicated to prevent secondary bacterial infection.

I.c.6. Meningitis

Patients with acute meningitis classically present with fever, headache and symptoms of meningismus including nuchal rigidity, Kernig's and or Brudzinski's signs implicating inflammation of the meninges. Symptoms are more pronounced in bacterial than viral meningitis.

The diagnosis is made on the clinical picture and a lumbar puncture with an increased white blood cell count in the cerebrospinal fluid. These cells are generally neutrophils in acute, bacterial meningitis and lymphocytes in viral and subacute or chronic meningitis. A gram stain of the CSF has a sensitivity of 60–90%. Although cerebrospinal fluid is wanted for a definite diagnosis and identification of the pathogen, the lumbar puncture should not delay the prompt administration of antibiotics.

Bacterial meningitis remains a very important disease worldwide. Attack rates of 46 cases per 100,000 population with a case fatality rate of 33% have been described. Early recognition and prompt treatment remain essential for the prognosis of this serious illness.

The three most important organisms causing meningitis are *Haemophilus influenzae*, *Neisseria meningitidis* and *Streptococcus pneumoniae*. The introduction of efficacious vaccines for all three organisms will decrease their incidence rates in the future. *Listeria monocytogenes* causes meningitis mainly in neonates and immunocompromised hosts but also in previously healthy adults >50 years after ingestion of contaminated raw milk or French soft cheese.

The epidemiology of pathogens in newborns up to 3 months causing meningitis is different than at a later age. Aerobic gram-negative bacilli are important etiologic agents in neonates. *Streptococcus agalactiae*, present in 15–40% of vaginal cultures of asymptomatic pregnant women, is another common cause of meningitis in neonates. The immunocompromised state, basilar skull fracture, post neurosurgery including cerebrospinal fluid shunt are risk factors for meningitis. Recently a gene was found encoding for an increased coagulation during meningococcal sepsis. Patients with this gene had a worse prognosis.

Epidemics of bacterial meningitis have been described in crowded places such as military institutions and schools. In some countries in Africa ('meningococcal belt') the incidence of seasonal meningococcal meningitis is so high that meningococcal vaccination is advised.

No therapy is available for viral meningitis which is mainly caused by enteroviruses and in general has a good prognosis. For Herpes simplex meningoencephalitis i.v. aciclovir is recommended.

For acute bacterial meningitis rapid institution of antibiotic treatment is crucial for the prognosis. In the presence of meningeal inflammation penetration of a β-lactam antibiotic in the CSF is enhanced whereas only about 1% of exposed drug will penetrate when the blood–brain barrier is normal. In severe meningitis the CSF contains high concentrations of lactate and protein. Antibiotics that are highly protein bound or inactive in low pH environment are therefore not attractive for treatment. Empirically a third generation cephalosporin (e.g. ceftriaxone 2 × 2 g) is generally given and amoxicillin (6 × 2 g) is added when *Listeria* infection is suspected. The addition of dexamethasone (4 × 10 mg during 4 days) is recommended in children and adults as soon as possible at presentation.

When culture results of CSF and/or blood are available therapy should always be streamlined. If the meningococcus, pneumococcus, group B streptococcus or *Listeria* are penicillin sensitive, this small spectrum agent (benzylpenicillin 6 × 3 million units/day i.v.) would be the therapy of choice.

There is increasing penicillin resistance and some reports on increasing MICs for cephalosporins. In rare cases highly resistant pneumococcal strains have been successfully treated with meropenem or vancomycin.

In most cases one week of i.v. penicillin is adequate for meningococcal meningitis. Ten to 14 days is recommended for pneumococcal meningitis. Two to 3 weeks for *Listeria* and group B streptococcal meningitis and 3 weeks is necessary for gram-negative meningitis.

To prevent secondary cases of meningococcal disease prophylaxis with rifampicin 600 mg orally twice daily for two days is recommended for close contacts with the index case. A single dose of 500 mg ciprofloxacin orally is also effective in eliminating nasopharyngeal carriage of *N. meningitidis.*

I.c.7. Endocarditis

Endocarditis implies the presence and multiplication of viable micro-organisms on the endocardial surfaces, usually the valves, of the heart. Although many classes and species of micro-organisms can cause endocarditis most are of bacterial origin, and these are discussed here. Clinically the disease can present as an acute disease but subacute endocarditis is more common. Usually the left side of the heart is involved but right-sided endocarditis does occur. Endocarditis affecting prosthetic heart valves is a relatively new form of the disease. The disease is best classified according to its bacterial etiology.

In developed countries endocarditis is present in $\sim 1/1000$ hospital admissions or 1–2 cases per million population. An increasing number of endocarditis cases are associated with intravascular device infections and the placement of prosthetic valves; thus, endocarditis can be acquired during hospital stay. Men are afflicted more often than females, and most patients are >50 years of age. Pre-existing heart lesions predispose to bacterial endocarditis if they are accompanied by (thrombotic) alterations of the endocardial surface or blood flow such that bacteria

carried by the bloodstream are more likely to become attached to it. Such predisposing conditions include congenital and rheumatic and degenerative heart diseases as well as prosthetic materials. Only very few bacterial species, including *Staphylococcus aureus*, can attach to an intact, undisturbed, endocardium. Since seeding via the bloodstream is a prerequisite, the risk of endocarditis is related to the incidence of (transient) bacteremia from distant sites (commensal mucosa (e.g. peri-dental and gastro-intestinal sites) or infectious foci elsewhere).

The diagnosis (definite or possible endocarditis) according to the 1992 Duke's criteria (see Mandell et al., 2000) is based on blood cultures and echocardiography, the patient's history and findings upon physical examination. This diagnosis should always be considered in patients presenting with fever of unknown origin, especially when they also have a heart murmur and/or normocytic, normochromic anemia.

Gram-positive cocci, especially viridans streptococci and *Staphylococcus aureus*, cause the vast majority of episodes of endocarditis in individuals without a prosthetic heart device. In prosthetic device endocarditis coagulase-negative staphylococci and *S. aureus* are major pathogens early after the implantation of the device; later episodes of prosthetic device associated endocarditis are more likely due to viridans streptococci. Enterococci-bacteremia is associated with lesions in the digestive tract and frequently causes endocarditis. Gram-negative bacilli cause <5% of episodes of bacterial endocarditis.

The very high number of bacteria packed and enclosed in thrombotic material on the endocardium wherein host leucocytes do not penetrate calls for antibiotic regimens that are rapidly bactericidal on their own. Since viable bacteria deep within the infected focus are not as sensitive to the action of antibiotics as in the laboratory test tube (due to their slow metabolic state in the vegetation) therapy usually needs to be continued for >4–6 weeks, and high doses are given. The selection of antibiotics preferably is based on the determination of the minimum bactericidal concentrations of agents that have shown activity in the first routine sensitivity tests. Therapy response is otherwise well monitored by serially measuring body temperature and one or more of the acute phase reactants in blood (e.g. C-reactive protein); repeated blood cultures during first weeks of therapy should become negative. Initially, the patient should preferably be admitted in or near a facility that can provide emergency open heart surgery for hemodynamic and thrombo-embolic complications. Also, since high doses during an extended period of time are given of potentially toxic agents (e.g. the aminoglycoside gentamicin) monitoring of side effects needs to be well organized.

Empiric treatment for subacute endocarditis likely to be caused by penicillin-sensitive streptococci consists of high dose penicillin G (6 × 3 million units i.v. daily) plus gentamicin (1 × 3 mg/kg). In acute endocarditis a staphylococcal etiology is more likely and, therefore, gentamicin is combined with (flu)cloxacillin (6 × 2 g i.v. daily).

Streptococci are generally highly sensitive to penicillin G (MIC < 0.1 mg/l), albeit that some strains are more resistant (MIC 0.1–1.0 mg/l). Thus, streptococcal endocarditis can be treated with a 2 weeks course of penicillin G (6 × 2 million units i.v. daily; strains with reduced resistance 6 × 3 million units i.v. daily), combined with gentamicin 1 × 3 mg/kg i.v. daily. Addition of gentamicin produces a more rapid killing effect.

Staphylococci are nowadays mostly penicillin-resistant and sometimes also methicillin-resistant. In the rare event that a fully penicillin-sensitive strain is found patients can be treated as stated for streptococcal endocarditis, albeit with the 3 million unit dose of penicillin G and for 6 weeks (gentamicin should be stopped after 2 weeks to avoid serious side effects). Penicillin-resistant staphylococcal endocarditis is the rule, and is treated with high doses of a penicillinase-resistant penicillin (e.g. [flu]cloxacillin 6 × 2 g i.v. daily for 6 weeks), combined with gentamicin (3 mg/kg i.v. daily) for the first two weeks. For methicillin-resistant staphylococcal endocarditis the [flu]cloxacillin in this latter regimen is substituted by vancomycin 2 × 1 g i.v. and daily rifampicin 1 × 600 mg (either i.v. or orally) is given instead of gentamicin. Recent trials show that daptomycin is equally effective for MSSA and MRSA endocarditis.

For a enterococcal endocarditis 4–6 weeks of ampicillin or amoxicillin (6 × 2 g i.v. daily) plus 4 weeks of gentamicin (3 mg/kg i.v. daily) is indicated. Enterococci are generally only inhibited but not killed by ampicillin or amoxicillin unless an aminoglycoside is added. Due to the prolonged dosing of gentamicin monitoring for nephro- and ototoxicity is of paramount importance. In cases where enterococci are fully resistant to gentamicin (MIC > 2,000 mg/l) ampicillin or amoxicillin monotherapy should be continued for up to 8–12 weeks. Beta-lactamase producing strains can be treated by adding

a beta-lactamase inhibitor to the regimen (e.g. ampicillin plus sulbactam or amoxicillin plus clavulanic acid). Vancomycin (2 × 1 g i.v.) is given instead of ampicillin or amoxicillin when resistance to these latter agents is not due to the production of a beta-lactamase but due to changes in the target enzymes in the cell wall of the enterococcus.

I.c.8. Sepsis

Systemic infections are those that have micro-organisms (bacteria, viruses, yeasts, parasites) spread, usually via the bloodstream, beyond the portal of entry or original site of localized infection to multiple compartments of the body. When infections, either localized or systemic, are accompanied by signs and symptoms of a systemic inflammatory response (fever, rapid pulse, increase in white blood cells) the syndrome is called sepsis. Severe sepsis is defined by the additional occurrence of organ failure (either kidney, liver, brain, lungs), and is a potentially fatal condition (mortality around 50%). If there is hypotension not responding on fluid resuscitation it is called septic shock and the mortalty is even higher (60–70%).

Bacterial sepsis is a common event since 1–2 cases occur per 100 admissions to hospitals in the USA and Europe; these figures may be much higher in other parts of the world.

The majority of sepsis cases, especially the more severe forms, have bacterial etiologies. Common bacterial species include *Staphylococcus aureus, Streptococcus pneumoniae, Escherichia coli, Salmonella typhi* (and other enterobacterial species), *Pseudomonas* species and haemolytic streptococci; in children *Haemophilus influenzae* and *Neisseria meningitidis* are important whereas nosocomial episodes of sepsis are frequently caused by *Staphylococcus epidermidis*, *Streptococcus faecalis* (syn. *enterococci*), yeasts and anaerobes.

In community-acquired cases the source of the infectious agent may be in the environment (food, water, animals, contagious persons) or the commensal flora of the patient; in nosocomial cases the majority of infections are caused by commensals although cross-infections do occur under suboptimal hygienic conditions. Host factors usually determine the risk of nosocomial infection.

In patients with clinical signs and symptoms of (severe) sepsis the diagnosis is based on microbiological analysis of blood and material from the original site of infection and, if present, on signs and symptoms related to the focus of infection (e.g. subcutaneous abscess or bloody diarrhoea). New molecular methods (PCR, FISH) for faster detection of pathogens in blood are currently being developed.

In patients with sepsis treatment is indicated before an etiologic diagnosis is made. Patients presenting with severe sepsis need immediate intervention with antimicrobial agents that cover the most likely etiologies in that particular setting.

In endemic areas malaria should always be considered and, if possible, checked by blood film analysis; otherwise empiric antimalarial treatment may be indicated (see section on malaria). Empiric treatment should further cover the spectrum of bacterial agents likely to cause septic infections in the particular patient. The potentially fatal course of septic disease requires an antibiotic regimen that is rapidly lethal for the causative agent, and preferably attains adequate levels at the site of infection quickly. Therefore, treatment regimens usually include a combination of two (sometimes three) antibiotics that are given by a parenteral route (intramuscularly or preferably by intravenous infusion).

The combination of an aminoglycoside with a beta-lactam antibiotic, e.g. gentamicin with a second generation cephalosporin (or broad-spectrum penicillin), is appropriate. When more is known about the particular infection, the patient and the setting, one can modify this empiric regimen. Common modifications include the addition of an agent that has activity against anaerobes (e.g. metronidazole) or one that circumvenes resistance problems prevalent in that area (e.g. amikacin in stead of gentamicin) or because suspected micro-organisms have an intracellular localisation (use a fluoroquinolone) or are at a special site (e.g. meningitis, see Section 6, or a catheter related infection, use an anti-staphylococcal drug). Pre-existing renal dysfunction may also affect this regimen (see below).

Most episodes of sepsis are amendable to a seven-day course of empiric treatment and streamlining of the empiric regimen once the true etiology of the septic episode is known. For optimal use gentamicin (and other aminoglycosides) is best given once daily at a dose of 5–7 mg/kg body weight; cephalosporin levels, on the other hand, need to remain above the minimal inhibitory concentration for the micro-organism throughout most of the day, thus requiring either multiple doses or a constant infusion or the use of cephalosporin that has a prolonged half-life (e.g. ceftriaxone) and can be given once a day.

Gentamicin may accumulate to toxic levels in the kidney tubular cells and in the sensory cells of the auditory organs; the risk of clinical toxicity increases with duration of exposure and with age of the patient (less regenerative potential at old age). Therefore, gentamicin should not be given to patients with chronic renal dysfunction. Ideally, gentamicin dosing should be individualized by measuring a serum level 1 and 6 hours after the dose to calculate the elimination half-life. Treatment with aminoglycoside beyond seven days should be avoided. Cephalosporin use is associated with a risk of selecting resistant mutants of certain species (*Enterobacter, Serratia*) that have inducible chromosomal genes for beta-lactamases.

I.c.9. Infections in the Immunocompromised Host

The cancer patient and the HIV-positive patient are the two clinically important groups were the natural defence systems are disturbed either by the disease or by the treatment (chemotherapy, radiotherapy). Infections in the HIV-positive patient are discussed in Chapter 33B. Less prevalent immunocompromised hosts are patients with hypo- or agammaglobulinaemia or patients after splenectomy. These last patient groups with mainly humoral dysfunction generally suffer from infections by encapsulated bacteria (*S. pneumoniae, H. influenzae* and *N. meningitidis*). In this section we will discuss patients with cellular immune dysfunction, mainly granulocytopenia.

Critical for both prevention and therapy strategies is that most infections occur at granulocyte levels of less than 500 cells/µl. It is generally accepted to start selective gut decontamination with an oral quinolone (e.g. ciprofloxacin) and an oral fungicide (e.g. fluconazole) in those patients where, often due to the chemotherapy, prolonged granulocytopenia is expected.

An important reduction in gram-negative bacteraemia was observed after introduction of selective gut decontamination in the neutropenic patient. The most prevalent bloodstream infection on a hematology ward nowadays is the *S. epidermidis* bacteraemia associated with the use of intravenous central catheters. After prolonged neutropenia (e.g. after bone marrow transplantation) the patient is at risk for cytomegalovirus infection, candidemia and invasive aspergillosis.

Important factors in the immunocompromised host predisposing to infection are: granulocytopenia, T- or B-cell dysfunction, antibody deficiency, altered microbial flora, damaged anatomic barriers (mucositis, catheters, medical procedures), obstruction or dysfunction of natural passages (tumor related).

Nearly 85% of the organisms responsible for infections among patients with cancer are derived from the endogenous flora. Nevertheless, well-cooked food with avoidance of fresh fruits and vegetables is recommended during granulopenia. Special air filters (HEPAs) may prevent *Aspergillus* infections. Preventive measures such as 'reverse isolation' and aggressive decontamination of the environment are still not evidence based.

Fever $>38.5°C$ in a neutropenic patient demands antibiotic therapy. Often no focus for the infection is found with physical and radiographic examination. Mucositis causing translocation of bacteria, sinusitis, and anal fissure are frequently missed diagnoses in these patients.

When gram-negative prophylaxis is used and surveillance cultures of throat and rectum do not show gram-negative pathogens co-amoxiclav with a single administration of gentamicin 7 mg/kg is an option for empiric treatment. If surveillance cultures yield gram-negative bacteria a carbapenem (imipenem 4×500 mg) could be administered. Addition of an aminoglycoside for rapid bactericidal killing in a severely ill patient (without renal failure or concurrent use of nephrotoxic drugs such as cisplatin) should be considered. In prolonged neuropenia with fever not responding to antibiotics antifungal therapy (voriconazole) is indicated combined with an aggressive search for signs and sites of invasive aspergillosis.

When catheter-related septicemia is suspected or proven vancomycin ($(2–3) \times 1$ g) is started while vancomycin trough levels are monitored. Removal of the catheter must be considered with persistent fever or when blood cultures remain positive under effective vancomycin trough levels (10–15 mg/l). In a rapidly progressive infection (pneumonia) in a neutropenic patient anti-pseudomonas duo-therapy, e.g. ceftazidime with tobramycin, should be considered.

Treatment should be guided by the local or hospital resistance patterns. Extensive use of a quinolone for selective decontamination will increase the incidence of quinolone-resistant gram-negative pathogens. Alternative regimens for gut decontamination are oral colistin with an oral aminoglycoside such as neomycin.

A proven bacteraemia in a neutropenic patient is generally treated for 14 days with i.v. antibiotics.

Treatment can be of shorter duration when there is granulocyte recovery. When fever of unknown origin remains high despite 4 days of broad spectrum antibiotics, antibiotics are stopped and new cultures of blood are done. Antiviral or antifungal therapy must then be considered.

Adequate hand washing of personnel before and after patient contact is important to prevent the spreading of pathogens in this highly vulnerable population. Dependent on the duration and severity of immune dysfunction there is a role for antibiotic, antiviral, antifungal and anti-pneumocystis prophylaxis. Granulocyte recovery can in some cases be stimulated with granulocyte(-macrophage) colony-stimulating factor (G-CSF or GM-CSF).

I.c.10. Fungal Infections

Fungal infections (or mycoses) are unique in that they are caused by eukaryotic cells that are phylogenetically much closer to the human host than the prokaryotic pathogenic bacteria. Until recently the treatment of fungal infections was hampered by the relative lack of selective drugs that find targets that are present only in the fungi but not in the eukaryotic cells of the host. Fungal infections are medically classified as superficial (limited to skin, hair and nails), subcutaneous, and deep seated/invasive disease that involves various internal organs. Fungi have a chitin-containing cell wall and can morphologically be divided into yeasts (round/oval single cells) and molds (tubular, branching structures of multiple interconnected cells), and mostly reproduce asexually (by forming spores through mitosis).

Fungal infections are rarely transmitted directly from person to person. Fungi are derived from the commensal flora of the patient or from animal and innate sources in the environment, and are inoculated by (micro)trauma, ingestion or inhalation of spores. The incidence of invasive fungal infections among hospitalized patients has increased primarily due to the introduction of medical interventions that compromise the natural defenses of the patients.

Superficial mycoses are usually clinically evident (some will fluoresce when using a Wood's lamp) and can be confirmed by microscopy (using KOH solution) and culture of hairs, nails or scrapings from the edge of skin lesions. Species of *Microsporum, Trichophyton, Epidermophyton* (all moulds), and of *Malassezia, Candida, Pityrosporum* (all yeasts) cause most superficial infections. Subcutaneous mycoses are caused by *Sporothrix schenckii* (the yeast-like agent of sporotrichosis) and by *Madurella* or *Phialophora* species (molds of eumycetoma). Although often manifest from the outside, subcutaneous mycoses can be confounded with other infections (mycobacterial, Nocardia, Leishmania) and microscopy and culture of biopsy material is needed for a diagnosis. Deep/invasive mycoses in the non-immunocompromised host are caused by *Histoplasma capsulatum, Blastomyces dermatitides, Coccidioides immitis* and *Paracoccioides brasiliensis* in endemic regions. In the immunocompromised host species of *Aspergillus, Candida, Cryptococcus, Pneumocystis, Mucor* and *Rhizopus* are important pathogens. Diagnosis at an early stage of such infection may be difficult and usually requires imaging of lesions in internal organs, sampling of such lesions and microscopy and culture of the material obtained. Serological tests for antigen and/or antibody are useful in some diseases in this class (e.g. in aspergillosis (galactomannan assay), cryptococcosis (antigen), paracoccidioidomycosis (antibody), coccidioidomycosis (antibody against coccidioidin) and histoplasmosis (antibody)). Fungal antigen tests are applied in serum and other body fluids (urine, bronchoalveolar lavage fluid, pleural effusions, cerebrospinal fluid).

Subcutaneous sporotrichosis responds well to 6–12 weeks of oral treatment of the low cost potassium iodide ($3 \times (5–10)$ drops initially increasing to 3×40 drops per day). This regimen has side effects (nausea, diarrhea, acneiform rashes, thyroid dysfunction) that respond to dose reduction or temporary cessation. In iodide allergic patients oral itraconazole 100–200 mg daily has proven effective (but costly). For eumycetoma limited surgery (debulking) is combined with prolonged (approx. 1 year) use of oral ketoconazole (or itraconazole) 200 mg per day. For invasive mycosis systemic antifungal agents must be used, usually for prolonged periods of time (weeks to months). Amphotericin B deoxycholate remains the most effective low cost systemic agent for most cases of deep-seated or invasive mycosis. However, amphotericin B needs to be administered via an intravenous infusion (in a daily dose of 0.5–1 mg/kg) and is nephrotoxic; it causes a dose-dependent decrease in the glomerular filtration rate. Adequate hydration with saline is advocated during therapy. Amphotericin B infusion is also associated with acute febrile reactions that can be mitigated by co-administration of hydrocortisone (25–50 mg), an anti-histaminic or acetaminophen. Lipid-based formulations of amphotericin B are at least as effective and less toxic,

but much more costly, in particular liposomal amphotericin B. Liposomal and lipid-based formulations of amphotericin B are given at a higher dose (3 and 5 mg/kg daily respectively). Alternatively, lower doses of amhotericin B (<0.6 mg/kg/day) can be combined with flucytosine (4 × 40 mg/kg/day orally or i.v.) to obtain a comparable clinical effect as with amphotericin B monotherapy in some invasive yeast infections (e.g. in cryptococcosis and candidiasis). However, flucytosine is toxic to the bone marrow, potentially resulting in leukopenia and thrombocytopenia; monitoring of white blood cells and platelets during therapy is therefore warranted.

Ketoconazole is one of the early, low cost oral imidazole agents that have antifungal activity to treat invasive yeast infections. Fluconazole and itraconazole are later developed triazole derivatives of imidazole that display less side effects than ketoconazole (less interaction with human sterol metabolism) and have better pharmacological properties (better bio-availability, better distribution, longer half-lives, a parenteral formulation) and fewer drug interactions. These agents are effective at daily doses of 200–400 mg per day for many types of invasive mycoses either alone as the therapy of choice, or as follow-up treatment after an initial course of intravenous amphotericin B, with or without flucytosine (fluconazole for cryptococcosis). Fluconazole is available as a generic and is the drug of choice for treating Candida infections except *C. krusei* which is resistant, and for meningeal coccidiodomycosis. For meningeal cryptococcosis, fluconazole is used for 8 weeks after 2 weeks of amphotericin B+ flucytosine.

Voriconazole and posaconazole are newer broad spectrum azoles that have been studied extensively in invasive candida and aspergillus infections. In a recent trial voriconazole was superior to amphotericine for invasive aspergillus infections in haematological patients and has replaced 'good old' amphotericine as first line treatment. Posaconazole is promising as it is the first azole also active against zygomycetes.

Echinocandins (caspofungin, micafungin, anidulafungin) are a new class of parenteral fungal agents that act by inhibiting the glucan synthesis of the fungal cell wall. There is no cross-resistance to other antifungals. Excellent safety and tolerability, little interactions and no need for dose reduction in renal impairment are promising features for the future, especially for fluconazole-resistant candida infections. At present their pricing is as prohibitive as liposomal amphotericin B.

I.c.11. Obstetric Infections

Obstetric infections include infections which occur during pregnancy, delivery and in the postpartum period, and which affect the uterus or its content. Clinical entities are amnionitis, and post partum or post-caesarean endometritis and infected abortion. Symptoms are lower abdominal pain, fever and eventually foetid amniotic fluid or lochia.

Bowel flora colonising the vagina causes ascending infections through the cervix. Listeriosis is acquired by haematogenic route. Other pathogens leading to amnionitis and subsequent septicaemia in the foetus or the newborn are *E. coli* and group B beta-hemolytic streptococci. Infection with beta-haemolytic streptococci of group A (*S. pyogenes*) lead to life-threatening puerperal sepsis after spontaneous delivery or caesarean section. Delivery and/or complete emptying of the uterine cavity terminates the predisposition to these infections. Appropriate isolation measures should be taken to avoid obstetric and neonatal cross-infections by haemolytic streptococci.

Obstetric infections should be treated with antibiotics as soon as the diagnosis is made. Delay can cause fatal outcome. However, removal of infected necrotic tissue in the uterus or pelvis is the mainstay of treatment.

Severely ill patients should be treated with parenteral drugs. In these patients, broad-spectrum therapy is necessary, directed against bowel flora including *E. coli*, streptococci and gonococci. Aminoglycosides can be added in the first 3 days to broaden the spectrum and for their rapidly bactericidal properties.

Culture of lochia is of limited value in order to streamline these therapies, as specimens will be contaminated with vaginal flora.

Post-caesarean infections with MRSA require the administration of i.v. vancomycin, infections caused by resistant gonococci require a third generation cephalosporin.

Obstetric infections can be treated with penicillin–beta-lactamase inhibitors such as amoxicillin–clavulanic acid, with extended spectrum penicillins (with or without beta-lacamase inhibitors if justified by local resistance surveillance data), with a first or second generation cephalosporin combined with metronidazole. In severe cases of streptococcal infection high doses of penicillin in combination with clindamycin is the treatment of choice. In amnionitis, maternal morbidity resolves with delivery. In endometritis, antibiotics should be stopped after the

patient is afebrile for 48 hours. Thereafter, no further oral treatment is necessary. In case of persistent fever, pelvic abscess or myonecrosis should be excluded.

In high risk abortion and caesarean section, single dose preoperative prophylaxis is advocated (see Section II, prophylaxis).

I.c.12. Eye Infections

Infections of the external eye (the eyelids and conjunctiva or cornea) conjunctivitis, keratitis, corneal ulcer are distinguished from intra-ocular infections. The latter include infection of the vitreous (endophtalmitis), uveitis and retinitis. Orbital and periorbital infections are often due to complications of sinusitis.

Infections of the external eye range from frequently occurring benign uncomplicated conjunctivitis to severe corneal ulceration leading to loss of vision. Recognition of rapidly progressive bacterial intra-ocular infection (sometimes complicating corneal ulceration) is of utmost importance. Although many eye infections can be treated by general practitioners, impaired vision and severe pain in the presence of infection suggest endophtalmitis and warrant urgent ophtalmologic consultation.

Infections of the external eye can be caused by viruses and by bacteria from the respiratory tract such as pneumococci and *Haemophilus influenzae*. Infections of the internal eye can be caused by the same bacteria through spread from a corneal (traumatic) ulcer or by *S. aureus*. The same pathogens are responsible for periorbital spread in severe sinusitis. *Treponema pallidum*, CMV and *Toxoplasma* cause intra-ocular infections.

Ophtalmia neonatorum by *N. gonorrhoeae* and *Chlamydia trachomatis* is acquired during delivery. Contact lens wear predisposes to corneal infections, mostly by *Pseudomonas* sp. and the ameba Acanthamoeba and Naegleria. Immunocompromised hosts are predisposed to severe retinitis by CMV and to other intra-ocular eye infections by opportunistic pathogens.

In developing countries, trachoma caused by *Chlamydia trachomatis* is a recalcitrant form of chronic conjunctivitis that can cause scarring. Endophtalmitis is more frequently seen due to neglected corneal ulceration caused by trauma.

Often inflammation of the eye (‘red eye’) is caused by viruses or non-infectious causes such as allergy and irritation. Antibiotic treatment is not useful in this setting.

Only solutions of lipophilic antibiotics are able to cross the external barrier of the cornea (drops) and the internal blood–retina barrier (systemic administration) to yield sufficient concentrations in the internal eye (vitreous). Keratitis and ulceration of the cornea can be treated by frequent administration of highly concentrated (fortified) antibiotic drops. In endophtalmitis, emergency vitreous aspirate and intravitreal and subconjunctival injection of antibiotic solutions with a long half-life is the cornerstone of treatment. These solutions should be prepared by the hospital pharmacy. Empiric topical treatment of minor external eye infections consists of antibiotic containing gels or ointments.

In endophtalmitis, culture results of the vitreous aspirate can guide specific therapy. Periorbital cellulitis is treated with amoxi/ampicillin plus beta-lactamase inhibitor or a second generation cephalosporin.

Multiply resistant coagulase-negative staphylococci are frequently the cause of postoperative endophtalmitis and require the use of a glycopeptide (e.g. vancomycin). For topical treatment fusidic acid eye gel, tetracycline or chloramphenicol ointment are available, and can be administered 2 t.d. for 7 days. Trachoma should be treated with an oral macrolide (e.g. a single oral dose of 20 mg/kg azithromycin) or doxycyclin for 3 weeks (for moderate to severe cases). Keratitis needs hourly administration of fortified antibiotic eye drops for 2 weeks. Endophtalmitis needs specialist treatment for 6 weeks.

Ophtalmia neonatorum: povidone-iodine ophtalmic solution is more effective than silver nitrate or erythromycin.

I.c.13. Ear, Nose and Throat Infections

Specific bacterial infections of ear, nose and throat are treated in this section. Upper respiratory tract infections, such as common colds, are dealt with in the section respiratory tract infections. A few serious bacterial infections are described here. Otitis media acuta can be complicated by mastoiditis in children. Furuncles of the nose can lead to thrombosis of the sinus sagittalis (‘furunculus nasis furunculus mortis’). Streptococcal pharyngitis can lead to the rare but severe complication of tonsillar or retropharyngeal abscess. Environmental factors, genetic predisposition and specific virulence factors of group A streptococococcus serotypes determine regional differences in prevalence of rheumatic fever/heart disease

or glomerulonephritis. Epiglottitis (croup) can cause acute obstruction of the airways in children.

Acute infections simultaneously affecting ear, nose, throat and even the conjunctiva are very common and mostly of viral origin. Purulent, green secretions are caused by the presence of leukocytes, not bacteria and are not predictive for bacterial infection in rhinitis or sinusitis. Bacterial sinusitis can be the cause of persisting headaches and chronic cough. In western countries, only ten percent of pharyngitis in children is caused by haemolytic streptococcus group A (syn. *S. pyogenes*). The incidence in children in developing countries is estimated to be 2.7 times higher. The diagnosis can be guided by the streptococcal antigen test; it can be confirmed by culture. In case of pharyngeal abscess formation or severe sinusitis with peri-orbital extension, diagnostic imaging is necessary to evaluate the need for drainage procedures.

Acute otitis media (AOM) in children is mostly caused by pneumococci and *H. influenzae*. It should be differentiated from otitis media with effusion (OME) in which there are no symptoms of acute infection. Furuncles of the nose are caused by *S. aureus*. It has to be differentiated from diphteria (in unvaccinated children) caused by *Corynebacterium diphteriae* and from mononucleosis infectiosa caused by Epstein–Barr virus. Chronic ear infections are caused by *S. aureus* and gram-negative bacillae. Malignant otitis externa in diabetics is caused by *P. aeruginosa*.

Patients with leukemia often suffer from infections of the upper respiratory tract before the diagnosis of their haematologic malignancy is made. Chemotherapy for malignancy causes toxic stomatitis and superinfection with yeasts may follow. In patients with diabetes mellitus, malignant otitis externa and fungal sinusitis (mucormycosis) can be life-threatening.

Crowding of adolescents and low socio-economic status have been associated with streptococcal group A infections. Frequent swimmers are at risk for chronic ear infections caused by *Pseudomonas* sp.

As most acute upper respiratory tract infections are not of bacterial origin, antibiotics are not often necessary in cases of acute pharyngitis and sinusitis. Supportive measures such as aerosols or rinsing with sterile saline and antipyretics are often sufficient.

In acute otitis media in children oral amoxycillin is the drug of choice. Severe complications such as mastoiditis and parapharyngeal abscesses should be treated with high dose parenteral drugs, with or without puncture or surgical drainage.

A negative rapid streptococcal antigen test can be used to rule out streptococcal angina in patients with nonspecific symptoms and thus the need for antibiotics. When traditional throat cultures are used, complications of poststreptococcal infection can still be avoided when treatment is initiated upon a positive culture result.

Antibiotic treatment of otitis media with effusion (OME) is not indicated. It is one of the most prevalent errors in the prescription of antibiotics. Despite a world-wide increase of resistant pneumococci, minor infections can still be treated with (higher) doses of penicillin. Children treated with low (inadequate) doses of antibiotics and long treatment duration were found to be colonised more frequently with resistant pneumococci.

Oral beta-lactam antibiotics such as amoxycillin, cotrimoxazole or doxycycline for 7–10 days are suitable for the treatment of bacterial sinusitis. Furuncles of the nose should be treated with an antistaphyloccal drug for 5 days. Standard treatment for streptococcal pharyngitis consists of 10 days of penicillin. Malignant otitis externa responds to high dose quinolone therapy (e.g. ciprofloxacin 750 mg 2 t.d.) administered orally. For parapharyngeal abscess, high dose penicillin plus beta-lactamase inhibitors such as amoxycillin–clavulanic acid can be used. Duration of treatment is guided by clinical and parameters of inflammation, and abscesses often need several weeks to resolve by conservative treatment.

Prophylaxis against relapses of rheumatic fever (secondary prevention of rheumatic heart disease) is discussed in Section II of this chapter. In most developed countries, national vaccination programs with vaccines against diphteria and *Haemophilus influenzae type b* have virtually eliminated the complications of diphteria and acute epiglottitis.

I.c.14. Surgical Infections

A large proportion of infections treated in the hospital setting are the consequence of a trauma or a surgical procedure, require surgical intervention for treatment, or both. Surgical infections of the latter group, i.e. infections that are primarily treated by a surgical intervention consist mainly of acute intra-abdominal disease such as secondary peritonitis due to perforation, acute cholecystitis, appendicitis and necrotising pancreatitis. Another group of surgical infections

are necrotising infections and abscess formation in other sites of the body, primarily the head–neck region or subcutaneous tissue. Soft tissue infections defined as superficial include crepitant anaerobic cellulitis and necrotising fasciitis. Deep soft tissue infections involve the muscle and can lead to extensive myonecrosis. Tropical pyomyositis is defined as accumulations of pus in muscle. Finally, infections caused by trauma (wounds, bite wounds, complicated fractures) and postoperative wound infections are also discussed here.

Prompt diagnosis of intra-abdominal infections or of abscess formation elsewhere in the body by liberal use of ultrasound and other imaging techniques should lead to subsequent surgical treatment without delay. Soft tissue infections (superficial and deep) can have a dramatic clinical course. Timely diagnostic imaging and surgical treatment will equally reduce morbidity and mortality.

Intra-abdominal infections are mostly polymicrobial in nature and caused by bowel flora. Perforations of the colon more often lead to infections with anaerobes and subsequent intra-abdominal abscess formation. Necrotising soft tissue infections are often mixed infections with anaerobes, streptococci and *E. coli*. Fournier syndrome is caused by *Pseudomonas aeruginosa.* Penetrating wounds are often infected by *S. aureus* but can be contaminated by anaerobes and gram-negative bacillae when a hollow organ is perforated. Bite wounds of human origin often contain anaerobes. Dog and cat bites can lead to infections by *Pasteurella multocida* or *Capnocytophaga canimorsus*.

In immunocompromised patients and patients receiving corticosteroids, both the symptoms of intra-abdominal infections are attenuated and the resolution of infection is impaired. Patients with poor nutritional status (both over- and under-weight) or other causes of poor wound healing (cigarette smoking) are prone to complications.

In poor resource countries intramuscular abscesses are seen as a consequence of intramuscular injections by inadequately trained personnel handling contaminated needles, syringes and fluids for injections.

Although the need for surgical intervention distinguishes most intra-abdominal infections from non-surgical infections, antimicrobial agents also play a major role in controlling sepsis and limiting the extent of dissemination of the infection in abdominal sepsis. In clinically stable patients without systemic signs of infection, surgical treatment with drainage and/or debridement can be sufficient. This is also true for extensive infection of open wounds such as decubital ulcers.

In necrotising soft tissue infections surgical debridement is the mainstay of therapy. There is not much evidence in support of topical application of antibiotics in irrigation fluids; topical antibiotics are reported to cause allergic contact dermatitis in up to 5–20%. Irrigations with acetic acid can reduce colonisation of wounds with *Pseudomonas* sp.

Broad spectrum therapy is started on an empirical basis. Intra-abdominal infections can be treated by ampicillin (or amoxycillin) or clindamycin combined with aminoglycosides, penicillin–beta-lactamase inhibitors such as amoxycillin–clavulanic acid or a second or third generation cephalosporin combined with metronidazole are good alternatives. In patients with impaired immunity and/or prior use of antibiotics, i.e. when it is reasonable to expect resistant pathogens, a broad spectrum penicillin plus beta-lactamase inhibitor or a carbapenem can be used empirically in monotherapy. In septic patients, the rapidly bactericidal action of aminoglycosides is useful. Aminoglycosides should preferentially not be given for more than 3–5 days.

In fasciitis or necrotizing infections caused by beta-hemolytic streptococci of group A, parenteral high-dose penicillin combined with clindamycin is the treatment of choice. For the treatment of abscesses, antibiotics which are able to kill large quantities of resting bacteria, such as clindamycin and the quinolones, are preferred.

Local resistance patterns should guide the need for broader spectrum or multidrug regimens in severe nosocomial infections. In tertiary peritonitis, treatment of these resistant bacteria and Candida species with antibiotics and antifungals is still controversial, as the clinical outcome seems not to be altered.

Successful antibiotic treatment should be continued until return of the temperature and peripheral leukocyte count to normal. However, persisting or returning fever and leukocytosis should lead to discontinuation of the antibiotics and prompt re-evaluation with imaging and surgical re-exploration rather than an escalation of the antibiotic treatment. Open complicated fractures should be treated for 5 days. Animal and human bites are treated with amoxycillin–clavulanic acid for 5 days.

I.d. Tropical Infectious Diseases

I.d.1. Typhoid Fever

Typhoid fever caused by *Salmonella typhi* or *S. paratyphi* is an important and prevalent cause of continuous fever without localizing symptoms in the tropics. The diagnosis can be confirmed with a bloodculture. Response on therapy is often seen only after 3–4 days when the fever subsides. Chloramphenicol-resistant *Salmonella typhi* was first described in Vietnam in 1973. Its prevalence reached 95% in the 1970s and then decreased to 54% in the 1980s after cotrimoxazole became the treatment of choice. In the mid-1993, there was a dramatic increase in the number of strains of *S. typhi*, isolated in the hospital and from patients in the outbreaks, which are resistant to the three first-line antibiotics chloramphenicol, cotrimoxazol and ampicillin. This indicated that there was an urgent need for effective antibiotics for the treatment of typhoid fever.

In vitro, strains of *Salmonella typhi* are sensitive to third-generation cephalosporins and fluoroquinolones. Despite similar minimum inhibitory concentrations (MIC), 3rd generation cephalosporins have proved consistently inferior to fluoroquinolones. Patients treated with third-generation cephalosporins often have longer fever clearance times and higher relapse rates. Fluoroquinolones have been 95% effective with carrier rates less than 5% (related to the intraluminal activity of he drug), compared with failure rates of 20% with third-generation cephalosporins. The principal advantages of fluoroquinolones are: remarkable effectiveness with short course treatment (as short as 2–3 days) for mild and moderate cases infected with sensitive strains, simple administration (oral) and low cost treatments (5 USD). However the number of quinolone (or nalidixic acid) resistant *S. typhi* strains is growing (in Vietnam 80%). Therefore several studies were carried out to assess the efficacy of oral 3rd generation cephalosporin, amoxicillin/clavulanic acid, and azithromycin. Although effective, none of them shows a better than fluoroquinolone efficacy in quinolone-sensitive *S. typhi* infection. Recent studies have shown that uncomplicated typhoid fever due to isolates of multidrug resistant Salmonella with reduced susceptibility to fluoroquinolones can be successfully treated with a 7-day course of azithromycin (500 mg/day).

I.d.2. Malaria

Malaria must be considered in every patient with fever living in a malaria-endemic country or returning from a malarious area. The bite of a mosquito carrying *Plasmodium falciparum* can potentially cause the rapidly fatal tropical malaria in a patient with no immunity for this disease. Worldwide there are 200–300 million cases of malaria per year and about 1–2 million people die, mostly children in Africa between 1–5 years old. There is still no effective vaccine. The diagnosis is made by a thick and thin smear of peripheral blood of the patient who is suffering from high fever and chills, headache, myalgia and in severe cases loss of consciousness (cerebral malaria). The classical symptoms such as spiked regular fevers, splenomegaly and anemia cannot be relied upon. There are 4 types of *Plasmodia: P. falciparum* is the only form of malaria that can be fatal. The other non-fatal forms include *P. ovale, P. vivax* and *P. malariae.* Each type has a different worldwide distribution. They can be discriminated by microscopy. Parasitemia can be asymptomatic in people with premunity in malaria endemic areas. Premunity is an immunity that needs boosting by repetitive infections. After 1–2 years immunity is lost when residents leave the malarious area. In pregnancy the outcome of falciparum malaria is worse. HIV-infection does not greatly influence the course of a malaria infection.

Knowledge of local resistance patterns is important to determine the treatment regimen. There is increasing chloroquine and pyrimethamine–sulfadoxine (Fansidar) resistance in Africa and in some areas at the border of Thailand there is resistance for almost all antimalarial drugs including halofantrine, mefloquine and quinine. In these areas only the artemisinin derivatives (artemether, arteether, artesunate, dihydroartemisinin) are effective.

For uncomplicated falciparum malaria there are several options (with the major drawback in brackets): halofantrine (arrhytmia), mefloquine (neurotoxicity), quinine (vomiting, tinnitus), artemether (recrudescence), atovaquone-proguanil (possible fast development of resistance).

In complicated falciparum malaria exchange transfusion can be considered if high parasitemia's ($>5\%$) is present, although the benefit has not been proven with a randomised controlled trial. In these severe cases i.v. quinine (with loading dose) is gradually being replaced by artesunate, wich has proven less mortality and less side effects than 'good old'

quinine in a randomised trial. The fast onset of action and the lack of side-effects of the artemisinin derivatives make them attractive in the treatment and necessary for certain multi-resistant areas in South-East Asia. Concerning the neurotoxicity, results from several studies suggest that no relevant neurotoxic effects are associated with artemisinin and its derivatives in acute and severe falciparum malaria. These data provide reassurance that therapeutic doses of these important antimalarial drugs do not damage the nervous system.

Empirically it is known that effective drug concentrations are needed for at least 3 parasite-life cycles (=6 days) to obtain cure without recrudescence. By combining a drug with a fast action but short half life such as artemether and an agent with a slow action and long half life the treatment course can be short (2–3 days) which will benefit compliance, the patients condition will improve fast and resistance-development might be delayed.

Three currently-used artemisinin based combination therapies (ACT) artesunate–mefloquine, artemether–lumefantrine and dihydroartemisinin–piperaquine, have been proven highly simple, safe and effective in the treatment of multidrug resistant *P. falciparum* malaria.

- Artesunate × 3 days + mefloquine has been used in several Asian countries for MDR falciparum malaria. Artesunate: 4 mg/kg/day × 3 day and mefloquine: 25 mg/kg single splitting into 2 dose 6–8 hours apart (15 mg/kg then 10 mg/kg).
- Artemether–lumefantrine has been the unique GMP product (Coartem) among ACT drugs and has mostly been used in Africa but the absorption of lumefantrine is dependent on co-administration with fat may limit its effectiveness. For adults four tablets (1 tablet 20 mg artemether + 120 mg lumefantrine) twice daily for 3 days is used.
- Dihydroartemisinin–piperaquine has been proved highly effective and well tolerated in South-East Asia. It is a four dose regimen: 4 tablets on the 1st day and 2 tablets on the 2nd and 3rd day or 3 tablets per day for 3 days.

There is very limited evidence available on the effectiveness of the drugs in pregnant women. A possible increase in risk of stillbirth with the use of mefloquine in pregnancy has been reported. Standard adult dose of antimalarial drugs recommended for 2nd and 3rd trimester pregnancy did not cause harm or congenital abnormalities. Evidence on the safety of all recommended antimalarial drugs in the 1st trimester is still unclear.

Non-falciparum malaria (like *P. vivax*) can still be treated with chloroquine although chloroquine resistant *P. vivax* has been reported from Irian Jaya and Papua New Guinea. In those areas treatment with mefloquine is recommended. To treat the liverstages an additional 2–3 weeks treatment with primaquine is given. It appears that tafenoquine (dosed once a week), a new 8-aminoquinoline, would be a better replacement for primaquine in preventing relapses in *P. vivax* malaria.

For prophylaxis a permetrine-impregnated bednet, mosquito repellent with DEET (diethyl toluamide) and long sleeves and trousers after sunset are very effective measures to prevent bites from the female Anopheles mosquito that takes her blood meal only after sunset. Chemoprophylaxis depends on the local resistance patterns and can be mefloquine, chloroquine, proguanil, doxycycline. It should be started 2 weeks before until 4 week after leaving the endemic area. The current standard for many endemic areas is the new combination atovaquone-proguanil (malarone) which is started 2 days before entering until 7 days after leaving the malarious area. When the risk of acquiring a malaria infection is very low, the preventive measures mentioned with standby-treatment in stead of chemoprophylaxis is a consideration.

I.d.3. Dengue Fever and Dengue Hemorrhagic Fever

Dengue is a disease caused by any one of four closely related viruses (DEN-1, DEN-2, DEN-3, or DEN-4). The viruses are transmitted to humans by the bite of an infected mosquito. It is estimated that there are over 100 million cases of dengue worldwide each year.

Dengue hemorrhagic fever (DHF) is a more severe form of dengue. It can be fatal if unrecognized and not properly treated. DHF is caused by infection with the same viruses that cause dengue. With good medical management, mortality due to DHF can be reduced to less than 1%.

The principal symptoms of dengue are high fever, severe headache, backache, joint pains, nausea and vomiting, eye pain, and rash. DHF is characterized by a fever that lasts from 2 to 7 days, with general signs and symptoms that could occur with many other illnesses (e.g., nausea, vomiting, abdominal pain, and headache). This stage is followed by hemorrhagic manifestations, tendency to bruise easily or other types of skin hemorrhages, bleeding nose or

gums, and possibly internal bleeding. The smallest blood vessels (capillaries) become excessively permeable ('leaky'), allowing the fluid component to escape from the blood vessels. This may lead to failure of the circulatory system and shock, followed by death, if circulatory failure is not corrected.

There is no specific medication for treatment of a dengue infection. Patients should rest and drink plenty of fluids. DHF can be effectively treated by fluid replacement therapy if an early clinical diagnosis is made. Hospitalization is frequently required in order to adequately manage DHF.

Both Dengue fever and the Dengue Hemorrhagic Fever (DF/DHF) without shock (grade I, II) are managed similarly. Paracetamol is the only antipyretic recommended for use, since other nonsteroidal anti-inflamatory drugs such as aspirin may result in gastric irritation or provoke gastrointestinal bleeding. The recommended dose of paracetamol (60 mg/kg/day) should not be exceeded, because liver injury that accompanies Dengue viral infections may be aggravated. If the temperature still remains high despite administration of paracetamol, tepid sponging is recommended. Intravenous fluids are usually not indicated for DF/DHF patients, except for patients with severe vomiting or dehydration. Platelet count and hematocrite analysis should be done at least once a day and then twice a day at the beginning of the third day from the onset of fever, as the patient is likely to progress into the plasma leakage phase during this time. Platelet counts $< 100{,}000/\mu l$, and rises in packed cell volume of $>20\%$, reflect increased vascular permeability. Since Dengue fever is usually a mild and self-limiting disease, most patients can be managed at home. However, admission to hospital is needed if patients show any severe signs such as cold extremities with defervescence, bleeding, deterioration of consciousness, or laboratory evidence of DHF. In addition, those at high risk of developing severe DHF (age <1 year, overweight/obese, massive bleeding, changes in level of consciousness, presence of underlying disease, for example, heart disease, anaemia) should be monitored very carefully. Vital signs should be monitored every 1–2 hours to detect early progression to shock. The packed cell volume should ideally be monitored every 4–6 hours (or at least twice a day if this is not possible). The rate of fluid administration depends on body weight and degree of plasma leakage. This rate should be adjusted by frequent assessment of vital signs, urine output, and packed cell volume. Liver enzymes should be measured, as acute liver failure and hepatic encephalopathy are known complications especially in adults. Transfusion requirements correlate with the occurrence of bleeding in the gastrointestinal tract, but not with platelet counts. A significant reduction in active bleeding is observed following platelet transfusions. The degree of elevation of circulating platelets tends to vary inversely with the degree of shock and directly with the amount of platelets infused. Furthermore, the survival of transfused platelets is very short in cases with dengue shock syndrome. The critical phase usually lasts for 24–48 hours and is then followed by a convalescent phase. Intravenous fluid therapy could usually be stopped when the packed cell volume falls to 40%. It is important to identify the end of the leakage phase, as otherwise abundant fluid administration could lead to respiratory distress secondary to massive pleural effusions/ascites or pulmonary oedema.

Controversy exists regarding the type of fluid to be used for fluid replacement in DHF. WHO recommends using crystalloid solutions but some studies suggest that initial resuscitation using colloids (dextran 70 or 3% gelatin) restores the cardiac index and pulse pressure and normalises the packed cell volume sooner than crystalloid solutions. However there is no overall difference in the recovery times or the subsequent need for fluids. Intravenous fluid should be infused using a wide bore IV catheter. In children 15–20 ml/kg of body weight of Ringer's lactate or normal saline 0.9% should be infused in 1 hour but in adult, a smaller volume (15 ml/kg) is needed. In profound shock in children crystalloids should be given as rapid boluses. Result of a recent study has shown that initial resuscitation with Ringer's lactate is indicated for children with moderately severe Dengue shock syndrome. Dextran 70 and 6 percent hydroxyethyl starch perform similarly in children with severe shock, but given the adverse reactions associated with the use of dextran, starch may be preferable for this group. The maintenance fluid should be adjusted based on vital signs and clinical condition. There is insufficient evidence to justify the use of corticosteroids in managing dengue shock syndrome.

Polyserositis (manifesting as pleural effusions or ascitis) are common, but drainage procedures should be avoided unless the effusions worsen patient's ventilation, as they may lead to severe internal haemorrhage. Hypoglycaemia, metabolic acidosis, electrolyte disturbances should be looked for

and corrected. Disseminated intravascular coagulation is usually present and may lead to worsening of shock or massive bleeding. Therefore prothrombin time and partial thromboplastin time should be measured. Fresh frozen plasma, platelet concentrate should be considered if there are bleeding sign with low platelet count (<10,000/μl).

Patients may be discharged from hospital once they enter the convalescent phase and have a normal appetite. They can be safely discharged once platelet counts begin to rise and are over 50,000/μl. Patients who develop massive pleural effusions or ascites may take longer to recover and may be kept in for observation.

I.d.4. Avian Flu

At presentation, most cases of human H5N1 infections were characterized by a severe influenza syndrome, clinically indistinguishable from severe human influenza, with symptoms of fever, cough and shortness of breath, and radiological evidence of pneumonia. This new disease has a remarkable high case fatality rate of around 50%. Abnormalities on chest X-ray included extensive, usually bilateral infiltration, lobar collapse, focal consolidation, and air bronchograms. Radiological evidence of pulmonary damage could still be observed in surviving patients several months after the illness. Beside respiratory symptoms, a large proportion of patients also complained of gastrointestinal symptoms such as diarrhea, vomiting, and abdominal pain, which are common in children with human influenza, but not in adults. In some cases, diarrhea was the only presenting symptom, preceding other clinical manifestations. Unlike human infections with H7 or H9 viruses, conjunctivitis was not prominent in H5N1-infected patients. The clinical course of the illness in severe cases was characterized by rapid development of severe bilateral pneumonia necessitating ventilatory support within days after onset.

Complications included acute respiratory distress syndrome, renal failure, and multi-organ failure. Evidence that the clinical spectrum of human H5N1 infections is not restricted to pulmonary symptoms was provided by a reported case of possible central nervous system involvement in a Vietnamese boy who presented with diarrhea, followed by coma and death. Influenza H5N1 virus was isolated from throat, rectal, blood, and cerebrospinal fluid specimens, suggesting widely disseminated viral replication.

Striking routine laboratory results in H5N1-infected patients, especially in severe cases, are an early onset of lymphopenia, with a pronounced inversion of the CD4 + /CD8+ ratio, thrombocytopenia and increased levels of serum transaminases. While many laboratory-confirmed H5N1 infections are associated with severe, often fatal disease, milder cases have also been reported, especially during the outbreak in Hong Kong. An increasing number of milder cases also seemed to occur in Viet Nam, as the outbreak progressed in 2005.

Currently, two classes of drugs are available with antiviral activity against influenza viruses: inhibitors of the ion channel activity of the M2 membrane protein, amantadine and rimantadine, and the neuraminidase inhibitors oseltamivir, and zanamivir. H5N1 viruses isolated from poultry and humans in Thailand and Viet Nam in 2004 invariably showed an amantadine-resistance indicating that amantadine treatment is not an option during the ongoing outbtreak in South-East Asia.

Oral oseltamivir and inhaled zanamivir showed therapeutic and protective activities against Hong Kong H5N1 isolates in murine animal models. Recent murine studies suggest that, perhaps due to higher virulence, higher doses of oseltamivir and longer durations of treatment are necessary to achieve antiviral effects in mice against H5N1 strains causing the South-East Asian outbreak since 2004, when compared to the 1997 Hong Kong H5N1 strain. Oseltamivir treatment has been given to several H5N1-infected patients, but no conclusions can be made concerning its efficacy. However, the timing of antiviral treatment may not have been optimal in many cases of avian influenza so far. Beneficial effects of antiviral treatment in human influenza are believed to be optimal when started within 48 h after onset of the illness. During the H5N1 outbreak in Viet Nam in 2004, H5N1-infected patients were admitted 5 days or later after onset of symptoms. Earlier recognition of avian influenza in humans may improve the efficacy of antiviral treatment. While several H5N1-infected patients have received steroids in addition to oseltamivir, the potential benefit of this needs formal evaluation in clinical studies.

Patients living in areas with poultry H5N1 infections who present with fever and cough and who had close contact with ill poultry within 7–14 days (preparing of ill birds, handling of fighting cocks playing with poultry (duck), consumption of duck

blood or undercooked poultry products) and have leucopenia with or without infiltrates on the chest X-ray should be admitted to a hospital, isolated, a nasopharyngeal swab for PCR on H5N1 performed and oseltamivir started without delay.

I.d.5. Melioidosis

Melioidosis (or Whitmore's disease) is predominately a disease of tropical climates, especially in South-East Asia where it is endemic. The bacteria *Burkholderia pseudomallei* causing melioidosis is found in contaminated water and soil and are spread to humans and animals through direct contact with the contaminated source (e.g. bare food working in a rice field).

The diagnosis is made by isolating *Burkholderia pseudomallei* from the blood, urine, sputum, or skin lesions through conventional culture or by PCR. Illness from melioidosis can be categorized as acute or localized infection, acute pulmonary infection, acute bloodstream infection, and chronic suppurative infection.

Acute, localized infection is generally an abscess resulting from inoculation through a break in the skin. The acute form of melioidosis can produce fever and general muscle aches, and may progress rapidly to infect the bloodstream. Pulmonary infection can produce a clinical picture of mild bronchitis to severe pneumonia. The onset of pulmonary melioidosis is typically accompanied by a high fever. Chest pain is common, but a nonproductive or productive cough with normal sputum is the hallmark of this form of melioidosis.

Acute bloodstream infection more often affects patients with underlying illness such as HIV, renal failure, and diabetes and it usually results in septic shock. The symptoms generally include respiratory distress, severe headache, fever, diarrhea, development of pus-filled lesions on the skin, muscle tenderness, and disorientation. Chronic suppurative infection may involve various organs. It is typically an infection where pus or abscesses can be found throughout the body including the joints, viscera, lymph nodes, skin, brain, liver, lung, bones, and spleen. Melioidosis has a high mortality rate if untreated. Intravenous ceftazidime is the preferred therapy and should be initiated early in the course of the disease. Imipenem is an alternative. Drainage of abscesses is often warranted. Studies have shown good results with cotrimoxazole and doxycycline combination maintenance therapy for 12–20 weeks.

II. PROPHYLAXIS

II.a. General Principles

Prophylaxis is defined as antibiotics used to prevent infection. The reasons to administer prophylaxis can be the same for surgical and non-surgical prophylaxis, and for immunocompetent or immunocompromised hosts alike. These reasons are:

- Prevention of infection caused by local spread of skin pathogens or visceral commensal flora in the presence of tissue damage. Examples are surgical wound infections after high risk procedures. The most frequently encountered pathogen causing surgical site infections (superficial and deep wound infections) is *S. aureus*. Bowel flora can cause surgical site infections after intra-abdominal surgery.
- Prevention of infection caused by hematogenous dissemination of commensal skin or visceral flora due to:
  - dental work (oral streptococci),
  - (endoscopic) manipulation of hollow organs (streptococci, enterococci,
  - invasive procedures in infected spaces (*S. aureus, E. coli*).

  Patients at risk for infection are those with damaged heart valves or joint prostheses on which the bacteria may seed and respectively cause endocarditis and arthritis of the joint.
- Prevention of infection caused by hematogenous dissemination of endogenous flora due to the underlying immune status of patients, e.g. prolonged neutropenia, (functional) splenectomy, cirrhosis of the liver with ascites.
- Prevention of infection caused by the acquisition of specific microorganisms which can lead to overt infection, e.g. meningococci, malaria parasites, mycobacteria, *Pneumocystis jiroveci*.
- Prevention of relapses of rheumatic fever (secondary prevention) induced by throat infections caused by group A streptococci.

II.a.1. Resistance

Multiple indications for prophylactic use have been studied, and theoretically there are even more possible indications for the prevention of various infections. Prophylactic use already accounts for 30–50% of total antibiotic consumption in developed countries. This extensive use considerably contributes to the selection pressure of resistance. Furthermore,

other disadvantages of prophylactic use are the adverse effects caused by the antibiotics such as allergy and toxicity, and increased costs. Because of this, the use of prophylactic antibiotics should always be monitored and its application limited to strictly defined evidence based indications. If there is no standard or consensus, better refrain from prophylaxis.

II.a.2. Timing

As prophylaxis is intended to prevent the spread and/or multiplication of bacteria in blood and tissues, timing of its administration is crucial. For surgical prophylaxis the maximal effect is obtained when the antibiotic is in the tissues before contamination occurs (before incision of the skin). Adequate antibiotic levels should be in the blood at the start of an invasive diagnostic procedure in the GI tract to combat bacteraemia.

II.a.3. Duration

The duration of prophylaxis is limited to the period at risk for infection by local or haematogenous spread. For prophylaxis related to surgical or diagnostic procedures, the dosing schedule should provide sufficient blood or tissue levels throughout the procedure and/or the duration of bacteremia.

II.b. Applications

Prophylaxis with antimicrobial drugs has proven to be effective in many indications. However, the advantage of prophylaxis should always outweigh disadvantages such as increased selection of resistance and toxic reactions. Therefore, even some practices that have been shown cost-effective in well-conducted studies, are still considered controversial. Examples of these practices are the administration of prophylactic antibiotics in breast surgery or hernia repair. In breast and hernia surgery, the risk of surgical wound infection is low. Many patients have to be exposed to potentially toxic antibiotics to avoid only a few minor infections. Another example of controversial prophylaxis is the so-called Selective Decontamination of the Digestive Tract (SDD) in the intensive care setting. Patients are given antibiotics to eliminate gram-negative bacteria from the oropharynx and/or upper gastro-intestinal tract in order to avoid ventilator-associated pneumonia (VAP). From meta-analyses we know that the occurrence of VAP is reduced by SDD; mortality was reduced in some studies but there are concerns of increasing bacterial resistance especially in setting with high rates of MRSA, VRE and ESBLs.

Well-accepted practices of prophylaxis (usefulness documented by well-designed studies, recommended by professional societies) are:

- "Surgical prophylaxis". Procedures with a high risk for subsequent surgical site infection are the main indication. Procedures in which the risk of infection is low, but for which the consequences of surgical site infection are serious, are also a major indication for the prophylactic administration of antibiotics. The first generation cephalosporin cefazolin is most widely used. It is active against methicillin susceptible *S. aureus* and most enterobacteriaceae from the bowel. For bowel surgery, a drug directed against anaerobes (metronidazole) is added. In practice, the optimal schedule of administration is a parenteral iv injection given by the anaesthetist at induction of anaesthesia (i.e. within a period of 30 min before the surgical incision). For most procedures, a single dose is sufficient and surgical prophylaxis should not exceed 24 hours (3 doses).
- "Prophylaxis of endocarditis". For patients with congenital or acquired abnormalities of cardiac valves or large vessels specific guidelines are developed by various national professional societies. For procedures in which bacteraemia with oral flora is likely to occur (dental procedures), intramuscular penicillin or oral amoxycillin is still the first choice. Clindamycin has become the alternative antibiotic for patients who are allergic to beta-lactams. For urogenital and gastro-intestinal procedures, the regular surgical prophylaxis (cefazolin and metronidazole) is advised. Doses are chosen such as to provide adequate drug levels during the procedures and 12 h thereafter.
- Patients with prolonged neutropenia due to chemotherapy for haematologic malignancies are given oral trimethoprim-sulfamethoxazole or quinolones for the duration of neutropenia (generally about 3 weeks per episode of cancer chemotherapy). The goal is to eliminate gram-negative bacteria from the gut flora in order to prevent gram-negative sepsis. Antifungals are given concomitantly to avoid superinfection by yeasts and fungi.
- Patients with end-stage cirrhosis of the liver are given trimethoprim-sulfamethoxazole or the quinolone norfloxacin in order to avoid relapses

of spontaneous gram-negative bacterial peritonitis in the period awaiting liver transplantation.

- Children and young adults with a history of rheumatic fever are given monthly benzathin-penicillin injections or oral penicillin to prevent recurrent attacks of rheumatic fever (secondary prevention of rheumatic cardiac disease).
- Family members and close contacts of patients diagnosed with invasive meningococcal disease are given oral rifampicin 600 mg twice daily for 2 days or a single dose of a quinolone e.g. ciprofloxacin 500 mg.

Erroneous prophylactic practices are:

- Antibiotics given to patients with viral respiratory infections in order to prevent secondary bacterial infection.
- Antibiotics prescribed to children with chronic otitis media with effusion (OME).
- Antibiotics for asymptomatic patients with indwelling urinary catheters and bacteriuria.

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Chapter 33

B: Treatment of HIV/AIDS and of Tuberculosis*

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I. INTRODUCTION

Between December 2003 and June 2006, the estimated number of individuals receiving Antiretroviral therapy (ART; for the abbreviations used see Table 1) in low- and middle-income countries increased four-fold. The global efforts to increase access to ART have resulted in a massive treatment roll out, particularly in Sub-Saharan Africa. However, the goal set by the WHO in 2000 with the '3 by 5' program; to have 3 million people on ART in resource-limited settings (RLS) by 2005, was not met. In 2006 less then 1 million were receiving ART. In this setting the vital importance of treatment guidelines becomes even more critical for the optimal and cost-effective use of antiretroviral drugs on a national level. For the most part, the choice of the ART regimen (both first- and second-line) is limited to regimens available through the different funding for ART programs including PEPFAR, the U.S. President's Emergency Plan For AIDS Relief, www.pepfar.gov/ and GFATM, the Global Fund to fight AIDS, Tuberculosis and Malaria, www.theglobalfund.org/. Furthermore, choices are based on National ART guidelines of the different resource limited countries where they exist.

It is now well recognised that the choice of first line ART influences the choice of second and subsequent lines of ART regimens, and is therefore critical for long term treatment success. Adherence to ART remains the most critical factor for optimal treatment outcome. With more individuals surviving longer, a simple regimen with limited long-term side-effects is essential for effective and sustained therapy for HIV/AIDS as long as there is no effective vaccine. With longer ART experience among HIV-infected individuals in resource-limited settings (RLS), ART toxicities emerged as important limitations, particularly where stavudine is routinely used a part of first-line ART regimens.

The immune reconstitution inflammatory syndrome (IRIS) has emerged as an important clinical issue in the management of HIV-infected individuals on ART. IRIS is characterized by paradoxical worsening of symptoms and signs of inflammation in individual on ART (usually 2–6 months after ART initiation) related to the immunological gains of ART.

* Adapted from: C.J. van Boxtel. Mission Report: Development of Standard Treatment Guidelines (HIV/AIDS, Respiratory Diseases, Gastrointestinal Diseases), World Health Organisation, Manila, Philippines, 2003.

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Table 1. Abbreviations

NRTI: Nucleoside (or nucleotide) transcriptase inhibitor	NNRTI: Non-nucleoside reverse transcriptase inhibitor	PI: Protease inhibitor
3TC: Lamivudine*	NVP: Nevirapine*	RTV, r: Ritonavir*
ABC: Abacavir*	DLV: Delavirdine	PI/r: Ritonavir boosted protease inhibitor
d4T: Stavudine*	EFV*: Efavirenz	SQV: Saquinavir*
ddC: Zalcitabine		IDV: Indinavir*
ddI: Didanosine*		LPV: Lopinavir*
TDF: Tenofovir		NFV: Nelfinavir*
ZDV: Zidovudine, also abbreviated as AZT*		APV: Amprenavir
		ATV: Atazanavir
FTC: Emtricitabine		DRV: Darunavir

*Included in the WHO 14th Model List of Essential Medicines (2006), lopinavir only in the combination with low dose ritonavir.

IRIS occurs more often in patients with AIDS started on ART than in HIV-positive patients without opportunistic infections. Whereas IRIS is in many cases mild and self-limiting, the frequency of its occurrence (20–40%) in resource limited settings as well as the fact that it is occasionally life-threatening warrant special mention.

Finally, it is recognised that antiretroviral drugs, although they can temporarily suppress viral replication and improve symptoms, do not cure human immunodeficiency virus infection (HIV). Promotion of all possible measures to prevent new infections therefore remains essential and its need is not diminished by the availability of antiretroviral drugs.

II. DRUGS USED TO TREAT HIV INFECTION

Zidovudine (ZDV or AZT) is a nucleoside *reverse transcriptase inhibitor* (NRTI) and it was the first anti-HIV agent to be introduced. Other NRTIs include stavudine (d4T), lamivudine (3TC), didanosine (ddI), abacavir (ABC) and zalcitabine (ddC). Recent additions to this class are emtricitabine (FTC) which has a molecular structure similar to 3TC and tenofovir (TDF) a nucleotide reverse transcriptase inhibitor.

Three *non-nucleoside reverse transcriptase inhibitors* (NNRTI) are currently used: efavirenz (EFV), nevirapine (NVP) and delavirdine (DLV). The last NNRTI is not registered in Europe.

Agents within the group of *protease inhibitors* are nelfinavir (NFV), indinavir (IDV), lopinavir (LPV), saquinavir (SQV), (fos)amprenavir (APV), tipranavir (TPV), atazanavir (ATV), the recently licensed darunavir (DRV) and ritonavir (RTV, r). Ritonavir in low doses is used in combination with all PIs except NFV as a booster. The small amount of ritonavir in such combinations has no intrinsic antiviral activity but it increases the antiviral activity of the other protease inhibitors by reducing their metabolism through inhibition of the cytochrome P450, 3A4 enzyme in the liver and the gut mucosa. Ritonavir alone is not recommended. The dosages of these agents are given in Table 2.

II.a. Adverse Drug Reactions and Drug–Drug Interactions

Care and support are important in helping patients cope with the side effects of ART and a brief discussion of the most notorious reactions is therefore warranted.

As a class effect NRTIs are associated with lactic acidosis and hepatic steatosis, conditions which may occur more frequently in pregnant women. The individual NRTIs have their own adverse reactions. Pancreatitis is seen with lamivudine, stavudine, didanosine and rarely with zalcitabine while the latter three agents can also induce peripheral neuropathy.

Zidovudine and lamivudine may cause anaemia and in late-stage disease also neutropenia. Zidovudine can cause myalgia and myopathy.

Abacavir is associated in 5–10% of cases with severe hypersensitivity reactions combined with fever, headache, myalgia, gastrointestinal symptoms and rash. This hypersensitivity is related to the gene expression of HLA B57-01. Blood tests are being developed to monitor the presence of this gene before starting abacavir. If one has had a hypersensitivity

Table 2. Dosages of antiretrovirals[a]

	Adult dose	Paediatric dose
Nucleoside reverse transcriptase inhibitors (NRTIs)		
Zidovudine (AZT)	300 mg twice daily	<4 weeks: 2 mg/kg twice daily 4 w–13 yrs: 10 mg/kg twice daily
Stavudine (d4T)	<60 kg: 30 mg twice daily >60 kg: 40 mg twice daily	<30 kg: 1 mg/kg twice daily <60 kg: 30 mg twice daily
Lamivudine (3TC)	150 mg twice daily	4 mg/kg twice daily
Emtricitabine (FTC)	200 mg once daily	0–3 months: 3 mg/kg/day 3 month–17 yrs: 6 mg/kg/day
Didanosine (ddI)	<60 kg: 250 mg once daily >60 kg: 400 mg once daily	<3 months: 90 mg/m^2[b] twice daily >3 months: 90 mg/m^2 twice daily
Abacavir (ABC)	300 mg twice daily	>3 months: 8 mg/kg twice daily
Fixed dose combination of ZDV plus 3TC	300/150 mg twice daily	>13 yrs or >60 kg maximum dose
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)		
Efavirenz (EFV)	600 mg daily once daily	13 to <15 kg: 200 mg once daily 15 to <20 kg: 250 mg once daily 20 to <25 kg: 300 mg once daily 25 to <32.5 kg: 350 mg once daily 32.5 to <15 kg: 400 mg once daily
Nevirapine (NVP)	200 mg daily for 2 weeks, then 200 mg twice daily	15–30 days 5 mg/kg once daily for 2 weeks >30 days–13 yrs: 120 mg/m^2 daily for 2 weeks, then 200 mg/m^2 twice daily
Nucleotide reverse transcriptase inhibitor		
Tenofovir (TDF)	300 mg once daily	Safety and efficacy not well established in paediatric patients
Protease inhibitors (PI)		
Nelfinavir (NFV)	1.25 g twice daily	<1 yr 65–75 mg/kg twice daily[c] >1 yr to <13 yrs 55–65 mg/kg twice daily
Indinavir/ritonavir (IDV/r)	800/100 mg twice daily	
Lopinavir/ritonavir (LPV/r)[d] Capsules 133/33 mg Tablets 200/50 mg	400/100 mg twice daily (533/133 mg twice daily when combined with EFV or NVP)	7–15 kg: 12 mg/kg LPV/3 mg/kg ritonavir twice daily 15–40 kg: 10 mg/kg LPV/5 mg/kg ritonavir twice daily
Saquinavir/ritonavir (SQV/r)	1000/100 mg twice daily	

[a] With renal or hepatic dysfunction dose adjustments may be indicated.
[b] Body surface area calculation: square root (height in cm × body weight in kg divided by 3600).
[c] High doses required in infants <1 yr because of kinetic variability.
[d] LPV/r is included in the WHO model list of Essential Medicines.

reaction, abacavir should never be restarted in this patient.

The NNRTIs efavirenz and nevirapine interact with a number of drugs metabolized in the liver. The doses of protease inhibitors may need to be increased when they are given with efavirenz or nevirapine. Nevirapine is associated with a high incidence of rash (including Stevens–Johnson syndrome) and occasionally fatal hepatitis. Rash may also occur with efavirenz but it is usually milder. Mild rashes can be treated with an antihistaminic and moderate rashes with an oral corticosteroid. With a severe rash the NNRTI should be stopped Efavirenz treatment has been associated with an increased plasma choles-

terol concentration.

The protease inhibitors indinavir, nelfinavir, ritonavir and possibly saquinavir inhibit the cytochrome P450 enzyme system and therefore have a potential for significant drug interactions. Protease inhibitors may induce glucose intolerance and especially pregnant women should be instructed to recognize symptoms of hyperglycaemia. For years protease inhibitors were associated with the lipodystrophy syndrome. Now we know that especially AZT and d4T are causing lipoatrophy (decrease of subcutaneous fat esp. of the extremities and face) and the PIs are more related to lipohypertrophy (mainly visceral fat accumulation, breast enlargement and rarely fat formation in the neck 'buffalo hump'). This redistribution of body fat in some patients and can have severe cosmetic consequences. Protease inhibitors are also associated with hyperlipidaemia and insulin resistance, sometimes causing diabetes.

As with almost all adverse drug reactions the most effective management is to stop the offending drug and replaced it with another agent that does not have the same adverse effects.

There are some important interactions between ART drugs and agents that are worth noting particularly in a resource limited setting. Rifampicin, a rifamycin included in first line anti-tuberculous therapy is a potent inducer of cytochrome P450 and therefore leads to clinically significant reduction of especially nevirapine and protease drug levels. Thus combining these two drugs is not clinically recommended. Phenytoin (anticonvulsant) leads to reduce levels of lopinavir and the combination should be avoided. Co-administration of ketoconazole and nevirapine is not recommended as drugs levels for both drugs are increased with potential for toxicity An instructive website to look at drug interactions with ART is on the drug interaction chart on www.hivdrug-interactions.org.

III. DIAGNOSTIC REQUIREMENTS BEFORE ART

In RLS the assessment before initiating antiretroviral therapy heavily relies on an adequate clinical work-up of the patient including a detailed medical history, not in the least to identify possible HIV-related illnesses. Efforts to make a reliable clinical assessment of the seriousness of the clinical condition and any diagnosis of co-existing ailments are of importance because they may influence the choice of therapy.

The *absolute minimum laboratory tests* before initiating antiretroviral therapy are an HIV antibody test (in patients over 18 months of age) and a haemoglobin or haematocrit measurement.

Additional basic testing should include:

- a baseline white blood cell count and differential cell count (to identify a decline in neutrophils and the possibility of the occurrence neutropenia during ART);
- total lymphocyte count but preferably a CD4 count;
- serum alanine or aspartate aminotransferase concentration to assess the possibility of hepatitis co-infection;
- serum creatinine and/or blood urea nitrogen to assess baseline renal function;
- serum glucose;
- pregnancy tests for women.

In situations where CD4 counts cannot be assessed, the presence of a total lymphocyte count below 1200 mm^{-3} may be used as a substitute indication for treatment.

As opportunistic infections (OIs) are common in HIV/AIDS and as their treatment is part of the cost-effectiveness considerations of ART in RLS, requirements for the diagnosis of different OIs are listed in Table 3. Due to the significant burden of tuberculosis in HIV-infected individuals and its contribution to early mortality in cohorts of individuals initiating ART, screening for active TBC in individuals before initiating ART is generally recommended.

III.a. Eligibility Criteria for Receiving ART

Eligibility of HIV-infected individuals for ART depends on a clinical and immunological assessment that results into staging of the patient in terms of disease progression (see Table 4).

WHO recommends that in ART programmes in RLS HIV-infected adolescents and adults should start ARV therapy when they have:

- WHO stage IV of HIV disease (clinical AIDS) and some stage III events (notably pulmonary tuberculosis), regardless of CD4 count;
- WHO stages I, II or III of HIV disease, with a CD4 count below 200 mm^{-3};
- WHO stages II or III of HIV disease with TLC below 1200 mm^{-3}.

Table 3. Diagnosis of opportunistic infections

	Investigations	Requirements
PCP	Chest X-ray Induced sputum examination	X-ray Microbiology laboratory
Tuberculosis (Pulmonary)	Chest X-ray Sputum stain and culture	X-ray Microbiology laboratory
Tuberculosis (Extra pulmonary)	Biopsy and culture	Microbiology laboratory
Cryptococcal meningitis	Lumbar puncture Serum Cryptococcal antigen (sCRAG)	India-ink preparation Crypto Ag & titer
Toxoplasmosis	Cerebral CT scan	CT scanner
Esophageal candidiasis	Endoscopy	Endoscope
CMV retinitis	Fundoscopy	Ophthalmoscope
Cryptosporidium	Stool culture	Microbiology laboratory
Mycobacterium Avium Complex (MAC)	Blood, stool, sputum, bone marrow culture	Microbiology laboratory BACTEC medium

In addition, ART initiation is recommended in pregnant women with WHO stage III with a CD4 count below 350 cells mm^{-3} as well individuals with severe bacterial infections in this CD4 count range. One should consider starting ART in individuals with a CD4 count between 200 and 350 cells mm^{-3} who are asymptomatic. It is not generally recommended to start ART in asymptomatic individuals with counts above 350 cells mm^{-3}. This information is summarized in Table 5 adopted from the most recent WHO guidelines on ART in RLS.

In children, WHO recommends offering ARV combination therapy to HIV-positive children under the age of 18 months if they have virologically proven infection (using either HIV PCR or immune complex dissociated HIV p24 antigen detection or HIV culture) combined with clinical AIDS or to children without clinical AIDS and a CD4 percentage $< 20\%$. For children over the age of 18 months who are HIV antibody positive, WHO recommends ART if they have clinical AIDS regardless of CD4 percentage or if the CD4 percentage is $<15\%$.

Once eligibility has been objectively determined as above then the decision to initiate ART is further informed by the patients individual circumstances which include; readiness for and understanding of the implications of ART, and access to nutritional as well as social support.

Where HIV antibody testing suffice for adults in children les than 18 months of age, a positive HIV antibody test is not sufficient to confirm an HIV diagnosis since maternal antibodies cross the placenta into the infant's circulation. HIV-antibodies can be detected in the infant without HIV infection since they can persist up to 18 months from birth. Therefore establishing true HIV infection in this age group is definitively done by detecting the presence of HIV either by performing RNA or DNA PCR assays or testing for the presence of viral p24 antigen. The dried blood spots (DBS) technique has proved a reliable and robust way of storing blood for HIV RNA, DNA and p24 antigen testing and should resulted in more widespread virologic testing of children under 18 months (Tables 6 and 7).

IV. RECOMMENDED FIRST-LINE REGIMENS IN ADULTS

Only ART drug combinations containing at least 3 drugs from at least 2 ARV classes lead to durable suppression of HIV and translate into an improved immunologic state and quality of life. Individuals from RLS have been fortunate to benefit from earlier studies in developed countries and therefore early start of ART (CD4 count $> 500/\mu l$) or monotherapy/dual therapy have been avoided in these settings. Several combination regimens with demonstrated effectiveness in achieving durable suppression of HIV replication are available.

There is a lot of evidence now from HIV cohorts on first-line and second-line therapies that are most likely to achieve and maintain virologic suppression and lead to good immunologic and clinical

Table 4. WHO clinical staging of HIV/AIDS for adults and adolescents with confirmed HIV infection

- Primary HIV infection
  - Asymptomatic
  - Acute retroviral syndrome
- Clinical stage I
  - Asymptomatic
  - Persistent generalized lymphadenopathy (PGL)
- Clinical stage II
  - Moderate unexplained weight loss (<10% of presumed or measured body weight)
  - Recurrent respiratory tract infections (RTIs, sinusitis, bronchitis, otitis media, pharyngitis)
  - Herpes zoster
  - Angular cheilitis
  - Recurrent oral ulcerations
  - Papular pruritic eruptions
  - Seborrhoeic dermatitis
  - Fungal nail infections of fingers
- Clinical stage III
  - Conditions where a presumptive diagnosis can be made on the basis of clinical signs or simple investigations
    - Severe weight loss (>10% of presumed or measured body weight)
    - Unexplained chronic diarrhoea for longer than one month
    - Unexplained persistent fever (intermittent or constant for longer than one month)
    - Oral candidiasis
    - Oral hairy leukoplakia
    - Pulmonary tuberculosis (TBC) diagnosed in last two years
    - Severe presumed bacterial infections (e.g. pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteraemia)
    - Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis
  - Conditions where confirmatory diagnostic testing is necessary
    - Unexplained anaemia (<8 g/dl), and or neutropenia (<500 mm^{-3}) and or thrombocytopenia (<50,000 mm^{-3}) for more than one month
- Clinical stage IV
  - Conditions where a presumptive diagnosis can be made on the basis of clinical signs or simple investigations
    - HIV wasting syndrome
    - Pneumocystis pneumonia
    - Recurrent severe or radiological bacterial pneumonia
    - Chronic herpes simplex infection (orolabial, genital or anorectal of more than one month's duration)
    - Oesophageal candidiasis
    - Extrapulmonary TBC
    - Kaposi's sarcoma
    - Central nervous system (CNS) toxoplasmosis
    - HIV encephalopathy
  - Conditions where confirmatory diagnostic testing is necessary:
    - Extrapulmonary cryptococcosis including meningitis
    - Disseminated non-tuberculous mycobacteria infection
    - Progressive multifocal leukoencephalopathy (PML)
    - Candida of trachea, bronchi or lungs
    - Cryptosporidiosis
    - Isosporiasis
    - Visceral herpes simplex infection
    - Cytomegalovirus (CMV) infection (retinitis or of an organ other than liver, spleen or lymph nodes)
    - Any disseminated mycosis (e.g. histoplasmosis, coccidiomycosis, penicilliosis)
    - Recurrent non-typhoidal salmonella septicaemia
    - Lymphoma (cerebral or B cell non-Hodgkin)
    - Invasive cervical carcinoma
    - Visceral leishmaniasis

Table 5. Recommendations for initiating ART in adults and adolescents in accordance with clinical stages and the availability of immunological markers

WHO clinical staging	CD4 testing not available	CD4 testing available
1	Do not treat (A-III)	Treat if CD4 count is below 200 cells mm^{-3}[a] (A-III)
2	Do not treat[b] (B-III)	
3	Treat (A-III)	Consider treatment if CD4 count is below 350 cells mm^{-3}[a,c,d] and initiate ART before CD4 count drops below 200 cells mm^{-3}[e] (B-III)
4	Treat (A-III)	Treat irrespective of CD4 cell count (A-III)

[a] CD4 cell count advisable to assist with determining need for immediate therapy for situations such as pulmonary TBC and severe bacterial infections, which may occur at any CD4 level.

[b] A total lymphocyte count of 1200 mm^{-3} or less can be substituted for the CD4 count when the latter is unavailable and mild HIV disease exists. It is not useful in asymptomatic patients. Thus, in the absence of CD4 cell counts and TLCs, patients with WHO adult clinical stage 2 should not be treated.

[c] The initiation of ART is recommended in all HIV-infected pregnant women with WHO clinical stage 3 disease and CD4 counts below 350 cells mm^{-3} (see Section III.a).

[d] The initiation of ART is recommended for all HIV-infected patients with CD4 counts below 350 cells mm^{-3} and pulmonary TBC (see also Section VIII.a.9) or severe bacterial infection.

[e] The precise CD4 cell level above 200 mm^{-3} at which ARV treatment should be started has not been established.

A-III and B-III: Grading of recommendations and levels of evidence (see http://www.who.int/hiv/pub/guidelines/paediatric020907.pdf).

Table 6. Indications for ART in children

CD4 testing	Age (months)	HIV diagnostic testing	Treatment recommendation
If CD4 testing is available	<18	Positive HIV virologic test*	• Children with clinical AIDS, irrespective of CD4 cell percentage • Asymptomatic children with a CD4 percentage $<$ age-specific cut off
		HIV virologic testing not available but infant HIV seropositive or born to known HIV-infected mother (Note: HIV antibody test must be repeated at age 18 months to obtain definitive diagnosis of HIV infection)	Children with clinical AIDS and with CD4 cell percentage $<$ age specific cut off
	$\geqslant 18$	HIV antibody seropositive	• Children with clinical AIDS, irrespective of CD4 cell percentage • Asymptomatic children with a CD4 percentage $< 15\%$
If CD4 testing is not available	<18	Positive HIV virologic test	Children with clinical AIDS
		HIV virologic testing not available but infant is HIV seropositive or born to known HIV-infected mother	Treatment not recommended
	$\geqslant 18$	HIV antibody seropositive	Children with clinical AIDS

*HIV DNA PCR or HIV PCR RNA or immune complex dissociated p24 antigen assays, or HIV culture.

Table 7. Age specific recommendations to initiate ART

Immunological marker	Age specific recommendations to initiate ART			
	<11 months	12–35 months	36–59 months	>5 years
CD4 percentage	<25%	<20%	<15%	<15%
CD4 count (cell mm^{-3})*	<1500	<750	<350	<200

*Total lymphocyte levels that correspond to the CD4 cell cut offs for different age groups in the table above are 4000, 3000, 2500 and 2000 lymphocytes mm^{-3}.

Table 8. Recommended first-line ARV combination regimens in adults and adolescents with documented HIV infection

Regimen	Notes	Major toxicities
ZDV/3TC/EFVEFV or ZDV/3TC/NVP	No EFV in pregnant women or women for whom effective contraception cannot be assured	• ZDV-related anemia • Possible teratogenicity of EFV • EFV-associated CNS symptoms • NVP-associated hepatotoxicity and severe rash
TDF/FTC or 3TC/NVP or EFV D4T/3TC/NVP or EFV	As above	TDF-renal tubular acidosis D4T-neuropathy, lactic acidosis, lipoatrophy
Triple NRTI regimens AZT/3TC/ABC (Trizivir twice daily) AZT/3TC/TDF	Used in special circumstances (see text)	• ZDV-related anemia • ABV hypersensitivity

outcomes. These data are the basis of the recommendations that WHO has made for both first line and second line regimens for ART in RLS.

Considerations in the selection of ARV treatment regimens at both the programme level and at the level of an individual patient should include the potency, side effect profile, the potential for maintenance of future treatment options, the anticipated adherence of the patient population with a regimen, coexistent conditions (e.g., co-infections, metabolic abnormalities), pregnancy or the risk thereof, the use of concomitant medications (i.e. potential drug interactions), the potential for primary acquisition of resistant viral strains, and cost and access (Table 8).

The Guidelines Development Group of the WHO has continued to recommend a regimen consisting of 2 NRTIs and an NNRTI as the ideal first line in RLS. This combination as potent as a PI-based regimen, less costly, more convenient in terms of adherence and does not require a refrigerator. It saves the PIs for the second-line regimen in case of eventual treatment failure. In constructing the nucleoside backbone of ART the thiacytadine analogues (lamivudine and emtricitabine) are combined with any one of the other NRTIs (AZT, D4T, ABC) or the nucleotide RTI tenofovir. The preferred back bone in RLS is AZT/3TC however the TDF/FTC combination is gaining ground rather quickly given its lack of toxicity and once-daily administration. The current limitation for the widespread use of the FTC/TDF combination is mainly the cost; there are also concerns about its use in settings where renal disease can not routinely be screened for. The nucleoside backbone of D4T/3TC that is usually part of the generic product Triomune® is a very convenient and often used ART drug despite the worrying increase of D4T-associated neuropathy, lipoatrophy as well as lactic acidosis.

The most convenient regimen from the patients' point of view is a combination consisting of TDF/FTC/EFV that can be taken as a once-a-day pill. This is now available under the brand name of Atripla.

It is worth noting that some NNRTI combinations are not recommended in clinical practice. The AZT/d4T combination is antagonistic while a d4T/ddI combination leads to severe toxicity (neuropathy, acidosis and pancreatitis). A TDF/ddI combination with 3TC is associated with poor virologic

suppression and seems to lead to poor immunologic recovery even in the setting of good virologic suppression when given with a boosted PI without dose adjustment.

In RLS (where boosted PIs are reserved for second-line therapy) there are situations where triple NRTI regimens are considered. These include:

- women with CD4 counts between 250 cells and 350 cells mm^{-3} (significant risk of hepatotoxicity with NNRTI);
- viral Hepatitis co-infection (significant risk for hepatotoxicity);
- TBC co-infection;
- severe NVP and EFV reactions.

Countries with a significant prevalence of HIV-2 as well as Group O HIV-1 viruses might consider reserving the use of the non-nucleoside-containing regimens to patients with proven HIV-1 infection. HIV-2 as well as Group O HIV-1 viruses are naturally resistant to this class of drugs.

IV.a. Monitoring

Patients require close and regular (1- to 3-monthly) follow-up. The best indicator of antiretroviral activity is the HIV viral load, which should fall to below 20–50 copies per ml dependent on the detection limit of the viral load assay. However in most situations viral load testing is not feasible because of constraints on resources.

The CD4 cell count generally increases when viral replication is suppressed. WHO recommends that where ever possible ART monitoring should be based on CD4-cell measurement every 6 months.

Recommended testing should include a white blood cell count and differential to permit assessment of neutropenic side effects. The total lymphocyte count as a measure of ART treatment response is unreliable and not generally recommended. Serum alanine or aspartate aminotransferase (ALT, AST) level determinations are recommended to monitor for hepatotoxicity. Creatinine and phosphate should be measured 4 weeks after initiation of tenofovir.

Haemoglobin and haematocrit measurements are needed to assess anemia which occurs in 5–10 % of patients started on a regimen with AZT.

Desirable supplemental tests include measurement of bilirubin, amylase and serum lipids. Regular serum glucose measurements are desirable when PIs are used.

Clinical monitoring is essential for the provision of safe and effective ARV therapy. Where laboratory monitoring is limited, close clinical monitoring becomes even more crucial.

In patients deteriorating under ART with nausea and abdominal pain lactic acidosis should be suspected.

IV.b. The Immune Reconstitution Inflammatory Syndrome (IRIS)

Whereas ART leads to recovery of the immune systems resulting in protection from opportunistic infection in the majority of individuals, this recovery in a number of patients leads to heighten recognition of antigens which can lead to a clinical syndrome characterized by inflammatory symptom and signs. This situation is referred to as IRIS. The manifestations of IRIS are as diverse as the systems that can be affected ranging from meningeal symptoms, abcesses, fevers, cutaneous lesions, chest symptoms as well as hepatic liver enzyme abnormalities. The prevalence of IRIS in RLS ranges from 10–25% among individuals initiating ART. Fortunately most IRIS episodes are self limiting and only rarely is the syndrome life threatening (CNS manifestations with raised intracranial pressure and major airway obstruction by intrathoracic lymph nodes). The most common antigens that are associated with IRIS in RLS are *Mycobacterium tuberculosis*, *Cryptococcus neoformans* and Herpes simplex virus. However IRIS has been described for most opportunistic pathogens.

The diagnosis of IRIS is made when alternative explanations of clinical deterioration (intercurrent opportunistic infections, drug toxicities and HIV disease progression) are excluded and the following criteria are fulfilled; findings suggestive of inflammation (abscesses, fever, elevation of liver enzymes), evidence of treatment response (>1.0 log drop in viral load suppression or brisk CD4 count elevation) as well as a relationship with the initiation of ART (IRIS usually occurs 2–6 months following ART initiation). The treatment of IRIS consists of specific antimicrobial therapy targeted towards the antigen in question as well as anti inflammatory therapy (NSAIDs). Steroids are limited to individuals with severe IRIS episodes.

IV.c. Changing Therapy

When considering a change in ART regimen, it is of paramount importance to distinguish a failing ART

regimen from changes due to ART associated toxicities. When toxicity is the reason for changing the regimen and the offending drug is known this agent can be replaced with another drug that does not have the same adverse effects. When the reason for ART regimen change is treatment failure, a second-line combination regimen is indicated, with 3 new drugs, preferably agents belonging to a different class or with a low probability of cross-resistance to agents in the previous regimen. So the choice of the second-line agents heavily depends on which drugs were used in the first-line treatment regimen (Table 9).

In the absence of CD4 count and viral load measurements, the development of a WHO stage 4 illness is an indication of treatment failure in a setting where individuals has been on ART for at least 6 months, poor adherence to ART has been excluded as well as intercurrent opportunistic events an IRIS have been excluded. If these conditions are met then a second line regimen should be considered.

In settings with CD4 count monitoring, a fall of CD4 counts to levels below the baseline at ART initiation or a 50% drop in CD4 counts from the highest CD4 level attained as well as persistence of CD4 counts below 100 cell mm^{-3} (in the absence of intercurrent opportunistic infections) are recommended as cut offs for considering treatment failure by the WHO. Where viral load measurements are possible, the cut off for treatment failure definition is HIV RNA levels above 10,000 copies in individuals on ART for at least 6 months in whom adherence is assured.

V. POST-EXPOSURE PROPHYLAXIS

Treatment with antiretroviral drugs may be appropriate following occupational exposure to potentially HIV-contaminated material. It should be established if the source of the inoculated blood or body fluids is HIV antibody positive. If so, post-exposure prophylaxis with an antiretroviral regimen should be started as soon as possible.

For low risk situations the use of zidovudine (child: up to 10 mg/kg) 300 mg plus lamivudine (child: up to 4 mg/kg) 150 mg orally, 12-hourly for 4 weeks is recommended.

For percutaneous, intravenous or intra-arterial exposures or for exposures where a high viral load is to be expected lopinavir/ritonavir should be added to the above regimen.

Table 9. Recommended second-line regimens in adults and adolescents (WHO, 2006)

First-line regimen		Second-line regimen	
		RTI component	PI component[a]
Standard strategy	AZT or d4T + 3TC[b] + NVP or EFV	ddI + ABC or TDF + ABC or TDF + 3TC (± AZT)[c]	PI/r[d]
	TDF + 3TC[b] + NVP or EFV	ddI + ABC or ddI + 3TC (± AZT)[c]	
	ABC + 3TC[b] + NVP or EFV	ddI + 3TC (± AZT)[c] or TDF + 3TC (± AZT)[c]	
Alternative strategy	AZT or d4T + 3TC[b] + TDF or ABC	EFV or NVP ± ddI	

[a] NFV does not need refrigeration and can be used as a PI alternative in places without a cold chain.

[b] 3TC and FTC are considered interchangeable because they are structurally related and share pharmacological properties and resistance profiles.

[c] 3TC can be considered to be maintained in second-line regimens to potentially reduce viral fitness, confer residual antiviral activity and maintain pressure on the M184V mutation to improve viral sensitivity to AZT or TDF. AZT may prevent or delay the emergence of the K65R mutation.

[d] There are insufficient data to detect differences among currently available RTV-boosted PIs (ATV/r, FPV/r, IDV/r, LPV/r and SQV/r) and the choice should be based on individual programme priorities (see text). In the absence of a cold chain, NFV can be employed as the PI component but it is considered less potent than an RTV-boosted PI.

VI. CONSIDERATIONS FOR SPECIFIC SUBGROUPS OF PATIENTS

VI.a. Women of Childbearing Potential or Who Are Pregnant

WHO recommends the use of ZDV, 3TC, NVP, NFV and SQV combined with low dose ritonavir, as these have been the most widely used ARVs in pregnant women. EFV is not recommended for use in women who could become pregnant due to its potential teratogenic effects in the first trimester.

The choice of ART in women with the potential to become pregnant must include consideration of the possibility that the ARV drugs may be received during the early first trimester, prior to recognition of pregnancy and during the primary period of fetal organ development. Women who are receiving ART should have available to them effective and appropriate contraceptive methods to reduce the likelihood of unintended pregnancy. It is important to note that some antiretroviral drugs (the NNRTIs NVP and EFV and all the RTV-boosted PIs) can lower blood concentrations of oral contraceptives and additional or alternative contraception needs to be used to avoid pregnancy in women receiving these drugs.

For pregnant women, it may be desirable to initiate ART after the first trimester, although for pregnant women who are severely ill, the benefit of early therapy outweighs any potential fetal risks. Additionally, the dual NRTI combination of d4T/ddI should only be used during pregnancy when no other alternatives exist, due to the potential increased risk of lactic acidosis with this combination in pregnant women.

Various treatment schedules have been used to specifically prevent the transmission of HIV from mother to the neonate at term. With effective ART, suppressing HIV-RNA in the pregnant mother, Caesarean section is not necessary.

One large randomised controlled trial demonstrates that nevirapine given to mothers as a single dose at the onset of labour and to babies as a single dose within 72 hours of birth is more effective than an intrapartum and post-partum regimen of zidovudine. However this regimen can cause NNRTI resistant virus in mother and child.

VI.b. Children

The limited studies of ART in children suggest that broadly similar improvements are seen in surrogate markers with many different ART regimens.

Most ARVs available for adults are also available for children with specific child formulations including dosages that are based on either body surface area or weight. First-line treatment options for children include ZDV/3TC plus either a non-nucleoside (NVP or EFV) or ABC. EFV cannot be used in children under the age of 3 years due to lack of appropriate dosing information. However, EFV would be the non-nucleoside of choice in children on rifampicin, in case ARV needs to start before anti-tuberculous therapy is completed. Second-line therapy for children in the event of first-line regimen failure would include a change in nucleoside backbone (e.g., from ZDV + 3TC to d4T + ddI) plus a protease inhibitor.

Use of protease inhibitors other than LPV/r and NFV is problematic in children due to lack of suitable pediatric drug formulations for IDV and SQV (Table 10(a) and (b)).

VII. HIV AND OPPORTUNISTIC INFECTIONS

The prevention and treatment of opportunistic infections (OIs) in the ART era is still an important component of HIV care in RLS for three major reasons. First of all, many individuals present with life threatening OIs as the first indication of HIV infection. The proportion of the population at risk for HIV infection that is aware of its HIV serostatus is considerably very low. Secondly, whereas over the last two years access to ART has improved greatly, ART coverage in RLS is still less than 25% of the ART eligible population.

Therefore the protection ART offers against OIs is a missed opportunity in this population. Finally some individuals do not achieve immunologic responses despite receiving ART and are therefore still prone to developing OIs. This is especially the case when ART is initiated with advance immune deterioration, a common occurrence in RLS. The following section therefore highlights several aspects of the treatment and prevention of important OIs in RLS.

VII.a. Pneumonia due to *Pneumocystis carinii* (PCP)

The frequency of this yeast infection of the lung with *Pneumocystis jirovecii* (formerly called *P. carinii*)

Table 10a. Recommended first-line antiretroviral regimens for children

Regimen	Comments
ZDV/3TC[b] + ABC*	Preferred if concomitant anti-tuberculosis therapy being received
ZDV/3TC[a] + NNRTI	NNRTI choice: • if <3 years or <10 kg, NVP • if >3 years or >10 kg, NVP or EFV

*ZDV/3TC is the first choice dual NRTI regimen for children as it has the largest amount of clinical experience. Other dual NRTI components can be substituted for children, including ZDV/ddI, d4T/3TC, d4T/ddI and ddI/3TC. ZDV/d4T should never be used together due to proven antagonism.

Table 10b. Recommended second-line antiretroviral regimens for children

First-line regimen	Second-line regimen
ZDV/3TC/ABC	d4T/ddI/LPV/r[a] or d4T/ddI/NFV or d4T/ddI/NNRTI[b]
ZDV/3TC/NNRTI[b]	d4T/ddI/LPV/r[a] or d4T/ddI/NFV

[a]For children who can swallow capsules and for whom the current capsule formulations allow appropriate weight or body surface area calculated dosing, additional options to replace LPV/r include SQV/r and IDV/r.
[b]NNRTI choice: if <3 years or <10 kg, NVP; if ⩾3 years or ⩾10 kg, NVP or EFV.

varies world-wide, ranging from 64% in the US to <5% in reports from some areas in Africa, although other African studies suggest higher rates. The reason for this variability is uncertain, but may in part be due to under-reporting and under-diagnosis in developing countries or perhaps geographic variability. The most typical presenting symptoms of PCP in HIV-positive patients are a non-productive cough, dyspnoea on exertion and fever. The onset of illness is often subtle and many of these symptoms can develop slowly over a number of weeks.

Chest X-rays may reveal extensive interstitial infiltration, a mild peri-hilar haze or may be normal. Whenever practicable, attempts should be made to identify the organism using induced sputum or broncho-alveolar washings.

Mortality has been reduced significantly due to early recognition of disease, use of the most effective drug regimes and the inclusion of primary and secondary prophylaxis.

VII.a.1. Treatment of PCP

Sulfamethoxazole (SMZ)/trimethoprim (TMP) has been shown to be the best regimen for both the treatment and prevention of PCP (Table 11).

If the patient is unable to tolerate these regimens, pentamidine 4 mg/kg i.v. can be used. Signs of improvement may not be evident for 4–8 days, and treatment should be maintained for 2–3 weeks. For mild to moderate disease oral drugs can be used throughout the treatment (2 week course); in severe disease, treatment is normally administered intravenously during the first 7–10 days (total 3 weeks course).

However, if the patient is receiving second line treatment, components that are not available in the intravenous formulation are administered orally. When no improvement is evident after 7–10 days, clinicians often resort to switching to one of the other regimens. The severe toxicity of pentamidine compared to the other regimens has limited its use. This drug is now used only as a last resort. If switching to pentamidine is being considered, an overlap of two to three days should occur to allow pentamidine to accumulate in the body.

The first few days of antimicrobial treatment are critical since the decomposition of many dead parasites exacerbates the pre-existing inflammatory process and aggravates hypoxia. However, the risk of death at this stage can be substantially reduced especially in patients whose arterial oxygen tension (pO_2) is less than 70 mmHg (9.33 kPa) if a corticosteroid – oral prednisolone or, when necessary intravenous methylprednisolone – is administered as soon as antimicrobial therapy is started. Prednisolone given orally at a dose of 40 mg twice daily for 5 days, followed by 40 mg daily for 5 days, and then 20 mg daily for 10 days is a regimen that has

Table 11. Treatment of PCP

	Drug	Dose
1st choice	Sulfamethoxazole/trimethoprim oral or Sulfamethoxazole/trimethoprim i.v.	SMZ 75 mg/kg TMP 15 mg/kg divided in 3 doses daily for 2–3 weeks (typical oral dose is 2 double strength tablets (960 mg) TID)
2nd choice	Clindamycin i.v./oral and primaquine oral or Dapsone (oral) and trimethoprim (i.v./oral)	600 mg 3 × day 30 mg OD 100 mg OD 20 mg/kg OD (divided doses) daily for 2–3 weeks

been used. It has not shown to increase the vulnerability to other opportunistic infections, with the possible exception of candidiasis, herpes virus disease and cytomegalovirus disease. It is important to start the steroidal therapy at the same time the PCP treatment is initiated otherwise the benefit of the steroid is lost.

VII.a.2. Prophylaxis

In industrialised countries, every patient who has a CD4+ lymphocyte count of less than 200 mm^{-3}, or symptomatic disease (oral Candida, fevers, weight loss etc.) or another AIDS-defining illness such as Kaposi's sarcoma, or has been successfully treated for pneumonia due to *Pneumocystis carinii*, should receive continuous prophylaxis (Table 12). Prophylaxis can be stopped under ART when CD4 count is twice above 200 μl^{-1} Various estimates place the 3-month relapse rate among patients not receiving prophylaxis following a course of treatment for PCP at 10–40%; about one in five such episodes is fatal. In developing countries, where PCP is much less common, there have been no efficacy trials for the use of sulfamethoxazole/trimethoprim as PCP prophylaxis, though early results indicate it may be of benefit in reducing other HIV-associated infections.

Sulfamethoxazole/trimethoprim has been shown to be the best form of PCP prophylaxis and also provides protection against *Toxoplasma encephalitis*; therefore, every effort should be made to ensure that where possible patients receive it.

A recent trial showed that patients were more likely to tolerate sulfamethoxazole/trimethoprim if a low dose was used (800 mg/160 mg) three times a week), and it was as effective as the higher doses, although a higher dose daily may be preferable if the patient has a CD4+ count less than 100 mm^{-3} and is *Toxoplasma gondii* antibody positive. In patients that have experienced reactions to sulfamethoxazole/trimethoprim that are not considered serious (i.e. rash, fever, or mild elevations of liver function tests), either rechallenge or desensitisation should be attempted. It has been shown that in about 50% of patients this will allow continuation of sulfamethoxazole/trimethoprim.

VII.a.3. Desensitisation Schedule for Sulfamethoxazole/Trimethoprim

Sulfamethoxazole/trimethoprim has been shown to be the best agent for both the treatment and prophylaxis of PCP. It is therefore important that, where indicated, as many patients as possible receive sulfamethoxazole/trimethoprim and not other less effective medications. Desensitisation has been used as a method of increasing the number of patients able to tolerate sulfamethoxazole/trimethoprim.

Indications:

Patients who have a documented allergy, e.g. rash or itching due to sulfamethoxazole/trimethoprim and have failed rechallenge.

Contraindications:

Patients who have had a serious reaction to sulfamethoxazole/trimethoprim e.g. Stevens–Johnsons, anaphylaxis, hepatitis or pancreatitis.

Desensitisation of sulfamethoxazole/trimethoprim can be done over a day as an in patient or over 10 days as an out patient (Table 13(a) and (b)). Then continue with the regimen for *Pneumocystis carinii* pneumonia prophylaxis. If the regimen, to be used

Table 12. Prophylaxis for PCP

	Drug	Dose
1st choice	Sulfamethoxazole/trimethoprim oral	SMZ/TMP 800/160 mg OD
2nd choice	Dapsone oral or	50–100 mg OD[a] 100 mg 3 × week
	Dapsone oral and pyrimethamine[b] oral[c]	25 mg 3 × week
3rd choice	Sulfadoxine/pyrimethamine (fansidar)	1–2 tablets weekly
4th choice	Pentamidine (nebulised)	300 mg every 2–4 weeks

[a]The higher dose should be used if the patient is taking concurrent enzyme inducers e.g. rifampacin and/or drugs which increase gastric pH e.g. antacids, didanosine (ddI).

[b]When pyrimethamine is used if the patient is borderline neutropenic i.e. neutrophil count $< 1.0 \times 109\,l^{-1}$ folinic acid 15 mg orally should be given in conjunction.

[c]Dapsone and pyrimethamine should be used in patients that cannot tolerate sulfamethoxazole/trimethoprim with a CD4 count less than 100 mm^{-3} and Toxoplasma gondii antibody positive.

Table 13a. In patient desensitisation of sulfamethoxazole/trimethoprim

Time (hours)	Dose sulfamethoxazole (TMP)/trimethoprim (SMZ)
0	0.004/0.02 mg*
1	0.04/0.2 mg*
2	0.4/2 mg
3	4/20 mg*
4	40/200 mg*
5	160/800 mg*

*Dilute a solution containing 40 mg of TMP and 200 mg of SMZ per 5 ml.

Table 13b. Out patient desensitisation of sulfamethoxazole/trimethoprim

Day	Dose (mg)	Composition
1	2.4	1 ml 1 in 20 paediatric suspension
2	4.8	2 ml 1 in 20 paediatric suspension
3	9.6	4 ml 1 in 20 paediatric suspension
4	19.2	8 ml 1 in 20 paediatric suspension
5	28.8	0.6 ml paediatric suspension
6	60	1.25 ml paediatric suspension
7	120	2.5 ml paediatric suspension
8	240	5 ml paediatric suspension
9	480	10 ml paediatric suspension
10	480	One 480 mg tablet or half a 960 mg tablet
11	960	One 480 mg tablet or half a 960 mg tablet twice a day

is sulfamethoxazole/trimethoprim (cotrimoxazole) 480 mg daily, stop at day 10 and continue at this dose.

If sulfamethoxazole/trimethoprim cannot be continued due to intolerance or severe side effects dapsone may be given although a small percentage of patients may show cross intolerance.

Nebulized pentamidine at the dosage of 300 mg every two weeks should be used in patients with a CD4+ count less than 100 mm^{-3} if systemic therapy cannot be tolerated. Sulfadoxine/pyrimethamine (Fansidar), one tablet given once or twice a week, is useful in patients in whom compliance is considered to be a problem. However, it has been associated with hepatotoxicity, Stevens–Johnson syndrome and toxic epidermal necrolysis.

VII.b. Toxoplasmosis

Toxoplasmosis is caused by infection with the protozoan parasite *Toxoplasma gondii*. In the immunocompetent host most infections are self-limiting and do not require treatment. However, in immunodeficiency, primary infection may result in encephalitis, myocarditis or pneumonitis; impairment of immunity (such as occurs in AIDS) in a previously infected person, may result in encephalitis or meningoencephalitis. Congenital transmission may occur if there is a primary infection in early pregnancy or if the mother is immunodeficient. Such cases often result in spontaneous abortion, fetal death or severe congenital disease. Ocular toxoplasmosis causes chorioretinitis and is often the result of a childhood infection that becomes apparent in adulthood.

The treatment of choice for toxoplasmosis is pyrimethamine with sulfadiazine; a folate supplement is also given to counteract the megaloblastic

Table 14. Treatment and prophylaxis for toxoplasmosis

Primary treatment	Maintenance therapy (secondary prophylaxis)	Primary prophylaxis
Sulfadiazine 1–1.5 g orally or i.v. 6-hourly + Pyrimethamine 50 to 100 mg orally initially, then 25–50 mg daily	Sulfadiazine 500 mg orally 6-hourly or 1 g orally 12-hourly + Pyrimethamine 25 to 50 mg orally daily	Prophylaxis for *P. carinii* with cotrimoxazole is effective prophylaxis for toxoplasmosis

Table 15. Treatment for *Cryptococcal meningitis*

Primary treatment	Maintenance therapy (secondary prophylaxis)	Primary prophylaxis
Amphotericin 0.75 mg/kg i.v. daily for 2–4 weeks with or without Flucytosine 25 mg/kg i.v./orally 6-hourly for 14 days Alternative regimen: Fluconazole 400 mg daily for 8–10 weeks	Fluconazole 200 mg orally daily	Not indicated

anaemia associated with these drugs (Table 14). In cases of sulfadiazine hypertsensitivity clindamycin can be given.

VII.c. CMV Retinitis

Parenteral ganciclovir 5 mg/kg i.v. 12-hourly for 14–21 days arrests retinochoroiditis and enteritis caused by CMV in HIV-infected patients. Maintenance therapy with ganciclovir 10 mg/kg i.v. 3 times weekly should be given to prevent relapse of retinitis. Alternative therapy with intravenous foscarnet can be used if necessary.

VII.d. *Cryptococcal meningitis*

Intravenous amphotericin plus intravenous or oral flucytosine is the traditional treatment. There is an increasing role for fluconazole, particularly in maintenance therapy in acquired immunodeficiency syndrome (AIDS). The treatment for *Cryptococcal meningitis* is discussed in Table 15.

VII.e. Cryptosporidium

In immunocompetent patients cryptosporidium diarrhea is usually self-limiting.

In immunocompromised patients, crampy abdominal pain and prolonged severe watery diarrhoea occur. Fluid replacement and the use of antidiarrhoeals are the mainstay of treatment. In patients with acquired immunodeficiency syndrome (AIDS), ART will reduce symptoms. Nitazoxanide 500 mg TID or paromomycin (child: 7.5 mg/kg up to) 500 mg orally, 6-hourly may be tried in severe cases, but its value is controversial. Specialist advice should be sought.

VII.f. Histoplasmosis and Coccidioidomycosis

Patients with HIV infection are at risk of developing disseminated histoplasmosis and coccidioidomycosis. In otherwise healthy people such infections are usually subclinical, or self-limiting within the lungs.

The initial symptoms are often non-specific, but pulmonary involvement characterized by cough, fever, malaise and weight loss – and confirmed by radiological evidence of pulmonary interstitial infiltrates – can be prominent. Nausea, vomiting and diarrhoea are common. Haematogenous dissemination ultimately results in terminal septic shock.

Diagnosis is dependent upon demonstration of the organism in bronchoalveolar washings, biopsy material, or cultures from blood or bone marrow. In severely ill patients, initiation of treatment is warranted on the basis of clinical findings and a positive test for serum antibody.

VII.f.1. Treatment

Initial treatment for histoplasmosis is amphotericin B for moderate-to-severe cases, and oral itraconazole for mild cases. Maintenance therapy is then

required. Itraconazole is the preferred lifelong maintenance therapy, although amphotericin can be given weekly or biweekly. The bioavailability of itraconazole should be improved by ensuring that it is taken with food or the liquid formulation is used. Fluconazole is not as effective as itraconazole for the treatment and maintenance of histoplasmosis. Fluconazole has been used with some success for the treatment of coccidiodomycosis in patients that have been unable to tolerate amphotericin B.

1st choice:

Amphotericin B (0.5–1 mg/kg/day for 6 weeks).

2nd choice:

Histoplasmosis – Itraconazole (200 mg 3× day, 3–4 days, then 200 mg 2× day) for 6 weeks;

Coccidioidomycosis–Fluconazole (400 mg/day) for 6 weeks.

VIII. TUBERCULOSIS

The reason that it was decided to discuss the treatment of tuberculosis in a chapter together with HIV/AIDS is because tuberculosis is the most deadly opportunistic infection in people with HIV/AIDS, certainly in resource poor settings. We still felt that in this chapter tuberculosis should be a section on its own as also outside the HIV/AIDS context, tuberculosis poses a grave and growing threat to global public health.

VIII.a. *Mycobacterium tuberculosis*

Infection with *Mycobacterium tuberculosis*, in short Tuberculosis or TBC, is the commonest cause of death in people with HIV infection world-wide. There are indications of a resurgence of tuberculosis almost everywhere where HIV is prevalent. HIV infection increases a person's susceptibility to and progression of infection with *M. tuberculosis*. In an individual infected with HIV the presence of other infections including TBC allows HIV to multiply more quickly. This may result in more rapid progression of HIV infection.

The initial signs of disease may become apparent at any time during the evolution of HIV infection. In HIV-infected patients TBC may be pulmonary or extra-pulmonary. Pulmonary TBC is still the most common form of TBC. The presentation depends on the degree of immunosuppression. In advanced HIV disease the immune system is less able to prevent the growth and local spread of *M. tuberculosis*; thus, disseminated and extrapulmonary disease is more common, and unilateral or bilateral infiltrates in the lower lobes are seen more often than upper lobe lesions and cavities. The commonest forms of extrapulmonary disease are lymphadenitis, pleural effusion, pericarditis, military disease and meningitis.

VIII.a.1. Screening

Tuberculin skin testing is an important part of the care of all HIV-1-infected patients or persons at risk for HIV-1 infection. Tuberculin skin testing should be done using the Mantoux method. A tuberculin reaction of $\geqslant$5 mm of induration is classified as positive in persons known to have or suspected of having HIV-1 infection. Unfortunately, as the CD4 lymphocyte count declines with progression of HIV-1 disease, many patients no longer react to delayed-type hypersensitivity testing. More than 60% of persons with CD4 lymphocyte counts of $<$200 cells/μl may have skin test reactions of $<$5 mm. Thus, it is impossible to detect the presence of tuberculous infection in many HIV-1-infected individuals.

VIII.a.2. Evaluation

All patients who have a positive tuberculin skin test should have a chest radiograph performed in order to rule out the possibility of active disease. Patients should be asked about any symptoms (e.g. chronic cough, night sweats, fever, and weight loss) which suggest the presence of active TBC. Persons who are found to have an abnormal chest radiograph and/or are symptomatic should be evaluated for the possibility of active disease by sending three sputum specimens for AFB (Acid Fast Bacilli) smear and culture.

VIII.a.3. Treatment of TBC

Despite being immunocompromised, HIV-1-infected patients with TBC respond well to antituberculosis therapy, as long as the regimen contains INH and rifampicin. The current treatment guidelines recommend that all adult patients with TBC be treated similarly, regardless of HIV-1 serostatus (Table 16).

Because the effect of patient adherence on the outcome is much more critical, directly observed therapy (DOT) is strongly recommended for persons with HIV-1 infection to ensure that the patient takes every single prescribed dose. This protects against

Table 16. Dosage recommendations for treatment of tuberculosis

Drug	Dose			Adverse reactions	Comments
	Daily	2/week*	3/week*		
Isoniazid	(child: 10 mg/kg up to) 300 mg orally, for 6 months	15 mg/kg orally, for 6 months	15 mg/kg orally, for 6 months	Hepatic enzyme elevation Hepatitis Peripheral neuropathy CNS (mild) Drug interactions	Hepatitis risk increases with age and alcohol consumption. Pyridoxine can prevent peripheral neuropathy
Rifampicin	(child: 10 mg/kg up to) 600 mg (<50 kg: 450 mg) orally, for 6 months	15 mg/kg up to 900 mg orally, for 6 months	15 mg/kg up to 600 mg orally, for 6 months	GI upset Hepatitis Bleeding problem Flu-like symptoms Rash	Significant interactions with many drugs. Colors body fluids orange. May discolor soft contact lenses
Pyrazinamide	2 g (<50 kg or child: 35 mg/kg up to 1.5 g) orally, for 2 months	3.5 g (<50 kg or child: 75 mg/kg up to 3 g) orally, for 2 months	2.5 g (<50 kg or child: 50 mg/kg up to 2 g) orally, for 2 months	Hepatic impairment Renal impairment; arthralgia Gout	Blood glucose may change suddenly, monitor
Ethambutol	(child 6 years or older) 15 mg/kg orally, for 2 months	(child 6 years or older) 45 mg/kg orally, for 2 months	(child 6 years or older) 30 mg/kg orally, for 2 months	Optic neuritis	Not recommended for children too young to be monitored for changes in vision unless tuberculosis is drug resistant

*All regimens administered 2 or 3 times a week must be used with directly observed therapy (DOT).

the development of drug resistance. The risk of drug resistance is higher during the early stages of anti-TBC drug treatment when the number of TBC bacilli is very high.

Antituberculosis chemotherapy should be supplemented with pyridoxine (B_6). Patients should be monitored closely for adverse reactions.

Treatment regimens have an initial (intensive) phase and a continuation phase. The initial phase lasts for 2 months. During this phase there is rapid killing of TBC bacilli, infectious patients become non-infectious within about two weeks and symptoms improve. The vast majority of patients with smear-positive TBC become sputum smear negative within 2 months.

The continuation phase lasts for four to six months. A 6-month regimen consisting of INH, rifampicin, pyrazinamide and ethambutol (or streptomycin) given for 2 months followed by INH and rifampicin for 4 months is the preferred treatment for drug susceptible organisms. Pyrazinamide should be continued for the first 2 months regardless of the results of drug-susceptibility testing, whereas ethambutol can be stopped after drug susceptibility test results indicate that *M. tuberculosis* is sensitive to INH and rifampicin.

VIII.a.4. Paradoxical Reaction

Occasionally, patients with TBC may experience a temporary exacerbation of symptoms after beginning TBC treatment. This is known as a paradoxical reaction and has been noted to occur in HIV-1-infected patients with active TBC. These reactions are often related to the simultaneous administration of both antiretroviral and antituberculosis medica-

tions. Symptoms and signs include high fevers, lymphadenopathy, worsening of chest radiographic findings, and worsening of original TBC lesions.

The diagnosis of a paradoxical reaction should be made only after a thorough evaluation has been made to exclude other etiologies. Some patients have required the use of corticosteroids (in addition to TBC treatment) to treat these reactions.

The decision to use corticosteroids must be made on a case-by-case basis. Indications may include severe hypoxemia, airway obstruction, neurologic impairment, or possibly enlarged painful lymph nodes.

VIII.a.5. Reasons for Treatment Failure

Because the margin of error for treatment failure and relapse is probably less in HIV-1 infected patients, the 6-month regimen should be considered the minimum duration of treatment. Delayed response to treatment is defined by the presence of either of the following after the 2-month induction phase of therapy:

Patients continue to be culture-positive for *M. tuberculosis* or patients do not experience resolution of signs or symptoms of TBC (e.g. persistent fever, progressive weight loss, increase in size of lymph nodes, none of which can be explained by a disease other than TBC).

Patients having a delayed response to treatment should have treatment prolonged to 9 months (or 4–6 months after culture conversion is documented). Malabsorption of the antituberculosis should be considered as a possible cause of treatment failure or the acquisition of drug resistance, particularly if gastrointestinal symptoms or chronic diarrhea is present.

VIII.a.6. Drug Interactions between ART and Rifampicin

The nucleoside agents do not have clinically significant drug interactions with the standard antituberculosis medications. However, the PIs and NNRTIs may inhibit or induce cytochrome P-450 isoenzymes (CYP450) and thus, these drugs may alter the serum concentration of the rifamycins (Table 17(a) and (b)).

The rifamycins induce CYP450 and may substantially decrease blood levels of the antiretroviral drugs resulting in the potential development of resistance to these agents. The potential benefit of the antiretroviral drugs must be weighed against the importance of rifamycins in treating HIV-1-related tuberculosis. The loss of a rifamycin from the treatment regimen is likely to delay sputum conversion, prolong the duration of therapy, and possibly result in a poorer outcome.

Previous guidelines specifically stated that rifampicin was contraindicated for patients who were taking any PI or NNRTI. New data indicate that rifampicin can be used for the treatment of tuberculosis in three situations:

- In a patient whose antiretroviral regimen includes the NNRTI, efavirenz, and two NRTIs.
- In a patient whose antiretroviral regimen includes the PI, ritonavir, and one or more NRTIs.
- In a patient whose antiretroviral regimen includes the combination of two PIs (ritonavir and either hard-gel or soft-gel saquinavir).

In some patients, the combination of antiretroviral agents may be so complex that the use of antituberculosis regimens containing no rifamycins may be considered. For such patients, a 9-month, largely intermittent, regimen consisting of isoniazid, streptomycin, pyrazinamide and ethambutol for 2 months then isoniazid, streptomycin, and pyrazinamide for 7 months is an option.

VIII.a.7. Treatment of Latent Tuberculosis Infection

Treatment of latent tuberculosis infection (LTBI) with isoniazid (INH) is very effective in preventing persons infected with *M. tuberculosis* from developing tuberculosis, regardless of HIV-1 serostatus. Several recent studies have shown that rifampicin and pyrazinamide taken for 2 months is as effective as 6–12 months of INH for the prevention of active TBC in HIV-1 seropositive persons although more hepatotoxicity is seen.

HIV-1 seropositive persons should be treated for LTBI if they have a tuberculin skin test $\geqslant$5 mm and have not previously received treatment for LTBI. In certain cases, treatment of LTBI in persons who are not tuberculin positive may also be considered. Such therapy may be beneficial for:

- close contacts to an infectious case persons with a history of prior untreated or inadequately treated TBC who have fibronodular opacities on a chest radiograph (if active TBC is ruled out);
- HIV-1-infected adults who reside or work in institutions and are continually and unavoidably exposed to patients who have infectious TBC.

Table 17a. Protease inhibitors and rifampicin

Protease inhibitors	Use in combination with rifampicin	Comments
Saquinavir*		
Hard-gel capsules (invirase, Roche; als mesylate)	Possibly, if antiretroviral regimen also includes ritonavir	Coadministration of saquinavir SGC with usual-dose rifampicin (600 mg daily or two or three times per week) is a possibility. However, the pharmacokinetic data and clinical experience for this combination are limited
Soft-gel capsules (fortovase, Roche; F is 3 × hoger)	Possibly, if antiretroviral regimen also includes ritonavir	The combination of saquinavir SGC or saquinavir HGC and ritonavir, coadministration with usual-dose rifampicin (600 mg daily or two or three times per week) is a possibility. However, the pharmacokinetic data and clinical experience for these combinations are limited. Coadministration of saquinavir HGC or saquinavir SGC with rifampicin (in the absence of ritonavir) is not recommended because rifampicin markedly decreases concentration of saquinavir
Ritonavir	Probably	Coadministration of ritonavir with usual-dose rifampicin (600 mg daily or two or three times per week) is a possibility, though pharmacokinetic data and clinical experience are limited
Indinavir	No	Coadministration of indinavir with rifampicin is not recommended because rifampicin markedly decreases concentrations of indinavir
Nelfinavir	No	Coadministration of nelfinavir with rifampicin is not recommended because rifampicin markedly decreases concentrations of nelfinavir
Amprenavir	No	Coadministration of amprenavir with rifampicin is not recommended because rifampicin markedly decreases concentrations of amprenavir

*Usual recommended doses are 400 mg two times per day for each of these protease inhibitors and 400 mg of ritonavir.

Table 17b. NNRTIs and rifampicin

NNRTIs	Use in combination with rifampicin	Comments
Nevirapine	Possibly	Data are insufficient to assess whether dose adjustments are necessary when rifampicin is co administered with nevirapine. Therefore, rifampicin and nevirapine should be used only in combination if clearly indicated and with careful monitoring
Delavirdine	No	Contraindicated because of the marked decrease in concentrations of delavirdine when administered with rifampicin
Efavirenz	Probably	Coadministration of efavirenz* with usual-dose rifampin (600 mg daily or two or three times per week) is a possibility, however an increased dose of 800 mg efavirenz is recommended

*At the time of writing not all data on potential drug–drug interactions are available.

VIII.a.8. TBC Preventive Therapy

There is evidence showing the efficacy of TBC preventive therapy among HIV-infected people. TBC preventive therapy can be given to people with HIV who have been screened to exclude active TBC and who are PPD positive. Isoniazid is the recommended drug. A dose of 5 mg/kg (maximum 300 mg) may be given daily as self-administered therapy for 6 months.

VIII.a.9. People with Tuberculosis and HIV Co-infection

WHO recommends that people with TB/HIV complete their TBC therapy prior to beginning ARV treatment unless there is a high risk of HIV disease progression and death during the period of TBC treatment (i.e., a CD4 count <200 mm^{-3} or disseminated TBC is present). Paradoxical worsening of the TBC after starting treatment, side effects of all the drugs causing non-adherence to ART, drug interactions and liver toxicity are arguments to delay ART in a TB–HIV-co-infected patient for 2 months (after the induction phase is over).

In cases where a person needs TBC and HIV treatment concurrently, first line treatment options include ZDV/3TC or d4T/3TC plus either a non-nucleoside or ABC (Table 18). If a non-nucleoside regimen is used, EFV would be the preferred drug as its potential to aggravate the hepatotoxicity of TBC treatment appears less than that of NVP. However, its dosage may need to be increased to 800 mg/day. Except for SQV/r, protease inhibitors are not recommended during TBC treatment with rifampicin due to their interactions with the latter drug.

VIII.b. Mycobacterium Avium Complex (MAC)

Infection with Mycobacterium avium or Mycobacterium intracellulare occurs in patients with the acquired immunodeficiency syndrome. These organisms infrequently cause lung disease in older adults and children with normal immunity but abnormal lungs.

A triple therapy regimen with combinations of clarithromycin or azithromycin plus ethambutol plus rifabutin is the current standard of care. However rifabutin may be omitted in HIV-infected patients on protease inhibitors because of significant interactions (Table 19).

Quinolones are an alternative. Results of in vitro susceptibility tests do not always correlate with clinical effect and treatment should not necessarily be altered in the light of such results. Duration of treatment (usually >9 months) depends particularly on the response and on the recovery of immunity after ART.

Table 18. Antiretroviral therapy for individuals with tuberculosis co-infection

Situation	Recommendations
Pulmonary TBC and CD4 count < 50 mm^{-3} or extrapulmonary TBC	Start TBC therapy. Start one of these ART's as soon as TBC therapy is tolerated: • ZDV/3TC/ABC • ZDV/3TC/EFV • ZDV/3TC/SQV/r • ZDV/3TC/NVP
Pulmonary TBC and CD4 50–200 mm^{-3} or total lymphocyte count below 1200 mm^{-3}	Start TBC therapy. Start one of these regimens after completing 2 months of TBC therapy: • ZDV/3TC/ABC • ZDV/3TC/EFV • ZDV/3TC/SQV/r • ZDV/3TC/NVP
Pulmonary TBC and CD4 > 200 mm^{-3} or total lymphocyte count 1200 mm^{-3}	Treat TBC. Monitor CD4 counts if available. Start ART according the recommendations for adults or children after completion of TBC treatment

Table 19. ***Mycobacterium avium*** **complex treatment**

Primary treatment	Maintenance therapy (secondary prophylaxis)	Primary prophylaxis
Clarithromycin 500 mg orally 12-hourly or Azithromycin 600 mg orally daily + Ethambutol 15–25 mg/kg orally daily	As for primary treatment	• Recommenced when CD4 cell count 50–75 mm^{-3} • Azithromycin 1.2 g orally weekly

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Chapter 34

Cardiovascular and Renal Diseases A: Pharmacotherapy of Hypertension

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I. INTRODUCTION

There are about 500 million subjects suffering from hypertension in the world with a global population of about 6 billion. Developing countries contribute a greater share to the global burden of cardiovascular disease than the developed countries. Yet it has received less comment and little public health attention, even within these countries. A World Health Organization analysis showed that the prevalence of hypertension in developing countries varied from 1% in some African countries to more than 30% in Brazil. A cost analysis of possible antihypertensive therapy indicates that the developing countries cannot afford the same treatment as developed countries.

I.a. Self-measurement of Blood Pressure (BP)

The BP tends to be higher when measured in the clinic than outside the office. Whilst there is no agreed-on upper limit, BP readings of 135/85 or greater should be considered elevated. Self-measurement of BP has four advantages; it can help in distinguishing "white-coat" hypertension, in assessing response to antihypertensive agents, in improving patient's adherence to therapy and potentially in reducing costs.

I.b. Ambulatory Blood Pressure (ABP)

ABP is clinically most useful in patients with suspected "white-coat hypertension". It is also helpful in patients with apparent drug resistance, hypotensive symptoms with antihypertensive agents, episodic hypertension and autonomic dysfunction. However, this procedure should not be used indiscriminately, such as in the routine evaluation of patients with suspected hypertension.

I.c. Risk Stratification

Among patients with mild hypertension, differences in the risks of cardiovascular disease are determined not only by the level of BP, but also by the presence or levels of other risk factors (see Table 1). For example, a man aged 65 years with diabetes, a history of transient ischaemic attacks and a systolic–diastolic blood pressure (SBP–DBP) of 145/90 mmHg will have an annual risk of a major cardiovascular event that is more than 20 times greater than that in a man aged 40 years with the same BP but without either diabetes or a history of cardiovascular disease. In contrast, a man aged 40 years with a SBP–DBP of 170/105 mmHg will have a risk of a major cardiovascular event that is about two or three times greater than that of a man of the same age and similar other risk factor levels but with a SBP/DBP of 145/90 mmHg.

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Table 1. Components of cardiovascular risk stratification (adapted from Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure, 2003)

Major risk factors
Hypertension*
Cigarette smoking
Obesity* (body mass index $\geqslant 30$ kg/m^2)
Physical inactivity
Dyslipidemia*
Diabetes mellitus*
Microalbuminuria or estimated GFR < 60 ml/min
Age (older than 55 for men, 65 for women)
Family history of premature cardiovascular disease (men under age 55 or women under age 65)
Target organ damage/clinical cardiovascular disease
Heart diseases
Left ventricular hypertrophy
Angina or prior myocardial infarction
Prior coronary revascularization
Heart failure
Stroke or transient ischemic attack
Nephropathy
Retinopathy
Peripheral arterial disease

*Components of the metabolic syndrome.
GFR, glomerular filtration rate.

Thus, differences in the absolute level of cardiovascular risk between patients with hypertension will often be determined to a greater extent by other risk factors than by the level of blood pressure. The stratification of risk to quantify prognosis is shown in Table 1.

I.d. Hypertension versus Normotension

The definition and classification of blood pressure levels is shown in Table 2. BP levels are continuously related to the risks of cardiovascular disease and the definition of hypertension (or raised BP) is, therefore, arbitrary. Much BP-related disease occurs among individuals who would normally be considered normotensive. Most of the evidence about the benefits and risks of lowering BP comes from studies in patients selected on the basis of high BP. It is not clear whether estimates of treatment effect obtained from trials in hypertensives can be extrapolated to individuals with lower BP levels. There is a strong rationale for expecting high-risk patients without hypertension to benefit from BP lowering and trials are required to investigate this possibility.

Table 2. Classification of blood pressure for adults aged 18 years and older (adapted from Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure, 2003)

Category	Blood pressure (mmHg)		
	Systolic[1]		Diastolic[1]
Normal	<120	and	<80
Prehypertension[2]	120–139	or	80–89
Stage 1	140–159	or	90–99
Stage 2	>160	or	>100

[1]Treatment determined by highest BP category.
[2]Based on the average of two or more readings taken at each of two or more visits after an initial screening.

I.e. Interventions to Reduce Cardiovascular Risk in Hypertensive Patients

I.e.1. Effects of Blood Pressure Lowering treatments on Mortality and Morbidity from Cardiovascular Disease; Trials of Diuretic and β-Blocker-Based Regimens

Previous randomized controlled trials of diuretic- or β-blocker-based regimens, involving a total of about 47,000 patients with hypertension, have collectively demonstrated that, over an average of about 5 years, such treatment produced much of the epidemiologically expected benefit of the achieved BP reductions. A net reduction of 5–6 mmHg in usual DBP was associated with a 38% reduction in stroke risk and a 16% reduction in coronary heart disease (CHD) risk, with similar effects on fatal and non-fatal events.

I.e.2. Underestimation of the Effects of Blood Pressure Lowering Treatment in Randomized Controlled Trials

Estimates of treatment effects in the trials of BP lowering regimens generally provide conservative estimates of the full potential effects of treatment. In the trials, there was considerable cross-over between treatment groups. A proportion of patients assigned to active therapy groups stopped treatment; and a proportion of those assigned to control groups began active treatment.

Such cross-over is likely to have reduced the average difference in DBP between groups by 1–2 mmHg, in which case, the full relative effects of treatment on stroke and coronary heart disease

would be somewhat greater than the effects observed. The average duration of treatment in the trials was only about 5 years, and it is possible that longer-term treatment over many years, as is usual for hypertensive patients, might have led to larger relative risk reductions. To many trials low risk patients were recruited and the absolute effects of treatment among higher-risk patients seen in broader clinical practice are therefore likely to be greater than those typically observed.

I.e.3. Trials of Other Treatment Regimens

Data on the effect of calcium antagonists on cardiovascular disease risks in patients with hypertension are available from one moderate-to-large scale randomized, placebo-controlled trial. In the Systolic Hypertension in Europe (Syst-Eur) trial, nitrendipine-based therapy produced an approximate 10/5 mmHg reduction in SBP–DBP in patients with systolic hypertension and a 42% reduction in the risk of stroke. Similar results were observed in two large, nonrandomized, placebo-controlled trials (with alternate treatment assignment), i.e. the Shanghai Trial of Nifedipine in the Elderly and the Systolic Hypertension in China (Syst-China) trial.

I.f. Relative and Absolute Effects of Treatment

The relative effect of treatment reflects the proportional difference between treatment groups in the incidence of disease events. In the Systolic Hypertension in the Elderly (SHEP) trial, the incidence of major CHD events over 4.5 years in patients assigned active treatment was 4.4% while in those assigned placebo it was 5.9%. This represents a relative risk of 0.73 or a relative risk reduction of 27%.

However, the absolute effect of treatment is generally of greatest interest to doctors and patients. In the SHEP trial the absolute reduction in CHD risk over 4.5 years was 1.4%. This indicates that 14 events were prevented among every 1000 patients assigned active treatment, and that one major CHD event was avoided among every 71 patients assigned active treatment. Estimates of *relative* treatment effects from randomized trials provide a guide to the likely relative effects of treatment in other non-study patient populations. However, estimates of *absolute* treatment effects from trials of BP lowering are of limited generalizability because complex inclusion and exclusion criteria frequently resulted in the recruitment of patients at lower average risk than those seen in broader clinical practice.

The best predictor of absolute treatment effects for any individual patient will be provided by application of the estimate of the relative risk reduction from trials to an estimate of the absolute disease risk for the individual in question.

I.g. Absolute Effects of Treatment on Cardiovascular Risk

From the results of randomized controlled trials, it appears that each reduction of 10–14 mmHg in SBP and 5–6 mmHg in DBP confers about two-fifths less stroke, one-sixth less CHD and, in Western populations, one-third less major cardiovascular events overall. In patients with grade 1 hypertension, monotherapy with most agents will produce reductions in SBP–DBP of about 10/15 mmHg. In patients with higher grades of hypertension, it is possible to achieve sustained BP reductions of 20/10 mmHg or more, particularly if combination drug therapy is used. The estimated absolute effects of such BP reductions on cardiovascular disease risks (fatal plus nonfatal stroke or myocardial infarction) are as follows: Between these strata, the estimated absolute treatment benefits will range from less than five events prevented per thousand patient years of treatment (low risk) to more than 17 events prevented per thousand patient years of treatment (very high risk). The absolute benefits for stroke and CHD will be augmented by smaller absolute benefits for congestive heart failure and renal disease. These estimates of benefit are based on relative risk reductions observed in trials of about 5 years' duration. Longer-term treatment over decades could produce larger risk reductions.

II. CLASSIFICATION OF HYPERTENSION

In contrast to the classification provided in the JNC 6 (1997) report, a new category designated prehypertension has been added, and stages 2 and 3 hypertension have been combined. Patients with prehypertension are at increased risk for progression to hypertension; those in the 130–139/80–89 mmHg BP range are at twice the risk to develop hypertension as those with lower values in the JNC 7 report (see The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, 2003). Patients

Table 3. Recommendations for follow-up based on initial blood pressure measurements for adults (Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure, 1997)

Initial blood pressure (mmHg)*		Follow-up recommended**
Systolic	Diastolic	
<130	<85	Recheck in 2 years
130–139	85–89	Recheck in 1 year*
140–159	90–99	Confirm within 2 months***
180–179	100–109	Evaluate or refer to source of care within 1 month
>180	>110	Evaluate or refer to source of care immediately or within 1 week depending on clinical situation

*If systolic and diastolic categories are different, follow recommendations for shorter follow-up (e.g. 160/86 mmHg should be evaluated or referred to source of care within 1 month).
**Modify the scheduling of follow-up according to reliable information about past blood pressure measurements, other cardiovascular risk factors, or target organ disease.
***Provide advice about life-style modifications.

with prehypertension are at increased risk for progression to hypertension; those in the 130–139/80–89 mmHg BP range are at twice the risk to develop hypertension as those with lower values.

Table 3 gives recommendations for follow-up based on initial BP measurements.

III. PREVENTION AND TREATMENT OF HIGH BLOOD PRESSURE

Before considering active treatment an even greater need is the prevention of the disease. Primary prevention is necessary because a significant proportion of patients have a risk profile which is not high enough for the BP to be treated with drugs. A population-wide effort to lowering BP can reduce this risk. Furthermore, active treatment of established hypertension poses financial costs and potential adverse effects of drugs.

Most patients with established hypertension do not make sufficient lifestyle changes, do not take medication or do not take enough medication to achieve control. Even if adequately treated, patients may not lower their risk to that of persons with normal BP. It has to be emphasized that BP rise and high BP are not inevitable consequences of aging. Therefore an effective population-wide strategy to prevent BP rise with age could affect overall cardiovascular morbidity and mortality as much or more than that of treating only those with established hypertension. A population-wide approach has been shown to prevent or delay the expected rise in BP in susceptible people. A recent study has shown that a diet rich in fruit, vegetables and low-fat dairy foods and with reduced amounts of saturated and total fats, significantly lowers BP. This diet was also low in cholesterol, high in dietary fibre, potassium, calcium and magnesium, moderately high in protein and based on 2000 calories a day (8000 kJ/day).

For patients with SBP between 140 and 159 mmHg and DBF between 90 and 99 mmHg, the impact of the patient's life-style should be evaluated. It is recommended to firstly evaluate over 1 year (versus previously 3–6 months) before considering the implementation of pharmacological treatment (Table 4).

III.a. Goals

The goal of prevention and management of hypertension is to reduce morbidity and mortality. This is obtained by achieving and obtaining SBP below 140 mmHg and DBP below 90 mmHg and lower if tolerated. This is achieved by life-style modification alone or with added pharmacologic treatment (Table 5).

III.b. Life-Style Modifications

This consists of weight reduction, physical activity, moderation of dietary sodium and high dietary potassium intake. Implementation of lifestyle modifications should not delay the start of effective antihypertensive drug therapy. Patients with renal insufficiency with proteinuria greater than 1 g/day should be treated to a BP goal of 125/75 mmHg;

Table 4. Risk stratification and treatment*

Blood pressure stages	Risk group A (no risk factors; no TOD/CCDH)**	Risk group B (at least 1 risk factor, not including diabetes; no TOD/CCD)	Risk group C (TOD/CCD and/or diabetes, with or without other risk factors)
High–normal (130–139/85–89)	Life-style modification	Life-style modification	Drug therapy****
Stage 1 (140–159/90–99)	Life-style modification (up to 12 months)	Life-style modification*** (up to 6 months)	Drug therapy
Stages 2 and 3 (>160/>100)	Drug therapy	Drug therapy	Drug therapy

*Note: For example, a patient with diabetes and a blood pressure of 142/94 mmHg plus left ventricular hypertrophy should be classified as having Stage 1 hypertension with target organ disease (left ventricular hypertrophy) and with another major risk factor (diabetes). This patient would be categorized as Stage 1, risk group C, and recommended for immediate initiation of pharmacologic treatment. Life-style modification should be adjunctive therapy for all patients recommended for pharmacologic therapy.

**TOD/CCD, target organ disease/clinical cardiovascular disease.

***For patients with multiple risk factors, clinicians should consider drugs as initial therapy plus life-style modifications.

****For those with heart failure, renal insufficiency, or diabetes.

those with less proteinuria should be treated to a BP goal of 130/85 mmHg. Angiotensin converting enzyme (ACE) inhibitors have additional renoprotective effects over other antihypertensive agents. Patients with diabetes should be treated to a BP goal of below 130/80 mmHg.

III.b.1. Trials of Different Blood Pressure Targets

The Hypertension Optimal Treatment (HOT) trial used a calcium antagonist (felodipine)-based regimen (with the stepped addition of ACE inhibitors, β-blockers and diuretics) to investigate the effects of lowering blood pressure to three different targets (<80 mmHg, <85 mmHg and <90 mmHg) in 18,790 hypertensive patients. By the end of follow-up, BP had been substantially reduced in all three groups but there were only modest differences in SBP and DBF (about 2 mmHg) between adjacent target groups. These BP differences were less than expected, and the study was not able to determine reliably the most plausible effect of such modest BP differences. There was a non-significant trend towards lower cardiovascular event risk and a marginally significant trend towards fewer CHD events in the group with the lowest target. In the subgroup with diabetes, the trend for total cardiovascular events reached statistical significance. This is consistent with evidence from UKPDS 38 (UK Prospective Diabetes Study Group, 1998), demonstrating that a lower blood pressure target (using either ACE-inhibitor or β-blocker-based therapy) was associated with reduced risks of major macrovascular events as well as microvascular disease outcomes.

III.b.2. Life-Style and Blood Pressure

It is important that life-style measures be instituted within the framework of a structured plan that includes the use of counselling and monitoring by appropriate health professionals such as nurses, dieticians, clinical psychologists and other therapists, as well as the responsible physician. Recommendations should be tailored for each individual and greater use should be made of modern and well-validated counselling techniques.

Life-style measures that are widely agreed to lower blood pressure and that should be considered in all patients in whom they may apply are weight reduction, reduction of excessive alcohol consumption, reduction of high salt intake and increase in physical activity. Particular emphasis should be placed on cessation of smoking and on healthy eating patterns that contribute to the treatment of associated risk factors and cardiovascular diseases.

III.c. Drug Treatment for Lowering Blood Pressure

The six main drug classes used, worldwide, for blood pressure lowering treatment are diuretics, β-blockers, calcium channel blockers (CCB), ACE inhibitors, angiotensin II (AII) receptor blockers and α-adrenergic blockers. In some parts of the world, reserpine and methyldopa are also frequently used.

III.c.1. Benefits of Drug Treatment

All classes of antihypertensive drugs have specific advantages and disadvantages for particular patient groups. There is as yet no evidence that the main benefits of treating hypertension are due to any particular drug property rather than to lowering of BP *per se.* The randomized trials conducted to date have not provided any clear evidence of differential effects on outcome of different agents producing the same blood pressure reduction. However, most individual studies have been too small to detect plausibly modest differences in important outcomes such as stroke or myocardial infarction.

At the time of writing no less than 41 systematic reviews on pharmacotherapy for hypertension could be found in the Cochrane database. For a review on antihypertensive treatment in the elderly fifteen trials including 21,908 elderly subjects were identified. The reviewers' conclusions were: "Randomized controlled trials establish that treating healthy older persons with hypertension is highly efficacious. Benefits of treatment with low dose diuretics or β-blockers are clear for persons in their 60–70s with either diastolic or systolic hypertension. Differential treatment effects based on patient risk factors, pre-existing cardiovascular disease and competing co-morbidities could not be established from the published trial data'. An other important review dealt with the treatment of hypertension in diabetic patients. For this review fifty studies (13,215 patients) had data available for analysis. The reviewers' conclusions were: "Although the survival benefits of angiotensin converting enzyme inhibitors (ACEi) are known for patients with diabetic kidney disease, the relative effects on survival of ACEi compared to angiotensin II receptor antagonists are unknown due to the lack of adequate direct comparison studies".

III.c.2. Principles of Drug Treatment

There is general agreement on the principles governing the use of antihypertensive drugs to lower BP, independent of the choice of particular drugs. (Table 5). These principles (WHO-ISH 1999) include:

1. The use of low doses of drugs to initiate therapy, beginning with the lowest available dose of the particular agent, in an effort to reduce adverse effects. If there is a good response to a low dose of a single drug but the pressure is still short of adequate control, it is reasonable to increase the dose of the same drug, provided that it has been well tolerated.
2. Changing to a different drug class altogether if there is very little response or poor tolerability to the first drug used, before increasing the dose of the first drug or adding a second drug.
3. The use of appropriate drug combinations.
4. The use of long-acting drugs providing 24 h efficacy on a once-daily basis. The advantages of such drugs include improvement in adherence to therapy and minimisation of BP variability, as a consequence of smoother, more consistent BP control. This may provide greater protection against the risk of major cardiovascular events and the development of target-organ damage.

III.c.3. Initiation of Drug Treatment

For patients in the high- and very-high-risk groups drug treatment should be instituted within a few days, as soon as repeated measurements have confirmed the patient's BP. For patients in the medium- and low-risk groups the initiation of drug therapy will be influenced by: (1) consultation with the patient on preferred strategies; (2) the degree of BP lowering achieved with life-style measures; (3) the degree of control achieved for other risk factors; and (4) the availability of resources in the prevailing health system.

III.c.4. Pharmacological Treatment

Low-dose diuretics and β-blockers, which have demonstrated positive effects on mortality, are indicated as first choice treatment. This is still maintained in the new recommendations for patients with uncomplicated hypertension (Table 5). However, other treatments are recommended for hypertensive patients with associated diseases (Table 6). Hypertension with diabetes or renal dysfunction must be treated with an ACE inhibitor in the first instance. Patients with myocardial infarction should be treated with β-blockers and in specific cases with an ACE inhibitors. For patients with heart failure, the treatment of choice is an ACE inhibitor and diuretics. For older patients with isolated SBP, low-dose diuretics are recommended as the first step treatment and some of the CCB with long acting profile can be considered an "alternative" treatment.

III.c.4.1. Choice of antihypertensive drugs. The guidelines for selecting individual treatment are

Table 5. Algorithm for the treatment of hypertension

Begin or continue life-style medications	
Not at goal blood pressure (<140/90 mmHg)	
Lower goals for patients with diabetes or renal disease	
Initial drug choices (unless contraindicated)	
Uncomplicated hypertension (based on randomized controlled trials)	
Diuretics ACE inhibitors or CCB	
Compelling indications	Specific indications for the following drugs
(based on randomized controlled trials)	(see Table 6)
Diabetes mellitus (type 1) proteinuria	ACE inhibitors
ACE inhibitors	Angiotensin II receptor blockers
Heart failure	α-blockers
ACE inhibitors	α-, β-blockers
Diuretics	β-blockers
Isolated systolic hypertension (older persons)	Calcium antagonists
Diuretics preferred	Diuretics
Long-acting	
Dihydropyridine calcium	
Antagonists	
Myocardial infarction	
β-blockers (non-ISA)	
Ace inhibitors (with systolic dysfunction)	
Start with a low-dose of a long-acting once-daily drug, and *titrate dose*	
Low-dose combinations may be appropriate	
Not at goal blood pressure	
No response or troublesome side effects	Inadequate response but well tolerated
Substitute another drug from different class	Add second agent from different class (diuretic if not already used)
Not at goal blood pressure	
Continue adding agents from other classes	
Consider referral to a hypertension specialist	

ACE – angiotensin converting enzyme; ISA – intrinsic sympathominetic activity.

shown in Tables 6 and 7. All available drug classes are suitable for the initiation and maintenance of anti-hypertensive therapy, but the choice of drugs will be influenced by many factors, including socio-economic factors that determine drug availability in different countries or regions. The cardiovascular risk factor profile of the individual patient; the presence of target-organ damage, of clinical cardiovascular disease, renal disease and diabetes. The presence of other co-existing disorders that may either favor or limit the use of particular classes of anti-hypertensive drugs; variation in individual patient responses to drugs from different classes. The possibility of interactions with drugs used for other conditions present in the patient, and the strength of the evidence for reduction of cardiovascular risk with the drug class in question.

III.c.5. Hypertension Treatment Program in High-Risk Regions

The WHO-ISH guidelines 1999 (1999 World Health Organization – International Society of Hypertension Guidelines for the Management of Hypertension) recommend that in areas in which healthcare resources are scarce, investment in population-based primary prevention may yield the greatest dividend. This involves the use of the lowest cost drugs (e.g. diuretics, reserpine, β-blockers, generic formulation of ACE inhibitors, AII receptor blockers, CCB and other generic agents) in the highest risk groups. The selective treatment of patients with pre-existing cardiovascular or renal disease (SBP > 180 mmHg or DBF >10 mmHg) will result in the greatest ratio of events prevented to number of patients treated.

Table 6. Indications and contraindications for the major classes of antihypertensive drugs (adapted from the JNC 7 Guidelines, 2003)

Class	Conditions favouring use	Contraindications	
		Compelling	Possible
Diuretics (thiazide, thiazide-like)	Heart failure Elderly hypertensives Isolated systolic hypertension Black hypertensives	Gout	Pregnancy Beta-blockers (especially atenolol)
Diuretics (loop)	Renal insufficiency Heart failure	Not used in other hypertensives	Pregnancy
Diuretics (aldosterone antagonist)	Heart failure Post-myocardial infarction Resistant hypertension	Renal failure Hyperkalaemia	
CCB Long-acting only (dihydropyridine)	Elderly patients Isolated systolic hypertension Angina pectoris Peripheral vascular disease Carotid atherosclerosis Pregnancy Black hypertensives	Asthma and COPD	Tachyarrhythmias Heart failure Antiretroviral therapy
CCB non-dihydropyridine (verapamil, diltiazem)	Angina pectoris Carotid atherosclerosis Supraventricular tachycardia	Atrioventricular block (grade 2 or 3) Heart failure	Constipation (verapamil) Antiretroviral therapy
ACE-Is*	Heart failure Left ventricular dysfunction Post-myocardial infarction Non-diabetic nephropathy Type 1 diabetic nephropathy Type 2 diabetes mellitus Proteinuria	Pregnancy Hyperkalaemia Bilateral renal artery stenosis	Peripheral vascular disease
ARBs*	Type 2 diabetic nephropathy Type 2 diabetic microalbuminuria Proteinuria Left ventricular hypertrophy ACE-I cough or intolerance	Pregnancy Hyperkalaemia Bilateral renal artery stenosis	
Beta-blockers	Angina pectoris Post-myocardial infarction Heart failure (only some beta-blockers; must up titrate) Tachyarrhythmias After myocardial infarction Diabetes nephropathy	Asthma Chronic obstructive airways disease Atrioventricular block (grade 2 or 3)	Peripheral vascular disease Bradycardia Glucose intolerance Metabolic syndrome Athletes and physically active patients Non-dihydropyridine CCBs (verapamil, diltiazem) Pregnancy

*There is considerable overlap in outcomes of ACE-Is and ARBs in the management of Type 2 diabetes mellitus. Use the most efficacious class of drug according to patient circumstances.

General note: In resistant (refractory) hypertension centrally acting agents (selective and non-selective) and alpha-blockers may be required to control BP.

Table 7. Recommendations on compelling indications for a specific drug class

Compelling indications	Drug class
Angina	Beta-blocker OR CCB (rate lowering preferred)
Prior myocardial infarct	Beta-blocker AND ACE-I (ARB if ACE-I intolerant). Verapamil if beta-blockers contraindicated. If heart failure, see below
Heart failure	ACE-I (ARB if ACE-I intolerant) AND certain beta-blockers AND aldosterone antagonist For combination ARB and ACE-I see reference Loop diuretics for volume overload
Left ventricular hypertrophy (confirmed by ECG)	ARB (preferred) OR ACE-I
Stroke: secondary prevention	Low-dose thiazide-like diuretic and ACE-I or ARB
Diabetes type 1 or 2 with or without evidence of microalbuminuria or proteinuria	ACE-I OR ARB – usually in combination with a diuretic
Chronic kidney disease	ACE-I OR ARB – usually in combination with a diuretic
Isolated systolic hypertension	Low-dose thiazide or thiazide-like diuretic OR long-acting CCB

Note: Any drug that lowers BP (unless absolutely contraindicated) will confer protection against target-organ damage. However, the listed classes of drugs have additional protective properties in the case of the listed associated clinical conditions/target-organ damage.

III.c.6. Causes of Refractory Hypertension

There are unsuspected secondary causes (e.g. renal and endocrine), poor adherence to therapeutic plan, continued intake of drugs that raise blood pressure (e.g. non-steroidal anti-inflammatory drugs. Failure to modify life-style including weight gain and heavy alcohol intake (or binge drinking). Volume overload is due to inadequate diuretic therapy, progressive renal insufficiency, or high sodium intake. Causes of spurious refractory hypertension include cases with isolated office (white-coat) hypertension and failure to use a large cuff on large arms.

III.c.6.1. Considerations for adherence to therapy. This is a major therapeutic challenge as non-adherence contributes to a lack of control in more than two-thirds of patients with hypertension. Patients have a right and responsibility to be well informed. Follow-up visits should be aimed at maintaining target BP and encouraging continuing life-style modification. Most patients should be seen within 1–2 months of initiation of therapy, to assess control of target BP, degree of patient adherence and the presence of adverse effects. Associated medical problems, including target organ damage, other major risk factors and laboratory test abnormalities also play a role in assessing the frequency of patient follow-up.

Once the BP has been stabilized, follow-up at 3–6 month intervals is appropriate. In some patients and especially those orthostatic symptoms monitoring should include BP measurement in the seated position and, after the patient has been standing for 2–5 min in order to recognize postural hypotension.

Strategies to improve compliance are shown in Table 8. Pharmacists should be encouraged to monitor the use of drugs, to advise on potential side effects and to prevent adverse drug interactions. Nurse-managed clinics improve adherence and outcomes. The other members of the health care team can provide guidance in nutrition or exercise.

III.c.6.2. Resistant hypertension. Hypertension should be considered resistant if the BP cannot be reduced to below 140/90 mmHg in patients who adhere to a triple-drug regimen that includes a diuretic, with all three drugs in near maximal doses. For older patients with isolated SBP, resistance is defined as failure of an adequate triple-drug regimen to reduce SBP below 160 mmHg. The various causes of true resistance are listed in Table 9. One of the most common causes is volume overload as a result of inadequate diuretic therapy. Patients who have resistant hypertension or who are unable to tolerate antihypertensive therapy may benefit from referral to a hypertension specialist.

III.d. Antiplatelet Therapy

The use of aspirin, and of some other antiplatelet agents, has been well documented to reduce the risk

Table 8. General guidelines to improve patient adherence to antihypertensive therapy (Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure, 1997)

Be aware of signs of patient non-adherence to antihypertensive therapy
Established the goal of therapy: to reduce blood pressure to non-hypertensive levels with minimal or no adverse effects
Educate patients about the disease, and involve them and their families in its treatment
Have them measure blood pressure at home
Maintain contact with patients; consider telecommunication
Keep care inexpensive and simple
Encourage life-style modifications
Integrate pill-taking into routine activities of daily living
Prescribe medications according to pharmacologic principles, favoring long-acting formulations
Be willing to stop unsuccessful therapy and try a different approach
Anticipate adverse effects, and adjust therapy to prevent, minimize, or ameliorate side effects
Continue to add effective and tolerated drugs, stepwise, in sufficient doses to achieve the goal of therapy
Encourage a positive attitude about achieving therapeutic goals
Consider using nurse management

Table 9. Causes of inadequate responsiveness to therapy (adapted from Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure, 2003)

Improper BP measurement
Volume overload and pseudotolerance
Volume retention from kidney diseaase
Excess salt intake
Inadequate diuretic therapy
Drug induced or other causes
Non-adherence to therapy
Doses too low
Inappropriate combinations
Non-steroidal anti-inflammatory drugs
Cocaine and other illicit drugs
Sympathomimetics (decongestants, anorectics)
Oral contraceptives
Adrenal steroids
Cyclosporine, tacrolimus
Erythropoietin
Licorice (including some chewing tobacco)
Selected over-the-counter dietary supplements and medicines (e.g., ephedra, ma haung, bitter orange)
Associated conditions
Smoking
Increased obesity
Sleep apnea
Insulin resistance/hyperinsulinemia
Ethanol intake of more than 30 ml per day
Anxiety-induced hyperventilation or panic attacks
Chronic pain
Intense vasoconstriction (arteritis)
Organic brain syndrome (e.g. memory deficit)

of fatal and non-fatal coronary events, of stroke and of cardiovascular death in patients with established coronary or cerebrovascular disease. In the light of the results of the HOT study, it is reasonable to recommend the use of low-dose aspirin in hypertensive patients whose BP has been rigorously controlled, who are at high risk of bleeding from the gastrointestinal tract or from other sites.

III.e. Monotherapy versus Combination Therapy

III.e.1. Drug Monotherapy

When drugs from the main available classes are used as monotherapy at the recommended doses, they produce very similar BP reductions. In general, the sizes of the BP reductions increase with the initial level of BP, but typically the placebo-adjusted reductions average about 4–8% for both SBP–DBP. Thus, for patients with blood pressures of about 160/95 mmHg, the usual reduction produced by monotherapy would be about 7–13 mmHg systolic and 4–8 mmHg diastolic. Clearly, for many patients with hypertension, such reductions in BP would not restore optimal or even nonhypertensive blood pressure levels.

III.e.2. Drug Combination Therapy

Combination therapy of several of the available drug classes has been shown to produce BP reductions that are greater than those produced by any group of individual agents used alone. The HOT study, in which blood pressure was lowered to below 90 mmHg in over 90% of patients, demonstrated that combination therapy was necessary in 70% of participants. Combinations with fully additive hypotensive effects will deliver BP reductions that are around twice as great as those obtained with a single drug, of the order of 8–15%, or 12–22 mmHg systolic and 7–14 mmHg diastolic for patients with BP of 160/95 mmHg.

III.e.2.1. Effective drug combinations. Good drug combinations are a diuretic with a 3-blocker, a diuretic with an ACE inhibitor (or AII receptor blockers), CCB (dihydropyridine) and β-blockers, CCB and ACE inhibitors, and an α-blocker with a β-blocker.

Effective drug combinations utilize drugs from different classes in order to obtain the additive hypotensive effect that comes from combining drugs with different primary actions, while minimizing the compensations that limit the fall in blood pressure. Combinations of limited value generally result from combining drugs that work through similar mechanisms so that their hypotensive actions may be less than additive or drugs that have similar side effects so that the risk of adverse effects is increased.

IV. THERAPY FOR HYPERTENSIVE URGENCY

Patients with malignant-accelerated hypertension can usually be managed by oral therapy. Patients who are seen in a nursing home or clinic, whose BP is found to be above some arbitrary danger level like a BP of 180/120 should not automatically be given nifedipine sublingually. Indiscriminate use of nifedipine sublingually could lead to a major catastrophe like myocardial infarction or cerebrovascular episodes. Nifedipine activates sympathetic response and leads to precipitous drops of blood pressure followed by rebound hypertension.

The oral agents are effective in patients with severe uncontrolled hypertension, few having true hypertensive urgencies. There is no ideal anti-hypertensive agent for an hypertensive urgency situation. Nifedipine has been widely used for the treatment of hypertensive emergencies. Liquid nifedipine 5–10 mg sublingually or when chewed and the contents swallowed will rapidly lower pressure within minutes. The problem with sub-lingual or oral nifedipine is that it is often too effective and acts too rapidly and that there is no way to titrate or overcome the response. Grossman states:

> In true hypertensive emergencies, nifedipine capsules are contraindicated because of the unpredictability of the fall in arterial pressure. Given the seriousness of the adverse effects and the complete lack of outcome data, the routine use of short-acting nifedipine in hypertensive emergencies should be abandoned. Other slower and therefore probably safer CCBs can be used.

Captopril is the fastest of the oral ACE inhibitors. It can also be used sublingually in patients who cannot swallow. Captopril shifts the entire curve of cerebral autoregulation in such a way that cerebral blood flow is maintained as the systemic pressure falls. Caution is needed in patients with significant renal

insufficiency or who are volume depleted. Abrupt and marked first-dose hypotension after captopril is uncommon and occurs in patients with high renin status. Despite the small potential for hypotension, oral captopril may be the safest of nonparenteral agents for urgent hypertension. Moreover, if renovascular hypertension is suspected, a blood sample for plasma renin activity can be obtained before and 1 hour after the 25 mg dose as a reasonably accurate screening test.

Clonidine, a centrally acting oc_2-adrenoceptor agonist, has been widely used in a dosage of 0.3 mg, t.i.d. to reduce very high blood pressures. It acts more slowly than nifedipine and brings down the BP more safely and effectively. Its main disadvantage is sedation and rebound hypertension if the drug is stopped suddenly. It should not be given in patients who have been shown to be poor compliars.

Labetalol, an α- and β-blocker, has been used in hourly doses of 100–200 mg. It has reduced BP as effectively as oral nifedipine and acts more slowly and effectively.

Diuretics, specifically the loop diuretics furosemide or bumetanide, combined with the thiazide like diuretic metolazone are needed in hypertensive urgencies both to lower blood pressure by removing excess volume and to prevent loss of potency from tendency to cause fluid retention. Volume depletion should be watched in patients on diuretics.

After the patient is out of danger a careful search should be done to exclude a secondary cause for the malignant hypertension. The patient should then be put on a regime of multiple drug therapy.

V. VARYING RESPONSES TO ANTI-HYPERTENSIVE AGENTS IN BLACK PATIENTS

Thiazide diuretics are effective antihypertensive agents in black hypertensive patients and studies suggest that they cause a greater decrease in blood pressure in black patients than in whites. The better hypotensive response in black hypertensive patients is probably due to the fact that, in comparison with whites, more black patients have an expanded intracellular volume and low plasma renin activity. In developing countries, in which the majority of black people live, the cost of therapy is important. Thiazide diuretics are because of their low cost important baseline drugs in the treatment of hypertension. The low incidence of ischemic heart disease in the black population of Africa may mitigate the seriousness of the consequence of the metabolic effects of thiazide diuretics, for example hyperlipidemia and hypo-kalemia.

Reserpine or rauwolfia extracts, combined with hydrochlorothiazide in black patients, offer the advantages of low cost and once daily administration. Side effects like nasal congestion or depression are minimal provided the dosage of reserpine does not exceed 0.1 mg once daily. In developing countries where the cost of therapy is important, it may be preferable to use a combination of reserpine and hydrochlorothiazide as baseline drugs in hypertension. There are numerous studies that have shown that β-blockers are no more effective than placebo in black people. Comparative studies between white and black subjects have shown that white and Indian hypertensive patients respond better to β-blockers than black hypertensive patients. Available evidence suggests that β-blockers with sympathomimetic activity produce better hypotensive results than β-blockers with cardioselectivity and without intrinsic sympathomimetic activity. β-blockers, when combined with a thiazide diuretic, produce an appreciable hypotensive response in black hypertensive patients. Labetalol and carvedilol are antihypertensive agents which block β_1-, β_2- and α_1-adrenergic receptors. They may be more effective than non-selective β-blockers in black patients. Carvedilol, a new non-cardioselective, vasodilating β-adrenoceptor blocker, without intrinsic sympathetic activity, is an effective agent for treating hypertension in black patients. Available data show that black patients who are prone to a low plasma renin activity respond well to calcium channel blockers. CCB may also have a natriuretic effect and thus lower the blood pressure. A further additive hypotensive effect is achieved when CCB are combined with a diuretic in black patients.

Studies with ACE inhibitors have shown that in black patients the response is poor. However, the response becomes the same as in whites when ACE inhibitors are combined with a low-dose thiazide diuretic. ACE inhibitors can be effective in black hypertensive patients but in higher doses compared to white and Indian peoples.

There is only limited data available on the response to AII (AT) receptor antagonists in black hypertensive patients. The magnitude of the fall in blood pressure with losartan in black patients appears to be less than in non-black patients. Data on

Table 10. Antihypertensive agents in white and black communities

Agent	White	Black
Thiazide	+	++
Rauwolfia	+	++
β-blockers	+	±
β-blockers + thiazides	+	+
α- and β-blockers	+	+
Methyldopa	+	+
Vasodilators	+	+
ACE inhibitors	+	±
ACE inhibitors + thiazides	+	+
Calcium channel blockers	+	+
Angiotensin II antagonists	+	±

ACE, angiotensin-converting enzyme.

Table 11. Renal haemodynamic effects of antihypertensive drugs

	Glomerular filtration rate	Renal plasma flow
Loop diuretics	0	#
Thiazides	∃	∃
β-blockers	∃/0	∃/0
Calcium channel blocker	#	#
ACE inhibitors	0	#
Angiotensin I blockers	0	#
Renin inhibitors	#	#

ACE, angiotensin-converting enzyme; 0, no effect.

the efficacy of the new AT, receptor blockers like candesartan, irbesartan or valsartan in black hypertensive patients are few in terms of number of patients.

In summary, black hypertensive patients respond well to thiazide diuretics, CCB, vasodilators like prazosin, doxazosin or the vasodilating β-blocker labetalol. It is suggested that in black hypertensive patients a thiazide diuretic should be routinely added when a β-blocker or an ACE inhibitor is used. This above information is summarized in Table 10.

VI. TREATMENT OF HYPERTENSION IN RENAL DISEASE

All hypotensive drugs lower systemic BP but, due to the specific characteristics of the glomerular capillary system, different agents may affect glomerular hemodynamics in different ways. This could be of major importance. During antihyper-tensive therapy, systemic BP may be reduced but glomerular pressure may be elevated. This may explain why the incidence of some cardiovascular complications such as stroke, has decreased, whereas the incidence of hypertensive nephropathy has remained high.

The glomerulus is situated between two sets of resistance vessels, the afferent and efferent arterioles, thus preventing transmission of this pressure to the glomerulus. This compensatory mechanism may be one explanation for the relatively low incidence of hypertensive nephrosclerosis (1.5–4%) among patients with mile to moderate hypertension. In the intrarenal vasculature, angiotensin receptors are found in greater density in the efferent than in the afferent arterioles. Thus, blunting the effect of angiotensin not only lowers BP but may reduce glomerular pressure to a greater extent. CCB exert preferential vasodilation of the afferent arterioles, but may not reduce glomerular capillary pressure like ACE inhibitors do. The renal hemodynamic effects of antihypertensive drugs are shown in Table 11. Angiotensin II is a potent neurohormone in terms of both regulation of systemic arterial pressure and regulation of vascular structure and function. Substantial benefit can be obtained by both BP reduction and pharmacologic blockade of the rennin–angiotensin system since this will optimally attenuate vascular remodelling and restructuring. This is achieved with ACE inhibitors or AII receptor blockers or both. The ultimate goal is to prevent renal failure or slow its progression. ACE inhibitors may be more effective than β-blockers in slowing deterioration of renal function The dihydropyridine calcium antagonists like nifedipine are not as effective as the non-dihydropyridines like verapamil or diltiazem, in decreasing proteinuria. In animal experiments, coadministration of an ACE inhibitor and a CCB like verapamil caused a more marked reduction in glomerulosclerosis and this was seen in the stroke-prone hypertensive rat model even at non-antihypertensive doses. In human diabetic nephropathy at least, proteinuria (measured as a surrogate marker of the illness) was lowered more effectively by the combination of an ACE inhibitor and a CCB than either drug used as monotherapy, despite a similar fall in blood pressure. The renoprotective role of diuretics, α-adrenergic blockers and direct vasodilation is unclear, owing to inadequate data. Long-term controlled studies are needed to assess whether these agents can increase the glomeru-

lar filtration rate or fail to arrest glomerulosclerosis in the long run. The strategies for slowing progressive renal failure in patients with hypertension include early detection of hypertensive renal damage. Small elevations of serum creatinine may reflect significant losses of glomerular filtration rate. Evaluation should include urinalysis to detect proteinuria or hematuria and possibly renal sonography to exclude lower urinary tract obstruction. Reversible causes of renal failure should always be sought and excluded. The Joint National Committee on Detection, Evaluation and Treatment of Blood Pressure (2003), recommends that BP should be controlled to 130/80 mmHg – or lower (125/75) in the presence of albuminuria (>300 mg/day or 200 mg albumin/g creatinine) – aggressive BP management, often with three or more drugs. The recommendation of the JNC VII Report states that the most important action is to lower BP in order to prevent renal damage. All classes of antihypertensive drugs are effective and, in most cases, combinations of antihypertensive drugs may be needed. Impressive results have been achieved with ACE inhibitors in patients with proteinuria greater than 1 g/24 h and in patients with renal insufficiency. Consequently, patients with hypertension who have renal insufficiency should receive, unless contraindicated, an ACE inhibitor, in most cases, along with a diuretic, to reduce hypertension and to slow progressive renal failure. In patients with considerably elevated serum creatinine and potassium levels consideration should be given to the possibility of the existence of bilateral renal artery stenosis, hyporeninemia or hypoaldosteronism which occur mainly in diabetics or elderly persons, or the use of drugs which may cause potassium retention like potassium sparing diuretics, cyclosporine or non-steroidal anti-inflammatory drugs.

Thiazide diuretics are not effective with advanced renal insufficiency (serum creatinine level of 221 μmol/l) and loop diuretics are needed, often at relatively large doses. Combining a loop diuretic with a long-acting thiazide diuretic, such as metolazone, is effective in patients resistant to a loop-diuretic alone. Potassium-sparing diuretics should be avoided in patients with renal insufficiency.

VII. CONCLUSIONS

In spite of the effective drug therapy available for hypertensive patients in general, economic and social considerations continue to influence the lower rate of detection, treatment and control of hypertension in the population of the developing world. The Joint National Committee on the Detection, Evaluation and Treatment of High Blood Pressure (1997) stated that in 1993 age-adjusted stroke rates have risen slightly and the age-adjusted rate of decline of CHD appears to be levelling off. In contrast, JNC 7 (2003) states that recurrent stroke rates are lowered by the combination of an ACEI and thiazide-type diuretic (see also PROGRESS Collaborative Group, 2001).

Rates for the incidence of end stage renal disease have increased for which hypertension is the second most common cause. It has also been stated that hypertension control rates have not continued to improve (National Health and Nutrition Examination Survey, NHANES III, Phase 1) from 1991 to 1994. These disturbing trends support the need to enhance public and professional education and to translate the results of research into improved health.

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Chapter 34

Cardiovascular and Renal Diseases B: Treatment of Ischemic Heart Disease

Naoki Matsumoto, Shinichi Kobayashi

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I. INTRODUCTION

Ischemic heart disease (IHD) is defined as an insufficient blood supply from coronary arteries to the myocardium. This abnormality is usually brought about by atherosclerosis or vasospasm, except some special situations as e.g. severe aortic valve regurgitation. In any of these situations, chest pain symptom arises from imbalance of oxygen supply and the demand of the myocardium. Treatment of ischemia will be achieved by correction of this relative oxygen shortage, sometimes by increasing blood supply or by reducing oxygen demand. The former is usually accomplished by surgical methods including Percutaneous Coronary Intervention (PCI). Pharmacological intervention is usually instrumental for the latter mechanism, reduction of oxygen demand, except the treatment of vasospastic angina pectoris by vasodilating agents. Oxygen demand of the myocardium is determined by various parameters as preload, afterload and heart rate. This concept is identical through all types of heart problems, but the use of drugs very much depends on the patients' situation, as the outcome of treatment may differ considerably. In this section, the patient's situation will be divided into three patterns, and the treatment methods, mainly with pharmaceutical agents, will be summarized according to the AHA guidelines.

II. TREATMENT OF CHRONIC STABLE ANGINA

II.a. Treatment Objectives

The treatment of chronic stable angina is aiming at two objectives:
(1) Prevention of myocardial infarction (MI) and sudden cardiac death (SCD).
(2) Improvement of quality of life (QOL).
The prevention of cardiac events is the first priority. When there is a choice between two methods for effectively relieving the patient's symptoms, you have to choose the one for which there is proof or at least a high possibility for these events to be prevented. Because MI can be critical, non-pharmacological therapy might have a higher priority but the above mentioned principles for therapy selection is also effective for the choice of drugs. There is a need to keep updated with respect to treatment guidelines and the latest clinical studies.

II.b. Prevention of MI and SCD

II.b.1. Antiplatelet Agents

Aspirin (75–325 mg daily) administrated on a routine basis is highly recommended in all patients with acute and chronic ischemic heart disease if the patient has no contraindications. Clopidogrel will be the possible alternate choice if aspirin is totally

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contraindicated. Ticlopidine seems to be less effective than clopidogrel, and has adverse effects such as reduction of neutrophils. Dipyridamole has antiplatelet effects, but it should not be used, because it worsens exercise induced ischemia.

Given to patients with a history of typical angina accompanied by either a past medical history of coronary artery disease or ECG/cardiac enzyme changes, low molecular weight heparins (LMWH) were more efficacious in reducing MI and revascularization, but not mortality, with fewer serious side-effects than unfractionated heparin (UFH) (see Magee et al., 2003).

II.b.2. Lipid-Lowering Agents

Lowering LDL cholesterol is highly effective if LDL is higher than 130 mg/dl and in suspected coronary artery disease (CAD) patients. A 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor (statin) will be the first choice, and target LDL will be less than 100 mg/dl. LDL levels between 100–129 mg/dl will also be advantageous to be treated. Other than statins, cholestylamine, forate or other types will also be used.

II.b.3. Angiotensin Converting Enzyme Inhibitors

The Angiotensin Converting Enzyme Inhibitors (ACE-I) are recommended for all CAD patients, especially those with Diabetes Mellitus (DM) and/or left ventricle (LV) dysfunction.

Current European Society of Cardiology (ESC) guidelines recommend ACE-inhibitor therapy in CAD patients with co-existing indications for ACE-inhibitors, such as hypertension, heart failure, left ventricular dysfunction, prior MI with left ventricular dysfunction, or diabetes (class I, level of evidence A). These guidelines also recommend ACE-inhibitor therapy in all patients with angina and proven coronary disease (class IIa, level of evidence B).

II.b.4. Anti-ischemic Therapy

Highly recommended are β-blockers for those who have a prior MI event. They showed a significant effect on death. Recent studies suggest that patients who have coronary artery disease without acute myocardial infarction and/or congestive heart failure have approximately the same protective benefit against death.

Nitroglycerin will be effective for on-going chest pain relief. Ca channel antagonists and long-acting Nitrates can be used when β-blockers are contraindicated. These drugs may be also used for the initial therapy, additional to β-blockers or when β-blockers treatment failed. However, for the effectiveness of vasodilatation itself is relatively weaker evidence.

III. TREATMENT OF UNSTABLE ANGINA AND NON-ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION

Unstable Angina (UA) and Non-ST-Segment Elevation Myocardial Infarction (NSTEMI) are important situations which may cause SCD or MI. Treatment is aimed at the prevention of these events, mainly by revascularization after the immediate medical treatment. In this section, the medical therapy will be separately discussed for the hospital care and post-hospital discharge care.

III.a. Hospital Care

III.a.1. Anti-ischemic Therapy

Hospital care starts with the relief of chest pain. Nitroglycerin (sublingual tablet or spray, followed by intravenous injection) will be the first choice. Morphine sulfate is also effective for pain relief. A β-blocker is recommended. The dose will be started by intravenous injection, followed by oral administration. If this is contraindicated, a nondihydropyridine calcium antagonist such as gallopamil or verapamil will be a good alternative if LV function is not severely impaired or if such a calcium antagonist itself is not otherwise contraindicated. ACE-I will be a good choice if the following conditions are met: uncontrolled hypertension with β-blocker and nitrate, LV dysfunction, congestive heart failure (CHF), acute coronary syndrome (ASC) in DM patient, though with weaker evidence without DM. In all situations, long acting calcium antagonists may be added when β-blockers and nitrate are fully administrated, though the evidence is not so strong.

III.a.2. Antiplatelet and Anticoagulation Therapy

There is very strong evidence for the beneficial effects of Aspirin and it should be started as soon as possible. Clopidogrel has to be used as an alternative for aspirin if the latter is contraindicated in hospitalized patients. Otherwise, this drug has to be added to

aspirin as soon as possible when an early interventional approach is not planned for hospitalized patients. Once the interventional approach is planned, Clopidogrel has to be used for at least one month and is better to be used for up to nine months if there is no serious bleeding risk. Clopidogrel may have to be withheld for 5–7 days before the elective coronary bypass operation (CABG). Strong evidence exists that low molecular weight heparin (LMWH) sc or unfractionated heparin iv added to antiplatelet drugs has a favorable effect. A platelet glycoprotein (GP) IIb/IIIa inhibitor such as abciximab has to be added to aspirin and heparin just before the PCI will be started.

In contrast, intravenous fibrinolytic therapy is harmful without acute ST-segment elevation, a true posterior MI or a presumed new left bundle-branch block.

III.a.3. Early Conservative or Invasive Strategies?

Generally speaking, an invasive strategy will be recommended when there will be no contraindications for coronary revascularization. Risk factors which encourage to choose an invasive strategy are: (a) recurrent angina at rest or with low-level activities despite intensive anti-ischemic therapy, (b) elevated Troponin T or I, (c) new ST depression, (d) recurrent angina with CHF symptoms, (e) high risk findings on non-invasive stress testing, (f) depressed LV systolic function, (g) hemodynamic instability, (h) sustained ventricular tachycardia, (i) PCI within six months and (j) prior CABG. A recent Cochrane review concluded that early invasive strategy is preferable to a conservative strategy in the treatment of unstable angina and non-ST-elevation myocardial infarction (see Hoenig et al., 2006).

III.b. Post-hospital Discharge Care

Basically, the medical therapy that was required to control ischemia during the hospital stay will have to be continued after discharge from the hospital. If the patient did not undergo coronary revascularization, revascularization was unsuccessful or had recurrent symptom after revascularization, the medical therapy will have to be same.

For long term therapy, Aspirin 75–325 mg per day or Clopidogrel 75 mg per day, when Aspirin is contraindicated, is strongly recommended. Combination of Aspirin and Clopidogrel for 9 months, and a β-blockers will be also recommended. Lipid lowering agent in post-ACS, postrevascularization patients when LDL cholesterol greater than 130 mg/dl, and ACE-inhibitor therapy in CHF, LV dysfunction, hypertension or DM patients are both strongly recommended. If diet therapy did not improve LDL lower than 100 mg/dl, lipid lowering agent will be needed. Such risk factor modification including controlling blood pressure or LDL cholesterol will be very important for the long term outcome.

IV. TREATMENT OF ST-ELEVATION MYOCARDIAL INFARCTION

ST-Elevation Myocardial Infarction (STEMI) is a life-threatening event, thus prehospital treatment is expected to be available by establishing a sophisticated system for this purpose. In this condition a fibrinolysis protocol is advised.

The basic concept of prehospital care and patient transfer is carrying the patient to a facility capable of rapid revascularization, if fibrinolysis therapy is contraindicated. If the patient cannot be transferred to the facility capable of prompt intervention, fibrinolytic therapy is strongly recommended to start within 90 minutes of first medical contact. After such treatment, medical therapy will become important in managing the patient.

IV.a. Management

Nitroglycerin by sublingual tablet (0.4 mg) every 5 minutes for a total of 3 doses will be used for ischemic discomfort relief. Intravenous injection will be considered when the ischemic discomfort, hypertension or pulmonary congestion cannot be controlled. Nitrates should not be used when the blood pressure is lower than 90 mmHg or 30 mmHg lower than a known base line value, bradycardia less than 50 bpm, tachycardia more than 100 bpm or suspected right ventricular (RV) infarction.

Morphine sulfate will be acceptable for analgesic.

Prompt administration of Aspirin 162 mg and a β-blocker is strongly recommended.

IV.b. Fibrinolytic Therapy

As was said before, fibrinolytic therapy is recommended in many cases. It is recommended for patients with the onset of the STEMI within 12 hours, for patient with significant ECG changes having ST

elevations of more than 0.1 mV in at least 2 contiguous precordial leads or 2 adjacent limb leads and for patients having a newly developed left bundle branch block (LBBB). There is also a strong indication for cardiogenic shock patients who are unsuitable for invasive care. In contrast, it is not advisable to give fibrinolytic agents to asymptomatic patients whose onset was earlier than 24 hours prior to presentation, and to patients with only ST depressions unless it is a posterior MI. Other contraindications are any prior intracranial hemorrhage, intracranial lesions such as vascular lesions, any malignancy, ischemic stroke within 3 months except acute ischemic stroke within 3 hours and closed head/facial trauma within 3 months. Active bleeding and suspected aortic dissection are also contraindications. Streptokinase will not be readministrated in patients with recurrent ischemia. As additional therapy, stronger evidence for beneficial effects of Aspirin (162–325 mg on day one, followed by 75–162 mg thereafter) exist than for Clopidogrel or heparin, though both are acceptable. ACE-inhibitor therapy within 24 hours and blood glucose level maintenance is strongly advised.

IV.c. Other Medical Therapy

The use of a β-blockers within 24 hours is strongly advised, if possible. Nitroglycerin will be indicated within 48 hours to control persistent ischemia and elevated blood pressure. ACE-inhibitor therapy for long term use has to be started in the convalescence phase. Long-term aldosterone blockade is also advised.

IV.d. Low Output Status and Pulmonary Congestion

The use of inotropic support will be acceptable only in low-cardiac-output status. For pulmonary congestion, ACE-inhibitor therapy and aldosterone blockade will be best recommended, especially for long term use. It will be good to start with a β-blockers before discharge for secondary prevention.

V. CONCLUSION

Guidelines for the treatment of ischemic heart disease have become very sophisticated and even incorporate advice for the psychological treatment of the patient to improve outcome. They are very useful at the present day. However, in the actual clinical situation there may be difficulties, to assess the actual condition of the patient, and thus to apply existing guidelines. Guidelines are not always the Bible. There is always a need to be aware of the fact that careful observation and examination are very important.

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Chapter 34

Cardiovascular and Renal Diseases C: Treatment of Heart Failure

Naoki Matsumoto, Shinichi Kobayashi

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I. INTRODUCTION

Heart failure (HF), including congestive heart failure (CHF) is recently considered as having two aspects. One is the aspect of a symptomatic disease. The another is a progressive disorder, which is sometimes very difficult to recognize and to evaluate because it is an asymptomatic disorder. This progression may finally result in a patient's death. This slow, often asymptomatic progression necessitates an analysis with well-designed, large clinical studies.

When we talk about the symptomatic disease, it has to be realized that usually this does not contribute to the patients' prognosis. However, it is extremely important, because we are able to substantially improve the quality of life of the patient. On the other hand, when we talk about the progressive disorder, the importance is that a diminution of that progression leads to a better prognosis. However, for an individual patient it is hard to predict if this patient will be saved by the treatment for this disorder or not. What we can do for this disorder is mainly based on results obtained in population studies. For the individual patient we have to take into account the specific situation of the patient, and we have to be sure which signs and symptoms have to be handled first for a better outcome. In this section the medical treatment for HF, taking into consideration the above aspects, will be discussed mainly on the basis of the ACC/AHA Practice Guidelines. But again, we have to realize that the treatment has to have one final objective: improvement of the patient prognosis based on thorough clinical research.

II. STAGES OF HEART FAILURE

Before we discuss HF treatment, it is necessary to classify the four stages of HF during the natural history of the disease. The first two are Stage A and Stage B and can be classified as 'At Risk for HF', while the latter two, Stage C and D need to be classified as 'HF'. The detailed concept of this is summarized in the Table 1 as shown in ACC/AHA Guidelines. This table looks somewhat complicated, but the details are discussed in the following sections. After finishing reading these sections the review of the table will help to understand the whole picture.

In short, the risks for HF are: hypertension, atherosclerotic disease, diabetes mellitus, obesity, metabolic syndrome, use of cardiotoxins and a positive family history of cardiomyopathy.

If in patients with these risks the following structural disorders are added, the stage becomes Stage B: previous myocardial infarction, left ventricle (LV) remodeling, low ejection fraction (EF) or asymptomatic valvular disorders.

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If patients with the above structural disorders develop HF symptoms, the stage will be Stage C and Stage D will be refractory HF, the end stage.

III. TREATMENT OF RISKS FOR DEVELOPING HEART FAILURE

Treatments discussed in this section are for Stage A. These treatments focus on the risks for HF shown in Table 1 and in the previous section. Controlling these risks is extremely important for prevention of HF.

III.a. Hypertension

Reducing elevated blood pressure has been proven to be effective for prevention of HF. Both systolic and diastolic pressure are targets for treatment. For the treatment of hypertension it is advisable to use the updated guidelines of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Especially those who have diabetes mellitus will be better off if handled precisely according to these guidelines. Diuretics will be a good choice for many patients. Angiotensin converting enzyme inhibitors (ACE-I) and β-blockers are also effective for HF prevention, whereas Ca-antagonist and alpha-blockers are less effective.

If a patient is diabetic, ACE-I will be advised, because it may reduce new-onset of HF and protect against nephropathy. The use of an Angiotensin-II receptor blocker (ARB) is also a good choice for these diabetic patients and for their nephropathy. The basic concept of drug selection will be combination therapy using different classes such as ACE-I and

Table 1. Stages in the development of heart failure (from ACC/AHA guideline)

AT risk of hear failure		Hear failure	
Stage A	Stage B	Stage C	Stage D
At high risk for HF but without structural heart disease of symptoms of HF	Structural heart disease but without signs or symptoms of HF	Structural heart disease with prior or current symptoms of HF	Refractory HF requiring specialized interventions
• Hypertension • Atherosclerotic disease • Diabetes • Obesity • Metabolic syndrome • Using cardiotoxins • Family history of cardio-myopathy	• Previous MI • LV remodeling including LVH and low EF • Asymptomatic valvular disease	• Known structural heart disease • Shortness of breath and fatigue, reduced exercise tolerance	• Patients who have marked symptoms at rest despite maximal medical therapy (e.g. who cannot be safely discharged)
Drugs • ACE-I or ARB	Drugs • ACE-I or ARB in appropriate patients • Beta-blockers in appropriate patients	Drugs Routine use • Diuretics for fluid retention • ACE-I • Beta-blocker In selected patients • Aldosterone antagonist • ARB • Digitalis • Hydralazine/nitrates	Drugs Usually for palliation

β-blockers. This combination will be more effective for many patients than using these drugs alone.

III.b. Diabetes Mellitus

Insulin resistance, frequently accompanied by obesity, is an important risk factor for HF development. Diabetes Mellitus itself increases the risk for HF as well. Those who are positive for urinary albumin excretion may develop more sever HF and are more at risk for mortal events. A recent report showed that diabetes is a potent, independent risk factor for mortality in patients hospitalized with HF. Interestingly, the excess risk in diabetic patients appears to be particularly prominent in females. In treating the patient with diabetes, one should pay attention to such variables.

Interestingly, suppressing the Renin–Angiotensin–Aldosteron System (RAAS) using ACE-I or ARB will reduce the risk for HF in patient with diabetes, even if they do not have hypertension. These drugs have been shown to be beneficial for patients with diabetic nephropathy, and via the same mechanism to also reduce the HF risk. There is abundant support in the literature for the usefulness of RAAS suppression in diabetes combined with cardiovascular disease.

III.c. Metabolic Syndrome

Abdominal adiposity, hypertriglyceridemia, low high-density lipoprotein and hypertension are the key elements of this syndrome, formerly called Syndrome X. Patients who satisfy 3 of the diagnostic criteria are considered to be at risk for HF. This syndrome is a kind of pre-diabetic state, which means that we might have to start to treat these abnormalities earlier than was recognized before. Several studies are still on-going to clarify the effect of treating this syndrome, thus we have to pay attention to the outcomes of these studies.

III.d. Management of Atherosclerotic Diseases

In those patients with a history of diseases caused by atherosclerotic changes such as brain infarction, myocardial infarction, renal sclerosis, arterial sclerosis obliterance or others, it has to be assumed that the systemic atherosclerotic changes are on-going, in the process seriously jeopardizing the function of many organs. ACE-I is the proven strategy to improve the prognosis in these patient's by reducing cardiovascular death, the risk for myocardial infarction (MI) and for stroke. Studies also suggested that ACE-I may reduce the incidence of new HF as well as the decrease of the left ventricle ejection fraction (LVEF), though this remains controversial.

III.e. Cardiotoxins and Others

There are suggestions that for the prevention of HF some agents should be better avoided, although the logic for these believes has not been proven. Many HF programs, for example, limit alcohol consumption to some extent. Smoking, the use of cocaine or amphetamines are also believed to be toxic. However it is well known that certain anti-tumor agents such as anthracyclines and also irradiation of the mediastinum may cause cardiac dysfunction. There is no clear evidence for the benefit of early treatment of these subjects, but close attention is certainly advisable.

IV. TREATMENT OF ASYMPTOMATIC HEART FAILURE WITH STRUCTURAL ABNORMALITIES

Asymptomatic patients (Stage B) are usually treated with the guidance of surrogate markers such as blood tests, echo-cardiography, chest X-ray and others, but we still are not sure to what extend these markers are really useful. The only information we can trust in this situation is obtained by clinical observation and on the basis of this clinical information and by using appropriate guidelines these patients should be treated. It should be realized that the benefit of our interventions is then hard to estimate for individual patients.

IV.a. β-Blockers and Angiotensin Converting Enzyme Inhibitors (ACE-I)

Administration of one of the β-blockers and an ACE-I is mandatory for all patients with a recent MI, regardless of the ejection fraction (EF). If the LVEF is reduced in patients without a history of MI, β-blockers and/or ACE-I should be administrated as long as the patients do not have heart failure symptoms. If an ACE-I is contraindicated, it has to be substituted by an ARB, if the patient is post-MI with low EF, but no manifest HF. This may also be true without a history of MI. ACE-I and ARB are beneficiary for those with hypertension and left ventricular hypertrophy (LVH), without HF symptoms.

IV.b. Calcium Antagonist and Digoxin

Verapamil and diltiazem have negative inotropic effects. These calcium channel blockers may be harmful in asymptomatic patients with a low LVEF and in post-MI patients without HF symptoms. Digoxin will not be good to use in patients with low EF, with sinus rhythm and no history of HF symptoms, because the benefits will not exceed the risk.

V. TREATMENT OF CURRENT OR PRIOR-SYMPTOMATIC HEART FAILURE PATIENT

Once the patient experienced HF symptoms, the risks for this patient will substantially increase. The objectives of any treatment in this Stage C population are (1) relief of the HF symptoms, (2) disappearance of HF symptoms and (3) prevention of progression of HF and sudden cardiac death. Treatments described in Stage A and B are also of value for this Stage C population.

The drug regimens which are recommended in this text are considered to be evidence based.

As left ventricular dysfunction is a major predictor of sudden arrhythmic death, cardiac death and total mortality, it can be stated that in general sudden cardiac death prevention is achievable with the combination of an implantable cardioverter defibrillator (ICD) and medical therapy.

V.a. Diuretics

Symptomatic or prior-symptomatic fluid retention responds well to treatment with diuretics and salt restriction if LVEF is reduced. This will usually improve current HF symptoms. Especially, an aldosterone antagonist like spironolactone should be added in selected patients with advanced HF symptoms and reduced LVEF with preserved renal function. Potassium has to be normal and should be carefully monitored. Patients with renal dysfunction and with serum creatinine levels >2.5 mg/dl in men and >2.0 mg/dl in women are contraindicated for aldosterone antagonists.

V.b. ACE-I and ARB

ACE-I is recommended for all the patients in this stage unless contra-indicated. If contraindications for ACE-I exist an ARB can be given. However, the routine combination of ACE-I, ARB and aldosterone antagonists is not to be recommended.

V.c. β-Blocker

Bisoprolol, carvedilol and sustained release metoprolol succinate are β-blockers for which it has been proven that they can reduce mortality in stable patients. One of these should be prescribed unless contraindicated.

V.d. Vasodilators (Nitrate, Calcium Antagonist)

Vasodilators can be considered as 'symptom relievers' in this stage. However they are not the main agents for HF treatment because a reduction of mortality has not been established. A combination of hydralazine and a nitrate might be a reasonable strategy if HF symptoms are persistent despite ACE-I and β-blocker combination therapy. If this ACE-I and β-blocker combination is contra-indicated or is not tolerated, Vasodilators can be used without them.

Calcium channel blockers are not indicated for routine use in this stage.

V.e. Digitalis and Positive Inotropic Agent

Digitalis may be used in this stage for a reduction of hospitalization. However long-term infusion of positive inotropic drugs are harmful and their use is only indicated for palliation in end stage patient.

V.f. Anti-arrhythmic Drug

Beta-blocker will have anti-arrhythmic effects, but not all of them have been proven to reduce mortality. The use of amiodarone in heart failure was associated with an approximate 20–25% reduction in deaths. However amiodarone was also associated with a 120–124% increase in side effects. In patients with congestive heart failure, dofetilide can effectively convert atrial fibrillation to sinus rhythm and maintain sinus rhythm after conversion. Although hospitalization for congestive heart failure is reduced, dofetilide does not affect mortality. The use of sodium channel blockers is sometimes unavoidable, but one has to realize that verapamil and diltiazem, calcium antagonists classified as cardiosuppressive, have negative inotorpic and chronotropic effects. Vasoselective calcium antagonists will not decrease survival, but they do not have antiarrhythmic effects. The Class Ic antiarrhythmic agent flecainide or the Class Ia antiarrythmic disopyramide also reduce myocardial contractility.

VI. TREATMENT OF REFRACTORY END-STAGE HEART FAILURE

Drug therapy and the use of cardioverter defibrillators will not improve the prognosis of patients in this stage. Cardiac transplantation will be the only option. With the patient's informed consent, even inactivation of an ICD can be considered as a possible option in this stage of the disease. The critical issue is fluid retention control. To achieve this objective, the administration of intravenous positive inotropic agents cannot be weaned off. As a strategy for palliation, vasodilators are sometimes used even though they may worsen mortality.

VII. CONCLUSION

Once vasodilatation was considered to be a good strategy, as it improves HF symptoms. However later studies showed that the disease itself was not influenced. The accent of HF treatment has moved to progression prevention with rigorous suppression of the renin angiotensin aldosterone system. Therapy with β-blockers was also proven to be effective for the reduction of mortality. These treatments should be started early and the evaluation of their effectiveness in individual patients is difficult. As brain natriuretic peptide (BNP) is produced by the heart and more BNP is released in heart failure, the measurement of BNP in the blood has become popular as surrogate marker for the severity of heart failure and for the response of treatment for heart failure.

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Chapter 34

Cardiovascular and Renal Diseases D: Pharmacological Treatment of Cardiac Arrhythmias

Hirotsugu Atarashi

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I. INTRODUCTION

Cardiac arrhythmias developed when abnormal electrical impulses are formed in the heart. Arrhythmias can be classified clinically as bradyarrhythmias or tachyarrhythmias. The term antiarrhythmic agent is only used for drugs that treat tachyarrhythmias. Termination and prophylaxis of tachyarrhythmias are the major clinical effects of antiarrhythmic agents, and a reduction of cardiac mortality (including sudden cardiac death) produced by lethal ventricular tachyarrhythmias is also expected. The classic agents, such as quinidine and procainamide, are Na^+ channel blockers that act to reduce the conduction velocity or to prolong the refractoriness of myocardium. However, these electrophysiologic effects may also have the potential to produce new arrhythmias or to aggravate existing arrhythmias. Such undesirable actions of these agents are called proarrhythmic effects. Almost all antiarrhythmic agents have negative chronotropic and inotropic actions, which may also contribute to a proarrhythmic effect. Patients with organic heart disease have the highest risk for proarrhythmic effects, especially patients with a history of congestive heart failure or impaired left ventricular function. Therefore, antiarrhythmic agents should be carefully selected for the target arrhythmia and it should be recognized that not all arrhythmias need drug treatment. The major advantage of antiarrhythmic agents is improvement of the quality of life and may also be the prevention of sudden cardiac death.

In the conventional classification (see Vaughan-Williams, 1970), antiarrhythmic agents were grouped on the basis of the dominant electrophysiologic action of these drugs: Class I agents have a direct membrane action and depress Na^+ channel activity with or without a K^+ channel effect. Later, Class I drugs were divided into three groups: Ia agents that prolong the action potential duration (quinidine, procainamide, disopyramide, etc.); Ib agents that shorten the action potential duration (lidocaine, mexiletine, etc.); and Ic agents that cause marked slowing of conduction with little or no effect on ventricular repolarization (flecainide, propafenone, etc.). Class II agents are antagonists of sympathetic nervous activity (β-blockers: propranolol, atenolol, etc.). Class III agents act predominantly on refractoriness (amiodarone, sotalol, etc.), while Class IV agents alter Ca^{2+} channel mediated conduction (verapamil, etc.).

Clinical use of antiarrhythmic agents requires not only an accurate knowledge of the genesis of arrhythmias, but also an understanding of the precise mechanism of action of each agent. Antiarrhythmic therapy is complicated by the high incidence of severe and even fated adverse events. Most Na^+

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channel-blocking agents act as cardiodepressant poisons and consequently the possibility of antiarrhythmic drugs aggravating a preexisting proarrhythmic electrophysiological mechanism must always be considered. To improve the clinical approach to the use of antiarrhythmic drugs, the Task Force of the Working group on Arrhythmias of the European Society of Cardiology (see Task Force of the Working Group on Arrhythmias, 1991) proposed the Sicilian gambit based on the information concerning the electrophysiological properties of antiarrhythmic agents shown in Fig. 1.

II. ARRHYTHMIAS RELATED TO THE SINUS NODE

II.a. Sinus Tachycardia

When the electrocardiogram reveals a sinus rate greater than 100/min, this is defined as sinus tachycardia. This arrhythmia is usually non-pathological (reactive sinus rate acceleration). However, sinus tachycardia may be pathological under several circumstances. Pathological sinus tachycardia is mediated by increased sympathetic activity and/or catecholamine levels, thyrotoxicosis, or the ingestion of agents with sympathomimetic or direct cardiostimulating effects (include caffeine or cocaine). Removal of the offending agents and/or use of a β-blocker will usually control the symptoms. In patients with hyperthyroidism a β-blocker will be needed.

II.b. Sinus Bradycardia

Sinus rhythm with a rate of less than 60/min is defined as sinus bradycardia. This bradycardia is usually a physiological response. Pathological and/or symptomatic sinus bradycardia may suggest sinus node dysfunction (see sick sinus syndrome). Vagally induced sinus bradycardia may be responsive to atropine, but only needs to be treated if symptomatic. Atropine doses of less than 0.5 mg may cause a paradoxical increase in vagal bradycardia.

II.c. Sick Sinus Syndrome

Inappropriate sinus bradycardia, sinoatrial block, and bradycardia–tachycardia syndrome (bradycardia followed by supraventricular tachyarrhythmias such as atrial fibrillation) are included in this syndrome. Treatment of sick sinus syndrome is generally based upon the patients symptoms. In general, bradycardia or sinus arrest that is asymptomatic requires no therapy. At present, the accepted indications for implantation of a permanent pacemaker are marked bradycardia with a rate below 40/min or pauses longer than 3.0 s accompanied by symptoms. With respect to the pharmacological approach to this category of bradyarrhythmias, a new antiplatelet agent, cilostazol (a phosphodiesterase-III inhibitor), may produce a beneficial chronotropic effects. Theophylline may also effective for these bradyarrhythmias. However, it is not rare to encounter adverse reactions during long-term theophylline treatment.

III. SUPRAVENTRICULAR ARRHYTHMIAS

III.a. Atrial–Supraventricular Premature Contraction (APC/SVPC)

The therapy of atrial premature contractions (APC) depends on the patient's symptoms. Asymptomatic APC need not be treated. However, asymptomatic APC may be associated with an increased risk of atrial fibrillation. In such cases, suppression of APC may be useful in prolonging the time to the onset of atrial fibrillation. β-blockers or Class Ia/Ic agents may be effective for suppression of APC. The use of Class Ic agents, such as flecainide, may achieve almost complete suppression of APC, but the risk-benefit ratio of these agents has not been studied.

III.b. Atrial Tachycardia

Generally, atrial tachycardia has a rate between 120 to 220/min (slower than atrial flutter). Paroxysmal atrial tachycardia with block is classically associated with digitalis toxicity. The electrocardiogram of atrial tachycardia shows isoelectric intervals between the P waves. Digitalis-induced paroxysmal atrial tachycardia (usually associated with AV block) will slow in rate and may terminate following the discontinuation of digitalis therapy and/or administration of potassium. Some cases of paroxysmal atrial tachycardia may be suppressed by adenosine and/or verapamil, suggesting a possible role for triggered activity.

III.c. Atrial Fibrillation

Atrial fibrillation (AF) is one of the most common rhythm disturbances, and is characterized by the absence of discrete P wave and an irregular ventricular rhythm. Fibrillatory waves are either fine or

Drug	Channels						Receptors				Pumps	Clinical effects			ECG effects		
	Na			Ca	K	If	α	β	M_2	A_1	Na-K ATP	LV function	Sinus Rate	Extra cardiac	PR	QRS	JT
	Fast	Med	Slow														
Lidocaine	○											→	→	⊘			↓
Mexiletine	○											→	→	⊘			↓
Tocainide	○											→	→	●			↓
Moricizine	◐											↓	→	○		↑	
Procainamide		Ⓐ			⊘							↓	→	●	↑	↑	↑
Disopyramide		Ⓐ			⊘				○			↓	→	⊘	↑↓	↑	↑
Quinidine		Ⓐ			⊘		○		○			→	↑	⊘	↑↓	↑	↑
Propafenone		Ⓐ						⊘				↓	↓	○	↑	↑	
Aprindine		◐		○	○	○						→	→	⊘	↑	↑	→
Cibenzoline			Ⓐ	○	⊘				○			↓	→	○	↑	↑	→
Pirmenol			Ⓐ		⊘				○			↓	↑	○	↑	↑	↑→
Flecainide			Ⓐ		○							↓	→	○	↑	↑	
Pilsicainide			Ⓐ									↓→	→	○	↑	↑	
Encainide			Ⓐ									↓	→	○	↑	↑	
Bepridil	○			●	⊘							?	↓	○			↑
Verapamil	○			●			⊘					↓	↓	○	↑		
Diltiazem				⊘								↓	↓	○	↑		
Bretylium					●		◩	◩				→	↓	○			↑
Sotalol					●			●				↓	↓	○	↑		↑
Amiodarone	○			○	●		⊘	⊘				→	↓	●	↑		↑
Alinidine					⊘	●						?	↓	●			
Nadolol								●				↓	↓	○	↑		
Propranolol	○							●				↓	↓	○	↑		
Atropine									●			→	↑	⊘	↓		
Adenosine										□		?	↓	○	↑		
Digoxin									□		●	↑	↓	●	↑		↑

Relative potency of block: ○ Low ⊘ Moderate ● High A Activated state blocker
□ Agonist ◩ Agonist/Antagonist I Inactivated state blocker

Fig. 1. Summary of the most important actions of antiarrhythmic drugs on membrane channels, receptors, and ionic pumps in the heart. The drugs are arranged in a fashion similar to the columns, so that generally the entries for their predominant actions form a diagonal. Most of these drugs are already available in Europe and the USA, but aprindine, pirmenol, cibenzoline, and pilsicainide are only available in Japan. (Reproduced with permission from Ogawa et al., 1997.)

coarse, and occur at a rate greater than 400/min. AF can be either paroxysmal, persistent or chronic. Acute AF in hemodynamically compromised patients with shock or congestive heart failure and patients with angina is best treated with electrical cardioversion. To prevent thromboembolism, it is recommended that all patients with AF of unknown duration or persisting for more than 48 h, anticoagu-

lation should be given for 3 weeks before cardioversion and should be continued for 4 weeks afterwards. In an emergency, intravenous heparin can be given before electrical cardioversion in patients without contraindications. According to the ACC/AHA/ECS 2006 Guidelines for the management of patients with atrial fibrillation (see Fuster et al., 2006), flecainide, dofetilide, propafenone or ibutilide are recommended for the acute termination of AF. But it is important that before initiating antiarrhythmic drug therapy, treatment of predisposing or reversible factors contributing AF is important. In patients with paroxysmal or persistent AF, a single oral dose of propafenone, flecainide, or pilsicainide ('pill-in-the-pocket') can be administered to terminate early out side the hospital once this method has proved safe in hospital for the selected patients. Amiodarone and sotalol are not very effective for acute termination, but are very effective in preventing recurrence. In patents with AF without obvious heart disease, Class Ic drugs such as flecainide are effective for conversion or the maintenance of sinus rhythm. For patients with coronary artery disease, sotalol is recommended as first line drug for the preventing the recurrence. Amiodarone is useful in patients with reduced left ventricular function and other antiarrhythmics resistant patients. Digoxin and sotalol mey be harmful when used for the purpose of cardioversion. Recent advancement of electrophysiology and technology, catheter ablation become a reasonable alternative option for the prevention of recurrence of AF in patients with little or no left atrial enlargement.

III.c.1. Ventricular Rate Control in AF

Pharmacological agents that depress conduction and prolong refractoriness in the atrioventricular (AV) node are frequently required for control of symptoms and improvement of hemodynamics during AF. β-blockers, digoxin, diltiazem, and verapamil are commonly used drugs that prolong refractoriness and decrease the conduction velocity in the AV node. Acute rate control is most effective with intravenous esmolol (ultra-short-acting β-blockers), verapamil, diltiazem, or other β-blockers. For long-term rate control in chronic AF, β-blockers are more effective than verapamil, diltiazem, and digoxin and should be the initial drugs of choice. Digoxin should be considered as first-line treatment only in patients with congestive heart failure secondary to impaired ventricular systolic function. Digoxin is not effective to suppress the excessive increasing heart rate during exercise.

III.c.2. AF and Wolff–Parkinson–White Syndrome

Patients with anterograde conduction via an accessory pathway during AF may be at risk of sudden cardiac death if the pre-excited ventricular response is rapid (i.e., the shortest pre-excited RR interval less than 250 ms). Drugs such as digoxin, verapamil, diltiazem, and β-blockers will be ineffective in blocking conduction via the accessory pathway, and will frequently enhance conduction resulting in hypotension or an increased risk of ventricular fibrillation. These drugs should not be given in such a situation. For the termination of AF or ventricular rate control, intravenous procainamide or ibutilide (also Class Ic agents such as flecainide or pilsicainide) is the treatment of choice. At present, catheter ablation of the accessory pathway is strongly recommended, particularly those with syncope due to rapid heart rate or those with a short anterrograde accessory pathway refractoriness.

III.c.3. Prevention of Thromboembolism in AF

The rate of ischemic stroke among elderly patients with AF averages 5% per year and this rate is about six times that of individuals without AF. Most ischemic stroke associated with AF are probably due to embolism arising from stasis induced thrombi formed in the left atrium. At present, for all patients with AF, except those with lone AF and contraindications, antithronbotic therapy with a vitamin K antagonist (warfarin) is recommended. Aspirin for the prevention of stroke in patient with AF may increase the risk of bleeding and not recommended especially in aged women. For high-risk AF patients (including age 75 or greater, hypertension, heart failure, impaired left ventricular function, and diabetes mellitus), warfarin administration to maintain an PT-INR range of 2.0–3.0 is recommended.

According to the Cochrane database dealt with the efficacy of drugs for the prevention of stroke in patients with atrial fibrillation. The reviewers' conclusions with respect to antiplatelet therapy for preventing stroke in patients with nonrheumatic atrial fibrillation and a history of stroke or transient ischemic attacks were: "Aspirin may reduce the risk of vascular events in people with nonrheumatic atrial fibrillation, but the effect shown in the single trial was not statistically significant". A review of the efficacy of anticoagulants versus antiplatelet therapy for preventing stroke concluded: "The evidence from

one trial suggests that anticoagulant therapy can benefit people with nonrheumatic atrial fibrillation and recent cerebral ischaemia. Aspirin may be a useful alternative if there is a contraindication to anticoagulant therapy. The risk of adverse events appears to be higher with anticoagulant therapy than aspirin". The conclusions of a second review on the efficacy of anticoagulants for preventing stroke were: "The evidence suggests that anticoagulants are beneficial, without serious adverse effects, for people with nonrheumatic atrial fibrillation and recent cerebral ischaemia".

III.d. Atrial Flutter

Atrial flutter is generally seen in patients with significant underlying heart disease. The electrocardiographic diagnosis of atrial flutter is based upon continuous baseline 'sawtooth' oscillations in the inferior leads of the ECG. The ventricular response to atrial flutter may be regular or variable, depending upon whether there is a constant or irregular AV block. Class Ia or Ic agents (quinidine, procainamide, flecainide, etc.) are less effective for termination of atrial flutter than Class III K^+ channel blockers (dofetilide, ibutilide). Ibutilide is very effective for acute conversion to sinus rhythm, but is associated with a relatively high incidence of torsades de pointes.

Class I drugs should not be used initially, as they decreases the atrial rate and facilitate AV conduction, leading to the danger of producing an abrupt change to 1 : 1 AV conduction. Esophageal pacing is very effective for conversion of atrial flutter to sinus rhythm in hemodynamically stable patients. In the absence of digitalis therapy and provided potassium is normal, synchronized DC cardioversion (50 J) is safe and effective. If you have no cardioversion equipment or esophageal pacing system, you should chose intravenous digoxin (0.5 mg) or verapamil (0.125–0.150 mg/kg) as the initial therapy for ventricular rate control. Radiofrequency catheter ablation can be done safely and effectively to abrogate recurrence of the common type of atrial flutter.

III.e. Supraventricular Tachycardia

Supravantricular tachycardia is classified into several types depending on the localization of the reentrant circuit. The most common type is AV reentrant tachycardia via an accessory pathway (i.e., the bundle of Kent). The main objective of therapy is to increase vagal tone in order to inhibit conduction via the AV node. For the termination of this tachycardia, intravenous bolus injection of adenosine or ATP is very effective. Intravenous verapamil (0.125–0.150 mg/kg) is also highly effective. An Na^+ channel blocker with slow recovery kinetics such as flecainide or propafenone is reasonably effective in blocking the retrograde conduction via the accessory pathway. For the prevention of supraventricular tachycardia, a slow kinetic Na^+ channel blocker (Class Ic: such as flecainide or pilsicainide) should be chosen as the first line treatment because their pharmacokinetics are not affected by hepatic first-pass metabolism unlike verapamil. Following recent advances of clinical electrophysiology, almost all supraventricular tachycardias can be abolished by radiofrequency catheter ablation. Therefore, the pharmacological treatment of such tachycardias has become less frequent.

IV. VENTRICULAR ARRHYTHMIAS

IV.a. Ventricular Premature Contractions (VPC)

The goals for the treatment of VPC are to reduce the patient's symptoms and to prolong survival. As mentioned earlier, the presence of VPC is an independent risk factor for various heart diseases. However, successful suppression of VPC may not improve the prognosis. The results of the Cardiac Arrhythmia Suppression Trial (CAST) conducted in post-myocardial infarction patients with asymptomatic VPC provided some startling results. The study was interrupted because of higher mortality rate was demonstrated in the patients treated with encainide or flecainide despite successful reduction of the VPC frequency. The CAST II trial was subsequently conducted with moricizine, This trial was also terminated prematurely when it was found that any treatment benefit was unlikely to be demonstrated within the planned duration of the study. The results of these studies suggest that in patients with organic heart disease and reduced left ventricular function, it appears wise to avoid antiarrhythmic therapy with Class I agents for the suppression of asymptomatic VPC.

More recently, several large-scale clinical trials have been performed in patients with myocardial infarction and/or congestive heart failure. Some of the trials have confirmed a preventive effect on

sudden cardiac death in these patient populations. The first trial that suggested a decrease in cardiac mortality was the Basel Antiarrhythmic Study of Infarct Survival (BASIS) trial (see Burkart et al., 1990) with amiodarone. Two randomized double-blind placebo-controlled trials have assessed the effect of amiodarone after myocardial infarction. EMIAT (see Julian et al., 1997) investigated whether the drug reduced mortality in patients at a high risk of death after myocardial infarction, irrespective of whether they had ventricular arrhythmias. This study showed found that cardiac and all-cause mortality did not differ between the amiodarone and placebo groups, but also found a 35% reduction in the risk of arrhythmia-related deaths among amiodarone-treated patients. CAMIAT (see Cairns et al., 1997) assessed the effect of amiodarone on the risk of resuscitated ventricular fibrillation or arrhythmic death in 1202 survivors of myocardial infarction with frequent or repetitive VPC. Amiodarone reduced the incidence of these outcomes, and the risk reduction was greatest among patients with congestive heart failure or a history of myocardial infarction. Despite these apparent benefits, both studies showed no improvement in total mortality. Nul et al. (see Nul et al., 1997) pointed out that amiodarone-induced heart rate slowing may be an important benefit for patients with severe heart failure, and they suggested that chronic amiodarone therapy could be recommended for patients with congestive heart failure who had a high resting heart rate and should be avoided for those with slower rates. Because of its large volume of distribution, a higher loading dose of amiodarone is required initially. The oral loading dose of amiodarone is 400 to 800 mg for up to 14 days, followed by 200–400 mg/day as long-term maintenance therapy. Intravenous treatment is usually initiated with a dose of 150 mg over 10–15 min. Amiodarone interacts with many drugs and the doses of warfarin, digoxin, and other antiarrhythmic agents (flecainide, procainamide, etc.) may require reduction during concomitant amiodarone therapy. With long-term therapy the most serious adverse effect is pulmonary fibrosis, which can be progressive and even fatal. It is important to detect this problem early by performing serial chest radiographs or lung function tests.

β-Blocker therapy has been shown to reduce post-myocardial infarction mortality by approximately 20% and is well accepted as a part of the postinfarction therapeutic regimen. In patients without any organic heart disease, a proarrhythmic effect is less common, and Class I agents may be safe and effective for the suppression of symptomatic VPC.

IV.b. Ventricular Tachycardia

Ventricular tachycardia (VT) is defined as three or more successive beats of ventricular origin at a rate greater than 100/min. When the tachycardia lasts for less than 30 s, this termed nonsustained, while it is considered sustained if it lasts for more than 30 s or requires termination because of hemodynamic instability. Treatment of ventricular tachycardia depends upon the hemodynamic condition of the patient. Generally, patients with VT have serious hemodynamic problems and need immediate electrical defibrillation, especially if they also have organic heart disease. If the patient is in minimal distress, pharmacological treatment can be considered. The indications for pharmacological therapy in patents with non-sustained VT are almost the same as those for treating VPC. Intravenous Class I agents may terminate sustained VT, but in patients with impaired left ventricular function, a proarrhythmic effect is not rare. In patients with acute myocardial infarction, intravenous lidocaine is the most frequently used first-line drug for the termination and prevention of VT, because of its lesser proarrhythmic effect than other Class I agents. Lidocaine is given as a 1.0 mg/kg bolus injection for the termination of VT and infused at 0.2–4.0 mg/min for prevention. In hemodynamically unstable patients with sustained VT, an implantable cardioverter–defibrillator (ICD) should be the choice for prevention of sudden cardiac death.

IV.b.1. Idiopathic VT

This arrhythmia usually occurs in young people and preponderantly in men. The electrocardiogram often shows right bundle branch block with left axis deviation (superior axis deviation). This type of VT is often sensitive to verapamil or other calcium channel blockers, but not to β-blockers. Radiofrequency catheter ablation may be helpful to abolish it.

IV.b.2. Exercise-Related VT

Exercise-related VT frequently arises from the right ventricular outflow tract and may be easily evaluated by catheter mapping in an electrophysiology laboratory. The treatment of first choice for chronic therapy of this arrhythmia has been β-blockers, but radiofrequency catheter ablation should also be considered.

IV.b.3. Acute Coronary Syndrome

According to recent ACC/AHA/ESC Guidelines (see Zipes et al., 2006), in patients with sutained VT, direct-current cardioversion is appropriate and most effective, and also intravenous procainamide (or ajmaline in some European countries) is recommended as a reasonable choice for initial treatment for sustained monomorphic VT in patients with acute coronary syndrome. Intravenous amiodarone or lidocaine may be reasonable chose as alternative treatment.

IV.b.4. Cardiomyopathy

Patients with sustained monomorphic VT and dilated cardiomyopathy represent a very high risk group. Sudden death may occur in up to 50%, but the majority of the deaths are associated with ventricular fibrillation rather than VT. Many patients with recurrent VT and dilated cardiomyopathy that may not be responsive to drug therapy are ultimately candidates for heart transplantation. The ICD is especially useful, since it may permit significant reduction or elimination of the need for antiarrhythmic agents with potential negative hemodynamic effects. In patients with hypertrophic cardiomyopathy, the incidence of monomorphic VT is relatively low, and polymorphic VT is more common even in electrophysiology laboratory studies. Drug therapy for these patients may have two potential benefits, including arrhythmia reduction and prevention and a decrease of obstructive phenomena. Antiarrhythmic drugs that have a negative inotropic effects such as β-blockers or verapamil may be helpful. For drug-resistant patients, an ICD may be most useful.

IV.b.5. Mitral Valve Prolapse

No data exist regarding the efficacy of antiarrhythmic therapy in mitral valve prolapse patients with hemodynamically significant mitral regurgitation. At present, β-blockers seem preferable when ventricular performance permits. Class I agents should be used with careful follow-up by ambulatory monitoring and/or exercise testing to avoid any proarrhythmic effects.

IV.b.6. Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)

ICD implantation is recommended for prevention of sudden cardiac death in patients with ARVC with documented sustained VT or ventricular fibrillation. Drug therapy with amiodarone or stalol can be effective in selected patients with ARVC.

IV.c. Ventricular Fibrillation and Sudden Cardiac Death

The cornerstone of therapy for ventricular fibrillation is electrical defibrillation. In the acute setting, defibrillation is first-line therapy. Intravenous bretylium can occasionally contribute to conversion, but this is infrequent. In the management of out-of-hospital cardiac arrest, high-dose epinephrine (5 mg intravenously) improves the rate of successful resuscitation in patients with asystole, but not in those with ventricular fibrillation, when compared with the standard dose of 1 mg. Vasopressin (40 U intravenously) may more effective than 1 mg intravenous epinephrine in out-of-hospital patients with ventricular fibrillation that is resistant to electrical defibrillation. The OPTIC study (see Connolly et al., 2006) showed that amiodarone plus β-blocker is superior than sotalol or β-blocker alone for reducing ICD shocks in patients with reduced left ventricular function and history of sustained VT, VF, or cardiac arrest.

IV.d. Ventricular Tachyarrhythmias in Long QT Syndrome

Torsade de pointes (a twisting type of polymorphic VT) is the most typical ventricular tachyarrhythmias developing in patients with a prolonged QT interval. Congenital long QT (LQT) syndrome is known as the Romano–Ward syndrome or the Jervell and Lange–Nielsen syndrome. These are uncommon syndromes for which genetic studies have elucidated abnormalities in the last decade. The long QT syndrome can be divided into LQT1, LQT2, and LQT3 subgroups having abnormalities of chromosomes 3, 7 and 11, respectively. Patients with LQT1 appear to benefit most from β-blockers, LQT2 patients may benefit from an increase of the serum K^+ concentration and also from K^+ channel openers such as nicorandil, and LQT3 patients may respond to Na^+ channel blocking by mexiletine or by other Class Ib or Ia agents. These chromosomal abnormalities may be related to electrocardiographic T wave morphology, making it possible to select the therapeutic regimen from the electrocardiogram. Presently, pharmacologic therapy of congenital LQT syndrome should be started with a β-blocker and avoidance of hypokalemia, using mexiletine as adjunctive therapy. If this approach fails, an ICD should be implanted.

In patients with secondary (non-congenital) LQT syndrome, the factors that produce a prolongation

of the QT interval should be addressed. This syndrome may develop due to hypokalemia, hypomagnesemia, Class Ia agents (quinidine, disopyramide, etc.), Class III agents (sotalol, ibutilide, etc.), or noncardiovascular drugs. Acute treatment for torsades de pointes depends on the hemodynamic status of the patient. Short bursts of torsades may be treated with intravenous magnesium chloride and intravenous lidocaine. Temporary cardiac pacing to increase the patient's heart rate for the purpose of decreasing the dispersion of depolarization may also decrease or abolish the bursts of torsades.

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Chapter 34

Cardiovascular and Renal Diseases E: Pharmacological Treatment of Renal Diseases

Yackoob K. Seedat

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I. ACUTE RENAL FAILURE

I.a. Causes

Before one can investigate the causes of acute renal failure (ARF), prerenal and postrenal causes must be excluded. The most common causes of prerenal failure are hypovolaemia and impaired cardiac function. Prerenal causes of oliguria are characterized by a high urine osmolality, high urine-plasma urea nitrogen and urine-plasma creatinine ratios and low urinary sodium excretion. The postrenal causes of azotemia are: (1) bilateral obstruction of the ureters, either extra-ureteral due to neoplasia of the cervix, prostate, endometriosis or intraureteral obstruction due to sulfonamide or uric acid crystals, blood clots, stones or papillary necrosis; (2) bladder neck obstruction from prostatic hypertrophy, bladder carcinoma or functional as a result of neuropathy; or (3) urethral obstruction. The intrarenal causes of ARF include acute tubular necrosis (ATN) which may be postischemic or nephrotoxic, acute interstitial nephritis due to drug hypersensitivity, immunologic disorders or infections, acute glomerulonephritis, bilateral renal artery occlusion, hemolytic uraemic syndrome and thrombotic microangiopathy due to thrombotic thrombocytopenic purpura.

Hypoperfusion as a cause of ARF may occur after trauma, surgery, hemorrhage or dehydration. The hypoperfusion is a graded parenchymal injury that ranges from negligible damage in prerenal azotemia to frank ATN. The latter, which often manifests as oliguric renal failure is, in most cases, reversible. The duration is variable and lasts from a few days to 4–6 weeks. Once diuresis ensues the blood urea and serum creatinine will gradually decrease to normal values without any previous evidence of renal impairment. Myoglobinuria is a frequent cause of ARF and often occurs from alcohol abuse, crush injury, whiplash injury, muscle necrosis from prolonged unconsciousness and seizures. Red blood cells are not seen in the urine microscopically even though the urine is dipstick-positive for blood due to myoglobin. The patient will complain of muscle pain, and a high serum creatinine kinase usually occurs. Intravascular hemolysis secondary to a transfusion reaction is also a well-known cause of ARF. The aminoglycosides are commonly encountered in hospitalized patients as a cause of nephrotoxicity. The ARF is typically non-oliguric. Amphotericin may cause ARF when the total dose exceeds 2–3 g. Cyclosporin also displays dose-dependent nephrotoxicity. A renal biopsy may be necessary to distinguish transplant rejection from cyclosporine nephrotoxicity. Other agents which are associated with ARF include radiographic contrast media and herbal medicines such as *Callilepis laureola*.

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I.b. Diagnosis

The essentials for the diagnosis are a sudden increase in blood urea nitrogen or serum creatinine, often accompanied by oliguria. The oliguria is self-limiting over a few days to 4–6 weeks. In some instances, the distinction between acute renal failure (ARF) and chronic renal failure (CRF) may not be overt. Kidney size estimations through ultrasonography may be helpful to differentiate ARF from CRF, since patients with ARF often have kidneys of normal size or slightly larger and patients with CRF often have kidneys of small size. Renal osteodystrophy suggests CRF.

I.c. Management of Acute Renal Failure

I.c.1. Dialysis

This should be initiated once oliguric ATN has been established – and performed on an intermittent basis. Mental status abnormalities, pericarditis, gastrointestinal and hemorrhagic disorders are indications for dialysis; other indications are fluid overload and hyperkalemia. Non-oliguric patients in general do not require as many dialyses as do patients with oliguria generally because hyperkalemia is not a problem.

I.c.2. Medical Treatment

I.c.2.1. Fluid intake. This includes restriction of fluid intake to less than 1 liter per day if, as in oliguric renal failure, daily urine volumes are 500 ml or less and daily insensible losses are estimated to be 500–700 ml. In non-oliguric renal failure daily urine losses plus insensible losses may be in excess of 2 l/day and daily intake obviously has to be adjusted accordingly. Careful balance of intake and output of fluid and electrolytes is extremely important in ARF patients, both oliguric and non-oliguric.

I.c.2.2. Protein and calorie intake. Regulation of protein and calorie intake is also important in acute renal failure. Dietary protein restriction may be used to slow the development of azotemia. An intake of adequate non-protein calories in the form of carbohydrates is necessary to minimize the rate of endogenous catabolism, that is the so-called protein-sparing effect of carbohydrates. The use of supplemental amino acids in the hope of hastening recovery from ATN has been suggested. However, the available data do not indicate clearly that hyperalimentation programs, using combinations of glucose and amino acids, are of benefit in the management of the stress-related ARF patient.

I.c.2.3. Hyperkalemia. Treatment of hyperkalemia depends on the level of the serum potassium, the state of neuromuscular irritability and the chronicity of the hyperkalemic state. In acute hyperkalemic states, if the serum potassium is less than 6.5 mEq/l and there are no ECG changes or only peaked T waves, potassium intake can simply be decreased. If the serum potassium is greater than 6.5 mEq/l or with more advanced ECG changes like peaked T waves, decrease R-wave amplitude and advanced QRS abnormalities, more decisive steps are necessary. There should be continuous monitoring with ECG during therapy. Intravenous calcium counteracts the neuromuscular effects of hyperkalemia. Calcium therapy has an onset of action within minutes. The effect lasts only half an hour. Redistribution of potassium from the extracellular to the intracellular space is an effective way of treating hyperkalemia. This is done with sodium bicarbonate, administered as one to two ampoules (44–48 mEq) intravenously or by the infusion of glucose and insulin. A solution of 500 ml of 10% glucose with 10 units of regular insulin is recommended. Glucose and insulin have an onset of action within half an hour and this effect lasts for several hours. The lowering of serum potassium by alkalinization may take several hours and is more effective in acidemic patients. β-Agonists, either administered parenterally or inhaled are additional methods of treating hyperkalemia. Ten or 20 mg of nebulized albuterol lowers the serum potassium concentration by approximately 0.6 mEq/l at higher doses. The effect of β-agonists to decrease serum potassium is apparent within 30 min and lasts for at least 2 h. Permanent loss of potassium from the body can be achieved with exchange resins like sodium polystyrene sulfonate (Kayexalate) which can be administered orally or rectally. These resins are not absorbed and they exchange sodium for potassium in the lumen of the gastrointestinal tract. One gram of Kayexalate will remove approximately 1 mEq of potassium from the body. Forty grams of the resin given orally in four divided doses cause a 1.0 mEq/l decrease in the serum potassium concentration in 24 h in patients with renal failure. The duration of the effect depends on the rate of endogenous release of potassium.

I.c.2.4. Other drug regimens. The use of loop diuretics in oliguric patients with ARF may result in diuresis. There is no evidence that these drugs can

alter outcome however. Low-dose dopamine, a renal vasodilator, has been used empirically in critically ill patients with oliguria and acute renal failure, particularly in congestive heart failure. However, from a systematic review it was concluded that there is little justification for the routine administration of low-dose dopamine in patients at risk of renal failure (see Zacharias et al., 2005). Large controlled clinical studies are needed to determine whether dopamine improves renal function or prevents ARF in patients at risk. The combination of multiple medical problems requiring complex drug therapy with rapidly changing organ functions that lead to pharmacokinetic alterations, makes drug regimen design in the intensive care unit challenging. ARF leads to even greater physiologic disturbances requiring additional pharmacologic, nutritional and dialytic support. A variety of renal replacement modalities, both intermittent and continuous, are used to manage the solute, volume and acid-base derangements of patients with ARF. The clinician must consider the importance of both disease and treatment if drug prescribing is to be optimal. Principles of solute removal and concepts of drug regimen design are reviewed by Subach and Marx (see Subach et al., 1997).

II. CHRONIC RENAL FAILURE

Chronic renal failure is characterized by progressive azotemia over weeks and months. It may be a consequence of many primary glomerulonephritic and tubular diseases. The urine abnormalities are dependent upon the underlying disease, although isosthenuria is common when CRF is advanced. Hypertension develops in the majority of patients.

II.a. General Management

II.a.1. Dietary Management and Protein Restriction

Dietary protein has long been thought to play a role in the progression of chronic renal disease, but clinical trials have not consistently shown that dietary protein restriction is beneficial. A meta-analysis including the Modification of Diet in Renal Disease (MDRD) Study, of 1413 patients from 1966 to 1994 showed that dietary protein restriction slows the progression of both diabetic and non-diabetic renal disease (see Klahr et al., 1994). It is advisable to restrict protein intake moderately to 1 g/kg daily.

II.a.2. Electrolyte and Water Restriction

Most patients should eat a diet with no added salt because of associated hypertension or edema. In dialysis patients, sodium intake should be reduced in patients who gain excessive weight between dialysis. Potassium restriction is not usually necessary until oliguria supervenes. Dialysis patients, however, should be educated to what foods are high in potassium, such as citrus foods, nuts, bananas, in order to avoid very high serum levels of potassium before each dialysis. Water restriction may be necessary if predialysis hyponatremia becomes prominent.

II.a.3. Dialysis

Many patients with chronic renal failure start dialysis when the serum creatinine is around 1000 µmol/l and the glomerular filtration rate (GFR) < 10 ml/min. Patients with diabetic nephropathy often require dialysis at an earlier stage, namely GFR 15 ml/min. Most patients at this level of GFR are symptomatic on conservative management. Acceptance to a chronic renal program consisting of dialysis and/or renal transplantation depends on strict criteria of excluding associated clinical disorders and on the availability of resources. Several types of haemodialysis are available. Most patients will require haemodialysis three times weekly. Continuous ambulatory peritoneal dialysis (CAPD) is performed by the patients, and the continual nature of the dialysis has led to better clearance of poorly dialyzable compounds, especially phosphate. This leads to less dietary and fluid restriction and is not associated with symptom swings observed in hemo-dialysis. Peritonitis is a major complication of CAPD. CAPD is a useful alternative to hemo-dialysis and allows more freedom. When vascular access is a problem, especially in children and in diabetic patients, CAPD is valuable. The total cost of CAPD is not much different to hemo-dialysis. However, CAPD is useful in developing countries, as it requires little skilled expertise compared to haemodialysis.

II.a.4. Kidney Transplantation

In most patients who develop CRF, renal transplantation from cadaver donors or living related donors is desirable. Post-transplant immuno-suppression with calcineurin inhibitors (e.g. cyclosporin, tacrolimus), anti-proliferative agents (e.g. azathioprine, mycophenolate mofetil) and steroids (prednisolone), singly or in combination, are required. It has been

shown that tacrolimus is superior to cyclosporin but that it also induces diabetes. The number of drugs and the duration of drug administration may be less in the case of living related donor transplants compared to cadaver transplants.

II.b. Complications

The treatment of the complications of CRF may occur before or during dialysis. They include pericarditis, congestive heart failure, hypertension, hemopoietic abnormalities and renal osteodystrophy.

II.b.1. Pericarditis

The most serious complication of pericarditis is cardiac tamponade which is manifested by shortness of breath and hypotension. Emergency pericardiocentesis is required. In most cases, the frequency and duration of dialysis should be increased after pericarditis develops. Pericarditis is an absolute indication for beginning haemodialysis if the patient has not been previously dialyzed. Indomethacin may be used in patients with chest pain, although its value has not been substantiated by placebo-controlled studies.

II.b.2. Congestive Heart Failure

Fluid overload occurs commonly in patients with renal failure, often in the absence of associated heart disease. If salt and water intake is not controlled in the patient who is oliguric or anaemic, plasma volume and symptoms of congestive heart failure ensue. Hypertension and coronary heart disease with increasing age contributes to the congestive heart failure. Diuretics like loop-diuretics or metolazone may be of value. Digitalis should be used with caution in patients on dialysis as cardiac arrhythmias may ensue in patients receiving dialysis in the presence of hypokalemia.

II.b.3. Hypertension

Hypertension is both a cause and a result of CRF. Most dialysis patients are salt and water sensitive. Thus, if one removes salt and water with the dialysis procedure and minimizes weight gain between dialysis with strict dietary control of salt and water intake, normal blood pressure can be achieved. The availability of newer and effective antihypertensive agents has largely replaced the use of bilateral nephrectomy to control the blood pressure.

II.b.4. Hemopoietic Abnormalities

II.b.4.1. Anaemia. The anaemia of CRF is typically normochromic and normocytic. It is due to decreased production of erythropoietin from diseased kidneys, although low-grade hemolysis does contribute to the anaemia. In patients on haemodialysis, iron is given regularly due to loss of red blood cells in the dialyzer. This is supplemented with water-soluble vitamins like folic acid. Recombinant erythropoietin is very effective in correcting the anaemia of CRF. The effective dose varies from patient to patient. It is given either intravenously (most commonly in patients on haemodialysis) or subcutaneously (for patients on peritoneal dialysis for those who have not started dialysis). Hypertension which may be associated with seizures occurs as a complication of erythropoietin. Blood transfusions have almost been eliminated for dialysis patients since erythropoietin has become available. Cognitive function, sense of well being and sexual function improves with erythropoietin therapy. Anaemia associated with ACE inhibitors may be a problem in renal disease. A decrease in erythropoietin level has been noted when trandolapril, an ACE inhibitor, was given over 3 days.

II.b.4.2. Coagulopathy. Purpura and bleeding tendencies commonly occur in untreated uremia. Bleeding tendencies are common and the platelet counts are only moderately decreased or normal. The bleeding time is prolonged due to a defect in platelet adhesiveness. Platelet transfusions have only a limited value. Cryoprecipitate has a transient effect. Desmopressin is quite effective and is used in preparation for surgery. Conjugated estrogen has been shown to have a beneficial effect and has the advantage of prolonged action.

II.b.5. Renal Osteodystrophy

Renal osteodystrophy is a complex disorder with several pathogenic factors. Histological evidence of bone disease is common in early renal failure and deficits in calcitriol synthesis seems to be an important factor in the pathogenesis of secondary hyperparathyroidism in early CRF. The most common component is osteitis fibrosa manifested as subperiosteal resorption of bone. This is due to decreased excretion as well as increased secretion of parathyroid hormone. In CRF small increments of serum phosphorus cause small decreases in serum calcium,

stimulating the secretion of parathyroid hormone. Because of the phosphaturic effect of parathyroid hormone, the serum phosphorus tends to be normalized but at the expense of higher circulating elevated parathyroid hormone. Osteomalacia is another important component of renal osteodystrophy. Defective kidneys fail to convert 25-hydroxycholecalciferol to 1,25-dihydroxycholecalciferol. This leads to increased losses of calcium in the feces and defective mineralization of the bone. The main goal in treating renal osteodystrophy is the lowering of parathyroid hormone activity by correcting hyperphosphatemia and administration of calcitriol given either orally or intravenously. Aluminum hydroxide has been used to bind phosphorus in the bowel in patients with hyperphosphatemia. Because of concerns about aluminum toxicity, calcium carbonate is often used. RenaGel appears to be an effective phosphate binder free of calcium and aluminum. It may offer an alternative for the control of phosphorus in end-stage renal disease.

Recent data suggests that chronic metabolic acidosis decreases albumin synthesis, increases muscle proteolysis and induces negative nitrogen balance in patients with CRF. Despite these experimental data, the clinical relevance of correction of metabolic acidosis in end-stage renal disease (ESRD) is still not defined. Even though therapy of metabolic acidosis in the adult patient with CRF remains conjectural at this stage, reports indicate that its correction might lead to healing of osteomalacia and osteopaenia, and possibly may decrease protein degradation and improve growth in children.

III. NEPHROTIC SYNDROME

This syndrome is characterized by proteinuria >3.5 g/day, hypoalbuminuria <3 g/dl, hyperlipidaemia with an elevation of serum cholesterol, edema and oval fat bodies and fatty casts in the urinary sediment. A variety of disorders may produce nephrotic syndrome but, in the majority of cases, no cause is found. It is appropriate to define the selection of studies from the history and physical examination. Tests to order are antinuclear antibody, rheumatoid factor, cryoglobulins, serum complement, HB_SA_G VDRL serology (syphilis), protein electrophoresis of the serum and urine and HIV. If the cause is unclear a renal biopsy is done to define the glomerular lesion as treatment may on the underlying glomerular lesion.

III.a. Primary Renal Diseases

III.a.1. Minimal-Change Disease

Minimal-change disease is more common in children than in adults. It is rare in black children and adults of sub-Saharan Africa. Minimal-change responds well to steroids. However, it may recur after prednisone is decreased or discontinued. In such cases, the addition of cyclophosphamide or chlorambucil may produce a response. The GFR is normal. Progression to renal failure does not occur unless focal glomerulosclerosis is present.

III.a.2. Membranous Glomerulonephritis

Membranous glomerulonephritis is one of the most common biopsy findings in adults with nephrotic syndrome. It may be idiopathic or associated with a variety of disorders like systemic lupus erythematosus (SLE), gold toxicity, penicillamine toxicity, hepatitis B, syphilis, neoplasm or human immunodeficiency virus (HIV). The natural history of membranous glomerulonephritis is so variable that it is difficult to assess specific drugs. Most placebo-controlled studies have not demonstrated a major benefit with steroids or immunosuppressive drugs. Many clinicians may favor a trial of steroids for 6–8 weeks. However a recent systematic review failed to show any long-term effect of immunosuppressive treatment, including corticosteroids, on patient and/or renal survival.

III.a.3. Mesangiocapillary Glomerulonephritis

Mesangiocapillary glomerulonephritis can occur as a complication of many diseases, such as SLE or as a primary disease. Treatment of the primary disease with steroids, immunosuppres-sives and antiplatelet agents have been attempted with unimpressive results.

III.b. Secondary Glomerular Diseases

III.b.1. Post-streptococcal Glomerulonephritis

Post-streptococcal glomerulonephritis is the result of infection with the nephritogenic strain of group A hemolytic streptococci. The streptococci are usually isolated from patients with a sore throat and, in developing countries, skin infection like impetigo or infected scabies is an important cause. There is no specific treatment except for antihypertensives, salt restriction and diuretics. Corticosteroids are of no value. The disease is self-limiting but, in some adults, it may progress to chronic renal failure.

III.b.2. IgA Nephropathy (Berger's Disease) and Henoch–Schonlein Purpura

Immunoglobulin A (IgA) nephropathy is a mesangial proliferative nephritis associated with IgA deposits in mesangial cells. Small amounts of complement and IgG are sometimes also found. The disease tends to present as an episode of macroscopic haematuria or may be diagnosed in asymptomatic patients on a routine urinalysis. In patients presenting with macroscopic haematuria, there is often a preceding episode of respiratory tract infection. IgA nephropathy is usually a benign disorder, some patients do progress to renal failure. Kidney survival is over 90% at 10 years and about 80% at 20 years. Patients with proteinuria (1.0–3.9 g daily) and serum creatinine concentration of <133 μmol/l have been shown in a randomized trial to benefit from a 6-month course of steroid treatment against deterioration in renal function with no notable adverse effects during follow-up. An increase in urinary protein excretion could be a marker indicating the need for a second course of steroid therapy. The value of fish oil is debatable. The medical literature does not prove the efficacy of fish oil therapy in IgA nephropathy, but suggests that an additional placebo-controlled trial is warranted. A sample size calculation indicated that such a trial should be longer than those to date or should attempt to increase the treatment effect perhaps for more than 2 years or enrolling more severely proteinuric individuals. Mesangial deposition of IgA is also observed in the disorder known as anaphylactoid purpura (Henoch–Schonlein purpura). There is no specific therapy. The crescentic form of Henoch–Schonlein purpura nephritis has been shown to respond to prednisone and azathioprine.

III.b.3. Rapidly Progressive Glomerulonephritis

Rapidly progressive glomerulonephritis can be defined as any glomerular disease in which there is rapid loss of renal function over days or weeks rather than months or years. Many conditions like vasculitis from polyarteritis nodosa, Wegener's granulomatosis, immune complexes from post-infection states (e.g. post-streptococcal or visceral abscess), collagen diseases, such as lupus nephritis, primary renal disease (e.g. IgA nephropathy), membranoproliferative glomerulonephritis and antiglomerular basement antibody disease (Goodpasture's syndrome) with or without lung hemorrhage, are known to produce this syndrome. Treatment for rapidly progressive nephritis has been difficult to evaluate because so many conditions are associated with it. There are uncontrolled trials which suggest corticosteroid therapy to be beneficial. Alternate day high-dose intravenous methylprednisolone for 3 or 4 days followed by oral prednisone is the commonest form of therapy. There is no evidence that plasmapheresis is of value. As many as 75% show some improvement although some who improve nevertheless progress to end-stage renal disease.

III.b.4. Goodpasture's Syndrome

Anti-glomerular basement membrane disease, or Goodpasture's syndrome, is characterized by progressive renal insufficiency with hemoptysis, linear immunofluorescence of IgG deposits in the glomerular basement membrane in kidney biopsy and circulating anti-glomerular basement membrane antibodies in the serum which cross react with pulmonary alveolar basement membrane. The disease is treated with steroids and with cyclophosphamide or azathioprine to suppress antibody production and with daily plasma exchange for 2 weeks to suppress circulating antibodies. Kidney transplantation has been successful. It should be done only after serum antibodies to glomerular basement membrane have been absent for several months.

III.b.5. Systemic Lupus Erythematosus (SLE)

Lupus nephritis is a serious complication of SLE. Approximately 10% of patients with SLE develop ESRD. A variety of renal histologic lesions have been observed in patients with SLE: focal, proliferative, membranoproliferative and membranous glomerulonephritis. Many of these lesions appear to respond to corticosteroid therapy with or without other immunosuppressant drugs. Aggressive immunosuppressive therapy should be considered for patients with proliferative lupus nephritis as the risk for progression to ESRD is high. Intermittent intravenous cyclophosphamide improves renal survival. Longer duration of therapy is associated with few relapses of nephritis and a decreased risk of diminished renal function. While the efficacy of azathioprine therapy does not differ statistically from that of steroids alone in prolonging renal survival, this therapy may be considered in patients with few risk factors for progression to renal insufficiency. Methylprednisolone as a single therapy does not prolong

renal survival compared with regimens including cyclophosphamide. Plasmapheresis remains under study but has not shown additional benefit in treatment of severe lupus nephritis. The potential roles for cyclosporin A and mycophenylate mofetil in the therapy of proliferative lupus nephritis remains to be defined. The current use of cyclophosphamide combined with steroids remains the best option to preserve renal function in proliferative lupus nephritis (see Flanc et al., 2004). Supportive care includes vigorous control of hypertension, consideration of angiotensin receptor inhibition or blockade to reduce proteinuria and prolong renal functions. Control of hyperlipidaemia, prevention of osteoporosis and prevention of pregnancy in certain instances, remain important clinical goals. In most SLE patients disease activity diminishes as ESRD approaches. The survival of SLE patients on dialysis (both hemo- and peritoneal) appears to be comparable to that of non-SLE patients. Recent evidence suggests that renal transplantation outcomes among SLE patients are inferior to those of non-SLE patients, primarily because of recurrent lupus nephritis in the allograft and the effect of antiphospholipid-related events on transplantation outcomes.

III.c. Management of Nephrotic Syndrome

III.c.1. Decrease of Proteinuria

The Ramipril Efficacy In Nephropathy (REIN) study found that, in patients with chronic nephropathies and proteinuria of 3 g per 24 h, ramipril safely reduced the rate of decline of the GFR and halved the risk of doubling of serum creatinine or ESRD as compared with placebo plus conventional antihypertensive drugs at the same level of blood pressure control (see Ruggenenti et al., 1998). A treatment period of sufficient duration (i.e. >36 months, in 97 patients) eliminated the need for dialysis. Even patients treated with antihypertensive drugs other than ACE inhibitors benefited from shifting to ramipril. One issue of concern with ACE inhibitors in patients with impaired renal function is the possible development of hyperkalaemia. It has been found that a low dose of ramipril (1.25 mg daily) can reduce proteinuria to the same extent as an eight-fold higher dose without significantly lowering blood pressure or increasing serum potassium.

A high-protein diet is of debatable value. Since increased protein intake seems to have a theoretic adverse effect on renal function in some disease states like nephrotic syndrome due to diabetes mellitus, moderation of protein intake (1 g/kg body weight/day) in nephrotic syndrome is reasonable.

III.c.2. Cholesterol Lowering

Hypercholesterolaemia and hypertriglyceridaemia commonly occur in patients with severe proteinuria. It may be associated with a higher incidence of cardiovascular disease. Dietary treatment is of limited value if the underlying cause of the nephrotic syndrome is not successfully controlled. Statins should be considered to lower the serum cholesterol.

III.c.3. Sodium Restriction and Diuretics

Sodium restriction is essential to control the edema. Diuretics like thiazides or loop diuretics are indicated in patients who are symptomatic from the edema.

IV. NEPHROPATHY WITH OTHER DISEASES

IV.a. Diabetic Nephropathy

Diabetes mellitus causes about 50% of all patients being treated for End Stage Renal Disease (ESRD) in the USA and this is because the disease (type 2 disease) is pervasive. Recent studies have shown that the onset and progression of the disease can be ameliorated if treatment is instituted early on in the course of the disease. ESRD is the commonest complication of type 1 diabetes. A higher proportion of individuals with type 2 diabetes was found to have microalbuminuria and overt nephropathy shortly after the diagnosis of diabetes, because the diabetes had actually been present for many years before the diagnosis was made. There is a correlation between the degree of albuminuria and cardiovascular disease.

The earliest clinical evidence of nephropathy is micro-albuminuria (albumin excretion 30–300 mg/24 hours or 20–200 μg/min) and patients are referred as having incipient nephropathy. Micro-albuminuria rarely occurs early in type 1 diabetes, therefore screening in patients is necessary after 5 years duration of the disease. Because of the difficulty of precisely dating the onset of type 2 diabetes such screening should begin at the onset of diagnosis.

Known risk factors for the onset of diabetes include: (a) genetic predisposition (indicated by a history of hypertension and cardiovascular events in

first degree relatives); (b) quality of glycaemic control; (c) level of blood pressure; (d) smoking. In patients with established nephropathy, hypertension is the most important factor which promotes progression and this is susceptible to intervention. The hypertension in diabetes shows: (i) more isolated systolic hypertension; (ii) more non-dippers; (iii) abnormal BP (variability with exercise and posture); (iv) pulse pressure is widened; (v) there is a correlation between systolic BP. Heart failure and cardiovascular disease in type 2 diabetes; and (vi) sodium handling by the kidneys is impaired in patients with type 2 diabetes, hypertension is present in about $\frac{1}{3}$ of the patients at the time of diagnosis. Hypertension in diabetes is aggressive, progressive and rapidly develops into renal failure, unless the hypertension is aggressively treated.

It has been shown that the ACE-inhibitor, captopril, relieves the albuminuria and prevents the progression of renal disease in type 1 diabetes. Other studies have shown that ACE inhibitors in type 2 reduce the progression of micro-albuminuria and also prevent the onset of micro-albuminuria compared with verapamil. The LIFE study compared an angiotensin receptor blocker with a β-blocker in diabetic hypertensive patients. Both antihypertensive agents produced the same decrease in BP on treatment. However, the ARB produced greater regression in cardiovascular morbidity and mortality, and a 25% reduction in stroke (see Lindholm et al., 2002). The choice of using an ACE inhibitor or ARB in type 2 diabetes should be left to the physician, and involves the cost of therapy and the affordability of the drug to the patient and to health administrators. We lack data on value-based evidence of ACE inhibitors and ARBs. Cost effectiveness is determined by the relationship between the benefits obtained for the expenditure. Affordability on the other hand is determined by the prevalence of a condition and the total cost of treating it in a specific setting. Because of limited resources, cost-effectiveness may not be affordable. The two main determinants of cost effectiveness are the cost of therapy and the initial cardiovascular risk of the patient treated. The major classes of antihypertensive drugs are probably equivalent in efficacy and safety. In most cases a thiazide-like diuretic is the cheapest option and is therefore more effective. However, for certain compelling indications like diabetes, other classes such as ACE inhibitors or ARBs provide additional benefits. Even if they are expensive, they are effective. Generic ACE inhibitors should be encouraged.

It is necessary to use combination therapy in order to obtain the desired target BP of $\leqslant$130/80 mmHg. ACE inhibitors or ARBs should be combined with a thiazide-like diuretic (in the absence of gout) as there is a synergistic effect. Other useful combinations are calcium channel blockers, alpha-blockers and centrally acting agents. In many cases, in order to achieve the desired target BP of $\leqslant$130/80 mmHg it will be necessary to use 2–3 antihypertensive agents.

The management strategies for diabetic nephropathy are to ensure effective control of common cardiovascular risk factors – for example, salicylates 80 mg daily (provided the BP is controlled), lipids with statins and/or fibrates and stopping smoking at all times, in the initial stages (albumin excretion $<$ 30 mg/24 hours) it is necessary to: (a) obtain optimal glycaemic control (haemoglobin $A_{1c} < 7\%$); (b) target BP $\leqslant$ 130/80 mmHg; and (c) monitor albumin excretion.

In incipient nephropathy (albumin excretion 30–300 mg/24 hours or 20–200 μg/min) it is necessary to have: (a) optimal glycaemic control (haemoglobin $A_{1c} < 7\%$); (b) target BP $\leqslant$ 130/80 mmHg; (c) control of urinary albumin excretion regardless of BP; and (d) rennin angiotensin inhibition. In overt nephropathy (albumin excretion $\geqslant$ 300 mg/24 hours) it is necessary to obtain: (a) optimal target BP $\leqslant$ 130/80 mmHg; (b) optimal glycaemic control (haemoglobin $A_{1c} < 7\%$); (c) angiotensin inhibition irrespective of BP; (d) avoid malnutrition and reduce protein intake in selected cases. In nephropathy with renal dysfunction, the following points should be observed: (i) optimal glycaemic control; (ii) avoid frequent hypoglycaemia; (iii) target BP $\leqslant$ 130/80 mmHg; (iv) angiotensin inhibition, but beware of the risk of hyperkalaemia with ACE inhibitors or ARBs; (v) avoid malnutrition – consider protein and phosphate restriction. In ESRD: (a) consider renal replacement – renal transplantation or dialysis; (b) monitor for hyperkalaemia; (c) hold angiotensin inhibition (when glomerular filtration rate $<$ 15 ml/min in selected patients) and only use these agents provided the serum potassium is normal.

IV.b. Benign Prostatic Hyperplasia

Benign prostatic hyperplasia is characterized by a decreased force and calibre of the urinary stream, nocturia, high post-void residual urine volume,

azotemia and urinary retention on occasion. Prostatism is a widely used term assigned to the symptom complex of older men with voiding dysfunction. Many men with such symptoms do not, in fact, have prostate enlargement or benign prostatic hyperplasia (BPH) and such symptoms are not a surrogate for BPH. Such recognition is essential if cost effective medical management of lower urinary tract symptoms (LUTS) is to be achieved. Prostate volume has emerged as a key factor in the selection of medical therapy of LUTS and BPH not only regarding symptom relief but also to the new concept of the prevention of disease progression and the avoidance of future adverse events in those men with true BPH. Indications for treatment have not been well defined. Absolute indications for treatment include recurrent urinary retention, azotemia, hydronephrosis and urinary incontinence as a result of bladder neck obstruction, recurrent urinary tract infection associated with increased residual urine volume; and severe haematuria. Medical therapy has made an impact in the management of LUTS and BPH. The α_1-receptor antagonists terazosin and doxazosin have become popular, because of their effectiveness in the urinary tract, reduced side effects, and simplicity of dosage. Tamsulosin is an α_{1a}-selective alpha blocker and is also used in the symptomatic treatment of benign prostatic hyperplasia. Although more prostate specific, it does not have the prostate apoptotic effects of other alpha-blockers such as doxazosin and terazosin. Tamsulosin provided a small to moderate improvement in urinary symptoms and flow compared to men receiving placebo in men with BPH. Effectiveness was similar to other alpha antagonists and increased only slightly with higher doses (see Wilt et al., 2002).

In addition, finasteride, a 5-α-reductase inhibitor, was found to be more effective in men with prostates $>$40 g. Furthermore, the larger the prostate at baseline, the greater the efficacy of finasteride on symptom relief and flow rate improvement. In addition to medical therapy, an array of device therapies has emerged in the management of LUTS and BPH. Laser prostatectomy, transurethral vaporization of the prostate and transurethral interstitial laser prostatectomy. Studies report beneficial outcomes approaching those achieved with transurethral resection of the prostate with lesser morbidity and a shorter hospital stay. The management of LUTS and BPH result in the expenditure of vast health care resources worldwide. The surgical strategies have an established record of outcomes documenting their potential for symptom relief and the avoidance of future complications. Medical and device therapies, although currently promising and attractive, therefore must prove to have comparable durability.

The evidence suggests that non-glucosidic β-sitosterols improve urinary symptoms and flow measures. Their long-term effectiveness, safety and ability to prevent BPH complications are not known (see Wilt et al., 2002).

For a review of the efficacy of Serenoa repens the results in 3139 men from 21 randomized trials lasting 4–48 weeks were assessed (see Wilt et al., 2002). The reviewers' conclusions were:

The evidence suggests that Serenoa repens improves urologic symptoms and flow measures compared with placebo. Serenoa repens produced similar improvement in urinary symptoms and flow compared to finasteride and is associated with fewer adverse treatment events. The long-term effectiveness, safety and ability to prevent BPH complications are not known.

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Chapter 35

Gastrointestinal and Hepatobiliary Disorders

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I. INTRODUCTION

The achievement of gastroenterology in the second half of the past century can be summarized as the application of new scientific knowledge, technology, and controlled clinical trials to the study of gastrointestinal problems, with considerable progress realized in, among others, motility-associated disorders, chronic inflammatory bowel diseases, and in the treatment of the complications of liver cirrhosis and the management of viral hepatitis. Therapy of peptic ulcers had been revolutionized by the introduction of H_2 receptor blockade, and acid pump inhibitors, and then with the elucidation of the role which *Helicobacter pylori* plays in ulcer disease. The turn of the twenty-first century has seen the practical introduction of molecularly targeted therapies currently focused on the modulation of inflammatory and neoplastic reactions. This chapter considers the current place of, evidence based, pharmacotherapeutic modalities in gastroenterology.

II. OESOPHAGEAL REFLUX DISEASE

II.a. Definition, Diagnosis and Aetiology

Symptomatic gastro-oesophageal reflux may occur with or without visible evidence of mucosal damage.

The spectrum runs from simple regurgitation in infancy through classical symptoms of heartburn alone, to endoscopy showing oesophageal inflammation and ulcer, with or without stricture or Barretts disease in adults. pH telemetry confirming acid refluxate is usually unnecessary, barium meal evidence of free reflux may be associated or unassociated with heartburn and endoscopy is needed to confirm oesophageal inflammation. Progressive

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dysphagia of recent onset suggest oesophageal cancer and non-progressive intermittent symptoms with solids a benign stricture but with achalasia possible. Odynophagia (pain on swallowing) associated with inflammation can be confused with obstruction.

The disease is commonly associated with obesity, and may be associated with smoking and the taking of certain drugs, notably anticholinergic agents (tend to relax the gastro-oesophageal sphincter) and also the bisphosphonate alendronic acid and non-steroidal anti-inflammatory drugs (causing direct damage).

II.b. Therapy

Initial treatment is usually based on antacids, weight reduction and stopping smoking, and may be enough in those with intermittent mild to moderate heart burn. Alginate antacid combinations may have particular value through providing a physical barrier of supernatant alginate floating on the gastric acid pool. Persistent more severe symptoms require antisecretory treatment (Table 1).

II.b.1. Pharmacotherapy Based on Acid Inhibition

Histamine H_2 antagonists: these relieve persistent heartburn and are generally safe and effective in acid reflux without mucosal damage. There is little reason to prefer one clinically over another. Treatment has to be continued indefinitely. They are relatively ineffective in established inflammation.

Proton pump inhibitors: these are effective in simple heartburn, but little more than H_2 antagonists, which may be preferred on grounds of cost. Patients with endoscopic evidence of oesophagitis, oesophageal ulcer or stricture respond better to the more potent acid inhibition associated with proton pump inhibition than that of H_2 receptor antagonists, with markedly higher healing rates, and probably a reduction in the tendency to stricture development. Barrett's change of oesophageal metaplasia, a premalignant condition does not appear to reduce in extent during treatment. The use of surveillance endoscopy in such cases is outside the scope of this text.

Symptom relief is at least as good as with histamine H_2 antagonists but takes two to three days to develop because of the time required for maximum inhibition of the parietal cell proton pump mechanisms. Treatment, as with H_2 receptor antagonists, has to be continued indefinitely. There are no grounds upon which one drug in the same class is to be preferred over another. Individual patients may require treatment with lower or higher (usually halved or doubled) doses and the choice can be made generally on the grounds of cost and simple clinical responses of symptoms. There are no grounds for combining H_2 receptor antagonists with proton pump inhibitors.

II.b.1.1. Adverse effects of anti-secretory treatment. Histamine H_2 antagonists and proton pump inhibitors are very safe as well as effective treatments. Cimetidine has small effects on hepatic drug metabolism which are only of clinical significance with drugs used in doses close to toxic levels, notably phenytoin, aminophylline and warfarin. Other adverse effects such as headache, rash and thrombocytopenia are rare.

Table 1. Acid neutralising or inhibiting regimes in oesophageal reflux disease

	Adverse effects
A. Occasional mild symptoms	
Antacids e.g., magnesium trisilicate or aluminium hydroxide or antacid–alginate combinations	Aluminium compounds tend to be constipating Magnesium compounds tend to be laxative
B. Heartburn without endoscopic damage	
H_2 antagonists, e.g., cimetidine 400 mg bd, ranitidine 150 mg bd, famotidine 20 mg bd	Usually well tolerated. Occasional skin rash, headache and dizziness, rarely thrombocytopenia, and other blood dyscrasia AV block and confusion, are recorded
C. Visible oesophageal inflammation, ulcer or stricture	
Proton pump inhibitors e.g., omeprazole 20–40 mg daily, lansoprazole 30 mg daily, pantoprazole 40 mg daily, rabeprazole 20 mg daily	Usually well tolerated. Diarrhoea, headache and skin rash are the commoner problems

Proton pump inhibitors are also generally safe. More frequent, but still rare, adverse effects are headache, rash and diarrhoea.

Anti-secretory treatment, by reducing the acid barrier to infection approximately doubles the risk of infective diarrhoea. Fears that treatment like H_2 receptor antagonists or proton pump inhibitors would increase the risk of gastric cancer have not been realised. Raised frequencies of oesophageal cancer in patients taking proton pump inhibitors reflect underlying predisposition in Barrett's disease.

II.b.2. Treatment to Enhance Oesophageal Motor Function

Logically it would be preferable to enhance oesophageal sphincter function or to improve motor clearing of reflux acid. Pharmaceutical options are limited.

II.b.2.1. Prokinetic agents. Cisapride: cisapride treatment can be demonstrated to improve sphincter and motor function and to improve modestly the symptoms of heartburn. However, it is relatively ineffective in severe disease, and adverse effects of impaired intracardiac electrical conduction causing ventricular tachyarrhythmias have resulted in its withdrawal from general use.

Metoclopramide: enhancement of oesophagogastric sphincter tone is demonstrable, particularly with intravenous drug treatment but clinical value is doubtful. Treatment can also precipitate dyskinetic reactions and galactorrhoea. Domperidone may be somewhat less likely to cause dyskinesias but has no greater therapeutic value.

Effective treatment of reflux disease has greatly reduced the need for anti-reflux surgery although the case for it remains in young people with persistent symptoms, and where responses to pharmacotherapy are poor. Endoscopic oesophageal dilatation with maintenance proton pump inhibitor treatment usually obviates the need for surgical reconstruction of the lower oesophagus in individuals with visible inflammation at endoscopy.

Children: reflux symptoms in infancy generally resolve spontaneously by the age of 18 months, but may require feed thickening or the use of alginates More severe symptoms require specialist advice and may need treating with proton pump inhibitors.

III. ACHALASIA OF THE CARDIA

III.a. Definition, Diagnosis and Aetiology

Achalasia of the cardia is a dysmotility disorder of the body of the oesophagus, which lacks a coordinated stripping (emptying) wave. As a result the cardia never relaxes, and patients complain of dysphagia and chest pain.

Generally it is diagnosed through demonstration by radiology or manometry of the lack of coordinated oesophageal movement on swallowing with associated narrowing at the cardia. Prime differential diagnoses are benign oesophageal stricture and cancer at the cardia.

Causes outside the South American variety caused by *Trypanosoma cruzei* are unknown.

III.b. Therapy

Forced dilatation at endoscopy or surgical cardiomyotomy are the treatments of choice, although injection of botulinum toxin (which needs repetition) is also effective. Temporary relief can, be obtained with sublingual or inhaled glyceryl trinitrate.

IV. PEPTIC ULCERATION

IV.a. Definition, Diagnosis and Aetiology

Peptic ulceration occurs as an acute or chronic non-traumatic epithelial breach typically in the gastric or duodenal mucosa, but also in the oesophagus (see above) and occasionally in the small intestine with the Zollinger–Ellison syndrome of gastrin overproduction or with an acid-secreting Meckel's diverticulum. Symptoms overlap with those of non-ulcer dyspepsia and cancer and the diagnostic cornerstone is endoscopy. Biopsy may be necessary to distinguish ulcer from cancer.

The (outdated) classical view was of perturbed balance between acid-peptic aggression and mucosal resistance. *Helicobacter pylori* infection and non-steroidal anti-inflammatory drug use, are now recognized as the major risk factors. *H. pylori* infection alone appears insufficient and other influences, notably smoking appear necessary associates.

Guidelines published include those of the National Institute for Health and Clinical Excellence in England and Wales on managing dyspepsia in primary care.

Table 2. Some seven day regimes for use in *Helicobacter pylori* eradication

Amoxycillin 1 g twice daily plus clarithromycin 500 mg twice daily, plus esomeprazole 20 mg twice daily (*or* lansoprazole 30 mg twice daily *or* pantoprazole 40 mg twice daily *or* daily or ranitidine bismuth citrate 400 mg twice daily *or* rabeprazole 20 mg twice daily)
Amoxycillin 500 mg thrice daily *plus* clarithromycin 500 mg twice daily, *plus* omeprazole 20 mg twice daily
Clarithromycin 500 mg twice daily *plus* metronidazole 400 mg twice daily *plus* omeprazole 20 mg twice daily (*or* lansoprazole 30 mg twice daily *or* pantoprazole 40 mg twice daily *or* rabeprazole 20 mg twice daily *or* ranitidine bismuth citrate 400 mg twice daily)

IV.b. Therapy

Treatment depends upon whether disease appears *H. pylori* or non-steroidal associated.

IV.b.1. H. pylori Associated Disease

Most duodenal ulcers, and the majority of gastric ulcers, which are not non-steroidal associated occur in individuals with active gastric antral *H. pylori* infection. The critical feature in treatment is *H. pylori* eradication. Symptoms can be successfully managed and ulcer healing induced by conventional measures of anti-secretory treatment with histamine H_2 antagonists or proton pump inhibitors, usually with advice to stop smoking but relapse is prompt on stopping treatment. Antacids now have no significant use.

The general principles of eradication can be summarised as follows:

A. One-week triple therapy regimes combining a proton pump inhibitor with two antibiotics chosen from amoxicillin, clarithromycin and metronidazole are effective in about 90% of cases.
B. Similar, two-week regimes can give higher cure rates, but adverse effects of the antibiotic treatment can hinder compliance.
C. Microbial resistance is generally more common to clarithromycin and metronidazole than to amoxicillin. Therefore amoxicillin should be used in initial treatment (except where the patient is sensitive to it), plus one of the others. Metronidazole should be avoided if there has been prior patient use of the drug as the organism may be resistant to it.
D. In resistant disease a bismuth-based compound is worth adding.
E. If the ulcer disease appears precipitated by non-steroidal use the value of concurrent eradication of *H. pylori* is unclear.
F. Bismuth based regimes, as part of dual or triple therapy are also effective.

Table 2 gives details of some conventional regimes (see British National Formulary, 2008). The efficacy of therapy can be checked by Radiocarbon-labelled urea breath testing (which depends upon release of labelled carbon dioxide by bacterial urease) or by testing gastric biopsy material for persistence of gastric urease, but should only be done after eradication therapy has been discontinued for at least a month, and whilst any anti-secretory treatment has been discontinued (because it tends to suppress but does not eradicate the organism).

Reinfection after successful eradication is uncommon.

IV.b.2. Non-steroidal Anti-inflammatory Associated Disease

Non-steroidal anti-inflammatory associated ulcer can be managed in various ways. There are no significant differences in principal between management of non-steroidal and aspirin associated disease or for aspirin whether at low cardioprotective or full doses. Risks are dose related and greater for some drugs, notably piroxicam, than others notably ibuprofen at low dose.

A. If the precipitant can be withdrawn then antisecretory treatment with a histamine H_2 antagonist or proton pump inhibitor, or misoprostol (an antisecretory and mucosally protective prostaglandin) for a month may be enough to induce ulcer healing.
B. If replacement analgesic or anti-inflammatory therapy is required then the current options include:
   (i) paracetamol in standard doses plus regime A.
   (ii) replacement of the anti-inflammatory drug in use by the lowest acceptable dose of ibuprofen which, though not COX-2 selective, is the safest gastrointestinally of the

non-selective drugs, plus a proton pump inhibitor. Current evidence indicates that potent acid inhibition with omeprazole is an effective means of continuing non-selective COX therapy whilst inducing ulcer healing.

(iii) replacement of the anti-inflammatory drug in use by a COX-2 selective inhibitor.

Evidence is divided as to whether *H. pylori* eradication is worthwhile in non-steroidal anti-inflammatory drug takers who are infected.

Gastrointestinal safety of COX selective inhibitors compared with non-selective NSAIDs: the principle areas of concern are upper gastrointestinal and cardiovascular safety.

Treatment with COX-2 selective drugs has shown a lower likelihood of symptomatic ulcer or ulcer complications than treatment with non-selective NSAIDs, with non-selective NSAID risks varying dose-dependently and between drugs, with ibuprofen lowest, and piroxicam and azapropazone amongst the highest. Whether COX-2 selective drugs pose no risk is unclear.

Cardiovascular safety. Both drug types promote salt retention, can exacerbate heart failure and tend to raise blood pressure. COX-2 selective drugs also appear to raise the risks of thrombotic events, notably stroke and myocardial infarction, and recent evidence suggests that non-selective NSAIDs also raise these risks, though it is unclear whether to the same degree. For both drug types, dose and duration of treatment appear to affect risk.

IV.b.2.1. Prevention of non-steroidal associated ulcer. Risks of precipitating such ulcers by non-selective COX therapy are particularly large in the elderly, in those receiving concurrent cardiovascular prophylaxis with aspirin, and in those receiving concurrent oral corticosteroids or anticoagulants and in those with histories of prior ulcer.

Risks can be reduced, approximately halved, by prophylaxis with a proton pump inhibitor. Evidence is particularly strong for omeprazole, but others should be similar, broadly equivalent results are obtainable by using the prostaglandin analogue misoprostol. Misoprostol is prone to cause abdominal discomfort and diarrhoea as a direct agonist effect of the drug. Newer COX-2 selective drugs are less prone to cause ulcer (though they may retard healing): whether risks are reduced to base expectation is unclear, risks of ulcer persist if cardioprophylactic aspirin is given concurrently.

IV.b.3. Zollinger–Ellison Syndrome

Sustained acid hyperscretion, due either (usually) to a duodenal or pancreatic gastrinoma, or to multiple endocrine adenomata, responds well to proton pump inhibition, often requiring high doses. Resection should always be considered as a cure for those with solitary adenomata, as should operation to reverse the retained antrum syndrome (partial gastrectomy where the antrum is inadvertently retained and isolated from acid inhibition, and secretes gastrin continuously).

V. HAEMATEMESIS AND MELAENA

V.a. Definition, Diagnosis and Aetiology

Acute fresh bleeding from the upper gastrointestinal tract is a mandatory cause of hospital referral. About half of all cases are due to peptic ulceration, and variceal bleeding accounts for a varying, but generally minor component of the remainder depending on the frequency of alcoholic cirrhosis or of hepatitis B-induced cirrhosis in the population.

The remaining commoner causes include oesophageal or acute gastric erosions, Mallory Weiss tears of the gastro-oesophageal junction and malignancy.

Diagnosis is established by a combination of clinical examination (variceal bleeding is unlikely in the absence of stigmata of liver disease) and endoscopy. Bleeding ulcers may then be recognised as actively bleeding, or though the presence of a black base to the ulcer with, occasionally a visible vessel.

V.b. Therapy

The prime need is to assess the severity of blood loss and start replacement therapy, then to determine the underlying cause.

Bleeding is likely to be severe if the patient is obviously shocked with a systolic blood pressure below 100 mmHg and tachycardia (and/or) with a postural drop of 20 mmHg in blood pressure on sitting up.

The haemoglobin concentration is not a good guide to recent blood loss because haemodilution may not have occurred.

Ulcer bleeding. In those with peptic ulcer risks of dying are markedly raised in the elderly, in those with concomitant general disease, and where bleeding is substantial, or with combinations of these. By contrast young patients, aged under 45, with no

haemodynamic problems, and where the source of bleeding is unclear, present minimal risks.

Although endoscopic therapy, by injection of sclerosant or use of heater probes of visible and actively bleeding vessels, has reduced the need for surgery, close physician and surgeon co-operation is needed. Surgery may be required particularly in the elderly who, have evidence of systemic cardiorespiratory or neurological disease and who after a significant episode of bleeding have clear evidence of recurrence.

Drug therapy may reduce transfusion requirements, but has not been shown to reduce the risk of death. Although some investigators have suggested that H_2 antagonist, proton pump inhibitor or prothrombotic treatment with the antifibrinolytic agent, tranexamic acid are useful, larger studies have generally been equivocal or negative in outcome.

Antisecretory drugs may reduce transfusion needs modestly, but evidence of material effects on mortality is lacking. This is in part because in well-managed units the risks of death are under 10%.

Variceal bleeding. Almost all studies of pharmacotherapy have been small and in consequence meta-analyses depend upon the aggregation of patients from multiple sets where comparability cannot be assured.

Active bleeding. Acutely bleeding varices can be treated by injection sclerotherapy, by tamponade and by infusion systemically of vasopressin analogues or octreotide (which reduce variceal pressure). Results of controlled trials generally reflect efficacy in oesophageal rather than gastric variceal disease, which form a minority of cases, and can be more difficult to manage.

Since diagnosis depends upon endoscopy, immediate injection sclerotherapy is the obvious initial therapeutic step, and is effective in some 90% of cases, reducing the risk of rebleeding and the chances of death. Ligation by banding may be more effective but can be more difficult in the presence of acute haemorrhage. Sclerotherapy has tended to be more effective than drug treatment with nitroglycerin plus vasopressin, octreotide, somatostatin, or terlipressin, although addition of drugs to sclerotherapy may further reduce bleeding risk compared with sclerotherapy alone. Where variceal bleeding is uncontrolled surgical devascularisation of the lower oesophagus or interventional radiology to construct a communication between the outgoing hepatic vein and an incoming intrahepatic branch of the portal vein can be considered. A major consideration is the availability of technically experienced staff. Drug treatment is administrable without significant technical expertise, is not without value and is the logical follow-on to prevent recurrence. By contrast few hospitals will have access to staff experienced in surgical shunt procedures and their variants. Prophylaxis of variceal bleeding is considered under portal hypertension.

VI. NON-ULCER DYSPEPSIA; FUNCTIONAL DYSPEPSIA

VI.a. Definition, Diagnosis and Aetiology

Upper alimentary symptoms in the absence of a clear pathological cause are referred to as non-ulcer dyspepsia or functional dyspepsia. The diagnosis is, in essence, by exclusion.

Since there is no clear cause a definable aetiology is impossible. Symptoms have variously been ascribed to Helicobacter gastritis without ulcer, to reflux of duodenal contents into the stomach and to delayed gastric emptying, and to adverse effects of drugs. In many patients, however, symptoms are likely to be central nervous or psychological in origin.

VI.b. Therapy

General measures include stopping smoking, reduction of excessive alcohol intake and exploration and, if possible, resolution of any significant psychological factors. Pharmacological treatments are of limited efficacy.

Proof of efficacy is lacking for the use of antacids for this condition but they are cheap, simple to take and, in ordinary doses, non-toxic.

Prokinetic agents, metoclopramide and domperidone, have been shown to relieve dysfunctional upper gastrointestinal symptoms, and are presumed to act through improving co-ordination of gastric emptying.

Adverse effects of cisapride in causing cardiac dysrhythmias have led to withdrawal from general use. Metoclopramide and domperidone are well described as occasionally causing dyskinesias, particularly in younger people. Treatment is generally licensed for short term typically six week prescription.

Antidepressants are commonly prescribed and claimed effective. Whether benefits come from the

relief of depression or thorough pharmacological effects on the gut (notably anticholinergic actions of tricyclic antidepressants), is unclear.

Helicobacter eradication is frequently undertaken using standard regimes in patients with infection without ulcer, and may be difficult to avoid in patients aware that infection is present, but symptomatic benefit appears limited.

VII. CHRONIC DIARRHOEAS

Empiric therapy has value during initial investigation, where a specific diagnosis cannot be made or where a specific diagnosis is made but targeted treatment is not available.

That initial assessment should consider whether diarrhoea is watery, or sugar or fat malabsorptive, or whether there is active bleeding or significant abdominal pain suggesting inflammatory disease. In the elderly constipation with overflow may be the real problem, and the possibilities of partial mechanical obstruction and neoplasia must be born in mind.

Opiates are the most effective non-specific agents, and the peripheral opiate agonist loperamide may be adequate in most individuals. Whilst giving such empirical treatment the possible need of fluid replacement must be remembered. Opiates are not replacements for oral rehydration fluids (based on salt and glucose) or intravenous rehydration fluids in acute diarrhoea.

Few controlled trials have been conducted with adsorbents (clays, activated charcoal and binding resins) but they may have value.

Antibiotic therapy is justified where there is suspicion of giardiasis (metronidazole) and bismuth subsalicylate is effective in acute travellers diarrhoea, as are agents such as ciprofloxacin. In tropical areas where there is suspicion of amoebic disease metronidazole should be given early.

VIII. ULCERATIVE COLITIS

VIII.a. Definition, Diagnosis and Aetiology

Ulcerative colitis is an inflammatory disease of unknown aetiology with mucosal involvement spreading continuously but to varying extent from the rectum to the caecum.

Disease is recognisable on sigmoidoscopy and colonoscopy by its continuous distribution, by evidence of an acute inflammatory infiltrate on mucosal biopsy and by barium enema appearances of acute or chronic inflammation. No active infectious agent has been isolated. General pathological features place it closest to the autoimmune group. The possible differential diagnosis of colorectal cancer, and in tropical areas, of amoebic colitis must be born in mind.

Stool culture for pathogens, notably salmonellae and shigellae, and examination for the exotoxin of *Clostridium difficile* in pseudo-membranous colitis, are important considerations in acute disease. *C. difficile* requires oral vancomycin or metronidazole treatment, and giardiasis generally responds to metronidazole.

VIII.b. Therapy

In severe acute disease parenteral steroids and other immuno-suppressants, ciclosporin, and infliximab may be required. There is little evidence to support the use of any accessory treatments. Constipation associated with colonic dysfunction may be helped by a high fibre diet but this will have no intrinsic effect on the inflammation. In severe acute exacerbations of extensive disease, fluid replacement intravenously and blood transfusion may be needed.

VIII.b.1. Acute Treatment

VIII.b.1.1. Proctitis. Disease limited to the rectum in the active phase can be treated with corticosteroids or aminosalicylates as suppositories or enemata (Table 3). Treatment has to be continued for one to two months until symptoms resolve.

VIII.b.1.2. Proctosigmoiditis. Suppositories are inadequate and enemata may be ineffectual due to inability to reflux sufficiently far back into the colon. Oral corticosteroids may then be necessary, although aminosalicylates may be adequate.

VIII.b.1.3. Extensive disease. Rectal therapies are insufficient, and patients should receive, if outpatients, oral corticosteroids, and if in-patients oral or parenteral corticosteroids with full supportive treatment including parenteral fluids and blood transfusion. The need for intensive in-patient treatment is indicated by the presence of severe diarrhoea, anaemia, fever and tachycardia with radiographic evidence of colonic mucosal oedema on plain X-ray, or of toxic megacolon.

The place of other immunosuppressive treatment is limited. The cytokine inhibitor infliximab by intermittent intravenous infusion is of value in moderate

Table 3. Aminosalicylates

		Typical oral dose daily	
		Acute (g)	Maintenance (g)
Mesalazine	Asacol	2.4	1.2–2.4
(coated tablets of 5ASA)	Pentasa	up to 4.0	
Olsalazine		1–3	1
(two azo-bonded molecules of 5ASA)			
Sulphasalazine		4	2
(5ASA azo-bonded to sulphasalazine)			
Balsalazide		2.25	–
(5ASA azo-bonded to para-aminobenzoic acid)			

Adverse effects. Nausea, anorexia, vomiting, skin rash, diarrhea, hypersensitivity reactions including to ordinary salicylates, rarely blood dyscrasias, pancreatitis, hepatitis, interstitial nephritis.

to severe, especially severe ulcerative colitis. Most information suggests that azathioprin is valuable in maintaining remission in resistant cases. Effects are slow to develop, and value in acute treatment is doubtful. Methotrexate is probably equivalent. Ciclosporin has been used in attempts to induce remission in severe disease, but evidence of value is mixed. Concurrent broad spectrum antibiotics have not been shown to give added benefit.

Simple antidiarrhoeals are generally contra-indicated, they do not help to reduce mucosal efflux, and may, by reducing colonic transit, predispose to megacolon development. Despite the strong association between non-smoking and the occurrence of ulcerative colitis nicotine patch treatment has shown little evidence of value.

In those with acute severe disease close cooperation with an experienced surgeon is essential. Those with disease which fails to settle in 5–7 days of intensive medical therapy require surgery.

Newer aminosalicylate preparations appear superior to placebo but differ little in efficacy from sulfasalazine SASP. Potential advantages in reduced adverse effects from removal of the sulfa moiety nevertheless may exist.

VIII.b.2. Maintenance Treatment

Most cases of ulcerative colitis will relapse within a year if no maintenance treatment is given.

The systemic adverse effects of corticosteroids make them inappropriate as maintenance treatments and the first line treatments are the aminosalicylates. The original drug sulfasalazine is a chemical combination of sulfapyridine and 5 aminosalicylic acid. Following the discovery that the active moiety is the 5 aminosalicylate (sulfapyridine acting as a carrier molecule to the proximal large intestine where bacterial action separates it) other products became available. These are coated tablets of 5 aminosalicylate (mesalazine), the coating being pH sensitive and removed in the terminal ileum or proximal colon; a directly bonded complex of two molecules of 5 aminosalicylate (olsalazine), or a para-aminobenzoic acid linked compound (balsalazide). All have broadly similar release characteristics and are of much the same efficacy and Table 3 contrasts them. Treatment has to be continued indefinitely, however long the period of remission. Removal of the sulfapyridine in the newer compounds has not removed the risks of skin rash or agranulocytosis, though it may have diminished then. Adverse reactions to sulfasalazine are generally less common than in rheumatoid patients.

Patients with frequent relapses despite apparently adequate prophylactic treatment should be reviewed carefully. Associated milk intolerance or coeliac disease need treatment on their merits. Colonoscopic evidence of dysplasia raises the question of undiagnosed malignancy. Occasionally the prophylactic agents themselves can cause watery diarrhoea (particularly olsalazine) or a hypersensitivity colitic disease. Prophylactic azathioprin should be considered in those in whom relapse is frequent despite use of aminosalicylates or if they are poorly tolerated. In the effective dose of 2 mg/kg adverse effects of bone marrow depression are uncommon, but still occur, and regular haematological review is essential (monthly or bi-monthly). Azathioprin-induced pancreatitis is an uncommon but well-recognised entity.

Undesirable responses of prevalent gut microflora has raised interest in modification of that flora by probiotic regimes, evidence of benefit is still too limited to justify general usage.

IX. CROHN'S DISEASE

IX.a. Definition, Diagnosis and Aetiology

Crohn's disease is a non-specific inflammatory disease differing from ulcerative colitis in causing full thickness disease, often involving the small bowel, and/or sparing the rectum, often segmental, which is associated with full thickness fissuring and with granuloma formation.

The diagnosis is made by appropriate combinations of colonoscopy, biopsy and contrast radiology. Disease has to be differentiated from ulcerative colitis (see above) and from infective disease, notably tuberculosis and amoebiasis as well as diverticular disease and cancer.

The causes are unknown, there is a strong familial and genetic element, as with ulcerative colitis (which can occur in the same families), and disease (in contrast to ulcerative colitis) is markedly more common in smokers.

IX.b. Therapy

Treatments are broadly the same as for ulcerative colitis being based on appropriate supportive measures, and the use of corticosteroids, the cytokine infliximab or adalimumab for severe and complicated disease and immunosuppressants, typically azathioprine, for reducing the chances of relapse. Full thickness disease leading to fistulation, free perforation, abscess formation and stricturing usually requires surgery. Aminosalicylates appear ineffective in reducing the chances of relapse.

IX.b.1. Large Intestinal Disease

This tends to behave in much the same way as ulcerative colitis and treatment differs in principle and in practice little if at all, either acutely in exacerbations or in continued suppression of disease once an exacerbation has responded to treatment.

IX.b.2. Small Intestinal Disease

Again principles are similar but responses are more variable. This may in part be because scarring associated with established disease is not reversible by corticosteroid or other therapy, and in part because delivery of drug to the target area cannot easily be done directly.

IX.b.3. Agents

IX.b.3.1. Corticosteroids. These reverse symptoms associated with active inflammation, but should be used with caution, if at all, in those suspected of having disease complicated by fistulation and abscesses. Although prednisone has been the standard treatment, the poorly absorbed steroid budesonide has shown equivalence of action whilst having reduced suppression of the pituitary-adrenal axis. The effect of corticosteroids is, in general terms, equivalent to that of an elemental diet.

The use of conventional systemic corticosteroids in patients with clinically quiescent Crohn's disease does not appear to reduce the risk of later relapse.

Anti-tuberculous therapy has not been shown to be effective in maintaining remission in patients with Crohn's disease and any value during acute disease treatment may stem from benefits in treating concurrent infectious disease complications.

IX.b.3.2. Aminosalicylates. Clear evidence of efficacy in acute disease is lacking, and furthermore the ability of any of the available compounds to reduce the chances of small intestinal disease recurrence is inadequate to justify general use for this purpose despite the high risk of recurrence.

IX.b.3.3. Immunosuppressants. As in ulcerative colitis low doses of azathioprine (2 mg/kg) are effective in preventing recurrence, but have little value in treating acute disease.

For ciclosporin evidence available from small studies is mixed, some suggesting efficacy in inducing remission (at the risk of adverse effects which include neuropathy and hypertrichosis) and others giving little evidence of benefit.

IX.b.3.4. Genetically engineered antibodies. Anti-TNF antibody treatment with infliximab or adalimumab is now accepted as of value in treating severe and fistulating exacerbations of Crohn's disease when standard treatments are not tolerated or have failed. Adverse effects which limit usefulness include the occurrence of tuberculosis and septicaemia, leucopenia and pancytopenia, and risk of exacerbation of demyelinating disease. Considerations of benefits versus risks of such treatment are complex, but probably positive.

IX.b.4. General Measures

Diet and life-style: clear benefit from general dietary modification has not been obtained.

Smoking predisposes to Crohn's disease, and those who continue to smoke are more likely to suffer recurrences than those who stop.

X. IRRITABLE BOWEL SYNDROME AND DIVERTICULAR DISEASE

X.a. Definition, Diagnosis and Aetiology

Complaints of abdominal pain associated with disordered bowel habit but with normal clinical and investigative findings, except in those with colonic diverticula, are referred to as irritable bowel syndrome.

The diagnosis is essentially by exclusion of discrete organic disease usually by barium enema and sigmoidoscopy, or colonoscopy.

Causes are largely unclear complaints of food intolerances are often made, but clear evidence of specific and consistent adverse effects is hard to obtain (a distinction is drawn here from genuine dietary allergy which responds to avoidance of the offending item, for instance shellfish, and use of oral sodium cromoglicate). The basis of irritable bowel syndrome rests somewhere in the hinterland of perception of dysfunction, and otherwise normal but exaggerated physiological colonic responses.

X.b. Therapy

The options depend upon the symptom patterns but all patients benefit from clear explanation of the lack of significant organic disease, and that simple dietary and other manoeuvres as well as reduction of stress may help. Treatment considerations are hindered by the disparity between the extensive analyses performed on modern possible treatments and the more skeletal information available about older ones.

Symptom patterns: those with alternating constipation and diarrhoea and predominant constipation may benefit from high fibre diets (although excess fibre may bloat). Those with predominant diarrhoea may require simple peripheral opiate agonists (loperamide), but may also be helped by raised fibre intake. Pain may respond in part to explanation that it does not indicate serious illness and in part to spasmolytic therapy with anticholinergic agents which tend also to be constipating or with agents such as peppermint oil or mebeverine which are probably directly spasmolytic, although supportive evidence is indifferent. Those with associated depression can respond well to antidepressants such as amitryptiline (also anticholinergic).

Constipation: bulk-forming laxatives by increasing faecal mass tend to soften stools and relieve constipation, and have value in a range of symptomatic problems associated with anal fissure, haemorrhoids, and with ileostomy and colostomy dysfunction. Faecal softeners, lactulose and macrogols (polyethylene glycol) retain fluid in the bowel. Stimulant laxatives, such as the anthraquinone, senna, and bisacodyl, increase motility and can cause colic: verdoses can cause diarrhea and electrolyte depletion. Chronic treatment for constipation is seldom needed, but may be in children with a tendency to faecal impaction, specialist advice should be sought.

Symptoms in those with colonic diverticula do not differ materially, except that localised or free perforation, a surgical emergency, may require exploration, drainage and broad spectrum antibiotic treatment.

XI. MALABSORPTION

Management depends upon definition of the causes. Table 4 sets out the main causes and any specific treatments indicated. In general therapy for malabsorption should be structured to consider possible consequences of disease and reversal or amelioration of the disease.

Consequences may include fluid and electrolyte imbalance and hypokalaemia, calorie deficit, deficiencies of haematinics (iron, folate and vitamin B_{12}) and vitamin deficiencies particularly fat-soluble (A, D and K).

In addition symptomatic treatment with opiates, with bile acid binding resins in those with bile acid malabsorption, with milk free diets in those who are lactose intolerant, and with low fat diets may materially help relevant symptoms.

XII. ACUTE PANCREATITIS

XII.a. Definition and Aetiology

Acute pancreatitis is an acute inflammation typically associated with alcoholism or gallstones, but occa-

Table 4. Main features of management of some conditions causing malabsorption

Mucosal lesion	
Coeliac disease	Gluten free diet Occasionally plus steroids
Tropical spruce	Tetracycline plus folic acid
Whipples disease	Antibiotics, e.g., penicillin and streptomycin followed by long-term trimethoprim plus sulphamethoxazole
Structural disease	
Crohn's disease	(see p. 627)
Post-gastric surgery	Vitamin B_{12}, vitamin D, iron
Intestinal resection	Assess specific needs
Blind loops with bacterial overgrowth	Oral antibiotics
Infection (see relevant section p. 625)	
Lack of digestive factors	
Pancreatic	Pancreatic supplements
Bile salt malabsorption	Oral binding resins
Acid hypersecretion inactivating pancreatic enzymes	Suppress acid output
Iatrogenic	
Drugs antibiotics/purgatives	Withdraw
Endocrine disease	
Thyrotoxicosis	Treat underlying disease

sionally with other causes (drugs notably azathioprine, hypercalcaemia, hereditary disease, with associated penetrating ulcer or pancreatic carcinoma).

XII.b. Therapy

In essence this depends on the individual features of the disease and the severity of inflammation.

These factors include:

(i) Hypovolaemia and hypoalbuminaemia and, occasionally, anaemia consequent upon sequestration of large quantities of inflammatory exudate retroperitoneally. This requires intravenous fluid replacement.

(ii) Hypocalcaemia with calcium sequestrated in inflamed tissue, requiring replacement.

(iii) Diabetes mellitus, temporary or permanent, requiring insulin treatment.

(iv) Gastric stasis, requiring nasogastric intubation and intravenous fluid balance maintenance. (Evidence that oral fluids should always be deliberately withheld is lacking, as is evidence that parenteral nutrition is superior to enteral nutrition.)

(v) Pain, for which opiate analgesia may be required, but avoid using morphine which causes spasm of the sphincter of Oddi. In those with localised collections of fluid (pseudo-cysts) drainage may be required.

(vi) Gallstones leading to retained ductal stones as originating causes of the disease should always be sought. Early retrograde cholangiopancreatography has been advocated since the 1980s but unequivocal evidence of added benefit from early intervention is lacking.

Mild disease, with little change in, interalia blood glucose, haemoglobin, serum calcium or blood urea may require little more than analgesia, crystalloid intravenous replacement and nasogastric drainage. Severe disease, typically in those aged 55 or more will be indicated by raised blood glucose (>11 mmol/l) raised white cell count ($>15 \times 10^9$), low serum calcium (<2.0 mmol/l) fall in haematocrit ($>10\%$), base deficit and rising blood urea.

Severe disease requires close attention to maintaining blood volume, and to oxygen saturation (low saturations may reflect pulmonary oedema or toxic damage) diabetes and hypocalcaemia seldom present significant problems. Close surgical collaboration is needed in managing developing fluid collections.

Enzyme inhibitors have not been convincingly shown to help, and there is no indication that antibiotics are of value.

XIII. CHRONIC PANCREATITIS

XIII.a. Definition and Aetiology

Chronic pancreatitis is a chronic inflammatory destructive process, often but not always, associated with alcoholism.

XIII.b. Therapy

This divides into management of pain, malabsorption and diabetes. Objective evidence of value in almost any treatment of pain in this condition is poor.

Alcoholics should abstain, but whether this actually helps is unclear. Antacids, anticholinergics and pancreatic supplementation have all been claimed to help, but classical analgesic agents may still be required. Others claim that surgery on inflammatory masses and opening up of obstructed ducts by dilatation, removal of stones, or stenting may also help.

Pain is often episodic, for no obvious reason, and often tends to remit slowly with time. Coeliac ganglion blocking tends to have little or temporary effect, and total pancreatectomy is now seldom undertaken.

For the management of malabsorption full doses of pancreatic supplements are required, often with antisecretory drugs to prevent acid breakdown of the supplement.

For chronic pancreatitis-associated diabetes insulin is required, but usually in quite modest doses.

XIV. GALLSTONES

XIV.a. Definition, Diagnosis and Aetiology

Radiolucent stones are composed predominantly of bile-salts. These stones are capable of dissolution with orally administered bile acids. Pigment and calcified stones are not, but may be removed by electrophysical means. Treatment solely directed at stone breakdown is only likely to be effective if gall bladder function is retained, but in those with retained gall bladder function without biliary colic their gall bladder stones may not be the causes of pain. Biliary duct stones should be sought in patients presenting with pancreatitis and where symptoms suggest biliary colic. They may be removed endoscopically and surgically.

XIV.b. Therapy

The advent of less invasive procedures of laparoscopic cholecystectomy and endoscopic ductal stone removal have reduced the use of classical open surgery, and made drug-induced stone dissolution less attractive.

Acute cholecystitis: management has been based conservatively on antibiotic treatment plus relief of pain before planned open cholecystectomy. However, it has become increasingly evident that early laparoscopic cholecystectomy is safe and shortens hospital stay.

Chronic symptoms: a major difficulty lies in deciding if stones present are causing symptoms. If the gall bladder is nonfunctional an assumption of causation is usually made. The direct comparative database for laparoscopic versus open cholecystectomy is limited, but both are generally effective procedures. The management of common duct stones, by endoscopic procedures or surgery, is outside the scope of this text but both seem to be effective.

Dissolution: dissolution, typically using ursodeoxycholic acid, is slow taking many months, and the intrinsic lithogenic properties of the bile which led to stone formation are unaltered so stones can reform when treatment stops. There are few adverse effects. Occasional patients develop diarrhoea, and minor derangements of liver function tests are described. The use of dissolution therapy has to be considered carefully. Stones present in a functioning gall-bladder are unlikely to cause symptoms other than through biliary colic if they impact in the bile duct. In such cases dissolution therapy can be attempted, but in the knowledge that recurrence is likely. If the gall bladder is diseased then removal of the organ is the right course. In managing patients it has to be remembered that gall stones are common, and that ill-defined symptoms may not have been caused by them.

XV. HEPATIC CIRRHOSIS

XV.a. Definition, Diagnosis and Aetiology

Hepatic cirrhosis is an end stage process of hepatic inflammation characterised by lobular scarring, distortion of the hepatocellular architecture and disordered function, frequently with associated portal hypertension.

Disease, in essence defined by hepatic histology, is commonly alcoholic, but frequently occult in

cause, or arising as a late consequence of hepatitis B infection or as an autoimmune disease. Rarer causes include copper and iron retention (Wilson's disease and haemochromatosis) and fibrocystic disease. Biliary cirrhosis can arise as secondary to long-standing obstruction and infection in the biliary tree, or as a primary disease, usually in middle aged or older women.

XV.b. Therapy

This can be divided into treatment for the complications: ascites, neuropsychiatric disease and variceal bleeding and specific treatments for, in particular, copper and iron retention, and for biliary and autoimmune disease.

XV.b.1. Fluid Retention and Ascites

Sodium retention and hypoalbuminaemia are constant features. The former appears consequent on disturbed blood volume distribution, withslanchnic dilatation and reduced effective central arterial blood volume leads to sodium retention. Hypoalbuminaemia associated with reduced hepatic albumin synthesis, and raised portal pressure associated with obstruction to flow, as well as active sodium retention all predispose to ascites. Hypoalbuminaemia is associated with reduced hepatic synthesis.

Reversal of sodium (and hence water) retention reduces the degree of ascites. The evidence base supporting the value of one particular regime over another is limited.

Diuretics, typically spironolactone, form the main therapy, combined with restricted salt intake. Sodium restriction is usually unnecessary where fluid retention is mild, and if marked limitation (less than 40 mmol per day intake) is imposed, may lead to impaired nutrition and is poorly accepted. Diuretic treatment often requires reinforcement with loop diuretics. Treatment can be maintained if urinary sodium excretion is at least 30 mmol per day. Removal of ascites through diuresis requires fluid transfer through the intravascular fluid compartment. If diuresis is too intense the intravascular fluid volume is reduced and hypotension causes hepatorenal failure to follow. The aim should be, through monitoring weight loss, to restrict fluid removal to 0.5 kg per day. In this way the risks of hyponatraemia, renal and hepatic impairment should be reduced.

Paracentesis with removal of up to 5 litres of ascitic fluid in those with tense ascites appears safe. Larger volumes can only be safely removed if there is simultaneous albumin replacement intravenously (with about 8 g of albumin per litre of ascites). Synthetic plasma-expanders may not be greatly inferior to albumin in the short term. Transjugular intrahepatic portal systemic shunting (TIPS) appears at least as effective as paracentesis in relieving refractory ascites without increasing mortality but with a raised risk of encephalopathy.

Hyponatraemia: impaired excretion of water and enhanced sodium retention is a feature of advanced cirrhosis. Fluid restriction is often imposed, but does not reverse the problem. Administration of hypertonic saline will exacerbate fluid retention.

Hepato-renal syndrome: rapid progressive (type I) with rising serum creatinine levels, or non-progressive and less severe (type II) impairment of renal function, often consequent on bacterial peritonitis, with persistent ascites responds to vasoconstrictor treatment, typically with terlipressin through constriction of splanchnic vessels and improved renal perfusion. Withdrawal of treatment does not seem to lead inevitably to recurrence. Haemodialysis may also stabilise patients.

Peritonitis: infection of ascitic fluid, characteristically by gram negative organisms without an obvious cause, is common in patients with increasing ascites, and is diagnosed by raised ascitic polymorphonuclear cell counts. Treatment with third generation cephalosporins, or amoxicillin and clavulanic acid is effective. Concurrent albumin supplementation helps prevent renal failure.

Accessory measures: insertion of a peritoneovenous shunt to allow transfer of ascitic fluid to the venous compartment has largely been abandoned due to frequent shunt obstruction, peritoneal infection and the occurrence of encephalopathy. TIPS is as effective in relieving ascites as paracentesis with albumin replacement, but shunts can quickly become obstructed, and hepatic encephalopathy is a common complication.

Liver transplantation: this is indicated for those with failing liver function, for instance with hepatorenal syndrome. Details are beyond this text.

XV.b.2. Neuropsychiatric Sequelae

Substantial shunting of portal venous blood into the systemic circulation through oesophageal varices and other systemic connexions, including those surgically established, restricts the hepatic clearance of nitrogenous waste products, and the formation of

urea prior to renal excretion. In addition hepatic gluconeogenesis may be impaired leading to hypoglycaemia. Symptoms due to toxins may be reversed but not the underlying basis, by restricting dietary protein intake, and by reducing toxin production in the gut. Treatment includes traditionally used low protein diet, evacuation of the gut and reduction of the bacterial load with oral neomycin or the synthetic sugar lactulose (or lactitol), the latter acting by reducing intracolonic pH to levels unsuited to colonic bacteria, and glucose supplementation in hypoglycaemia.

The value of pharmacological interventions is not as firmly established as is desirable. Control of precipitants notably gastrointestinal haemorrhage, systemic infection, constipation and electrolyte, particularly potassium imbalance is important. Despite lack of consistent evidence, use of synthetic sugars by mouth and oral antibiotics (neomycin or metronidazole) remains standard. Oral neomycin, though poorly absorbed, can still cause eighth cranial nerve damage.

XV.b.3. Variceal Bleeding

XV.b.3.1. Acute treatment. See the section on haematemesis and melaena.

XV.b.3.2. Prophylaxis. There is little evidence to justify prophylactic endoscopic or surgical intervention in patients with varices which have not yet bled. Available trials have often been small and assumptions based upon aggregation may not be well justified. Non-selective beta-blockade with propanolol appears however to halve the risk of bleeding.

In those who have bled variceal banding appears superior to injection in preventing rebleeding and complications of injection.

XV.b.4. Specific Cirrhotic Diseases

Alcoholic cirrhosis: apart from abstinence there is no coherent evidence of benefit from hepato-protective agents.

Biliary cirrhosis, secondary disease: this requires elimination of the obstructive cause. Itching associated with bile acid retention can respond to cholestyramine, a bile acid binding resin.

Primary biliary cirrhosis: the underlying cause is unknown. The disease is particularly common in older women. Associated itching is helped by cholestyramine. Hepatic function can appear to improve in primary biliary cirrhosis when ursodeoxycholic acid (UDCA) is administered, but unequivocal supportive evidence is lacking.

Sclerosing cholangitis: administration of UDCA has not been followed by benefit in patients with primary sclerosing cholangitis. Progression of disease commonly leads to the consideration of hepatic transplantation.

Wilsons disease: copper chelation using penicillamine is efficient and effective.

Corticosteroids, often given in conjunction with azathioprin, improve hepatic function and may reduce the risk of advancing autoimmune disease-associated cirrhosis.

XV.b.5. Supportive Treatment

Itching associated with retention of bile acids is ameliorated by treatment with the bile acid binding resin cholestyramine. Fat soluble vitamin (A, D and K) deficiency may require administration of supplements. Direct toxic effects of alcohol associated with dietary deficiency may require soluble B vitamin administration.

XVI. ACUTE HEPATITIS

This may be induced in the main by viral infection and by drugs, typically paracetamol (acetaminophen) overdose but occasionally dose independently by antidepressants and antituberculous drugs amongst others (Table 5).

There are no specific treatments for acute viral hepatitis and management is essentially supportive. Immuno-prevention is considered elsewhere.

XVI.a. Supportive Management

Corticosteroids have no value in supportive therapy. Acute liver failure is the main problem and specific features noted below require treatment:

A. Disturbed consciousness may be due to cerebral oedema, if suspected give intravenous mannitol. Otherwise lactulose or neomycin by mouth can help by reducing gutammonia loading.
B. Fluid balance should be maintained and close attention to oral and intravenous needs is required as renal failure is common, often with tubular necrosis.

Table 5. Drug induced liver damage, some well-described varieties

Cholestatic hepatitis	Phenothiazines Oral hypoglycaemics Erythromycin estolate
Pure cholestasis	Oral contraceptives
Hepatocellular damage (dose independent)	Monoamine oxidase inhibitors Tricyclic antidepressants Antituberculous drugs (isoniazid, pyrazinamide, rifampicin PAS) Anticonvulsants (phenytoin carbamazepine) Halothane (repeated exposure) Many others
Hepatic fibrosis	Methotrexate Amiodarone
Chronic hepatitis	Methyl dopa Sulphonamides
Fatty infiltration with cerebral oedema (Reye's syndrome)	Aspirin

C. Hypoglycaemia may occur as gluconeogenesis is reduced in the liver. 10% dextrose by central venous administration is needed, usually with extra potassium.
D. Gastrointestinal bleeding is usually due to acute erosions. Histamine H_2 antagonists reduce the risk.

For the management of paracetamol (acetaminophen) overdose see Chapter 32.

XVII. CHRONIC HEPATITIS

The main causes are hepatitis B and C, drug induced damage, metabolic disease (alcohol, haemochromatosis and Wilsons disease) and autoimmune disease. Management depends upon the diagnosis.

For alcoholic hepatitis is no specific treatment beyond alcohol withdrawal. Corticosteroids have no value. Fatty change in the liver is common, but should not be confused with fatty change associated with non-alcoholic disease, notably diabetes mellitus.

For auto-immune hepatitis relatively low doses of oral corticosteroids are effective, and concurrent azathioprin (2 mg/kg) is steroid sparing. Those in remission for two years can stop treatment, but relapse is common.

Drug-induced damage requires recognition and withdrawal. Methyldopa, isoniazid, and nitrofurantoin and are well-recognised causes.

Haemochomatosis should be treated with venesection, initially of 500 ml weekly and guided by serial serum ferritin levels and liver biopsy to assess residual iron stores.

In the case of hepatitis associated with Wilsons disease D-penicillamine, initially 1.5–2 g daily is indicated, then reducing to half after one year.

XVII.a. Viral Hepatitis

Treatment options for viral hepatitis include lamivudine, simple interferon alpha, polyethylene glycol-linked interferon (Peginterferon alfa-2a), and adefovir and ribavirin. Selected regimes have markedly improved response rates, but relapse is still common.

XVII.a.1. Hepatitis B

Peginterferon alfa-2a treatment results in more sustained responses than simple interferon alpha, although relapse is not uncommon. Such treatment should generally be avoided in those receiving immunosuppressants and those with decompensated liver disease. Lamivudine, a reverse transscriptase inhibitor is often used in initial treatment and in decompensated liver disease.

Adefovir dipivoxil, more recently introduced, is an option in those who have unsuccessful therapy with relapse after use of interferon alpha, and/or have become lamivudine resistant.

XVII.a.2. Hepatitis C

Peginterferon alpha, either peginterferon alfa-2a or peginterferon alfa-2b, with ribavirin is recommended for treatment of those aged 18 years and over who have not previously received an interferon, or who have received such treatment but where response was inadequate. Choice of treatment depends on viral load and genotype. Treatment of patients with coincident HIV infection requires specialist advice.

Adverse effects of such regimes are common, thus interferons can cause anorexia, influenza-like illness, myelosuppression, and cardiovascular, hepatic and renal adverse effects.

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Chapter 36

Pharmacotherapy of Chronic Obstructive Pulmonary Disease and Asthma

Emile F.L. Dubois, Dieter Ukena

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I. DEFINITIONS

Chronic obstructive pulmonary disease (COPD) includes either alone or in combination

- emphysema
- chronic bronchitis
- chronic airflow limitation (CAL)
- chronic airflow obstruction (CAO)
- chronic airways obstruction (CAO)
- non-reversible obstructive airways disease (NROAD)
- chronic obstructive airways disease (COAD)
- chronic obstructive lung disease (COLD)
- some cases of asthma with irreversible airways obstruction.

The American Thoracic Society (ATS) defined COPD as a disease state characterized by the presence of airflow obstruction due to chronic bronchitis or emphysema; the airflow obstruction is generally progressive, may be accompanied by airway hyperreactivity, and may be partially reversible.

Chronic bronchitis was defined as the presence of chronic productive cough for 3 months in each of two successive years in a patient in whom other causes of chronic cough have been excluded. Emphysema was defined as abnormal permanent enlargement of the airspaces distal to the terminal bronchioles, accompanied by destruction of their walls and without obvious fibrosis. The Global initiative for Chronic Obstructive Lung Disease (American Thoracic Society/European Respiratory Society (ERS) task force GOLD, 2005) describes Chronic Obstructive Pulmonary Disease (COPD) as a preventable and treatable disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and is associated with an abnormal inflammatory response of the lungs to noxious particles or gases, primarily caused by cigarette smoking. Although COPD affects the lungs, it also produces significant systemic consequences.

Chronic bronchitis is defined clinically as chronic productive cough for 3 months in each of 2 successive years in a patient in whom other causes of productive chronic cough have been excluded.

Emphysema is defined pathologically as the presence of permanent enlargement of the airspaces distal to the terminal bronchioles, accompanied by destruction of their walls and without obvious fibrosis.

Asthma is one of the most common chronic diseases, with an estimated 300 million people being affected worldwide, while this number is still increasing.

The definition of Asthma was previously described by the World Health organization in 1975 as a chronic condition characterized by recurrent bronchospasm resulting from a tendency to develop reversible narrowing of airway lumina in response to stimuli on a level of intensity not causing such narrowing in most individuals. Later on in 1991, the National Institute of Health and the National Heart

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Lung and Blood Institute re-defines in 1995 asthma again is redefined as a chronic inflammatory airways disorder which, in susceptible individuals, causes symptoms of general but variable airways obstruction and an enhanced sensibility to external stimuli: so-called hyper-reactivity or hyper-responsiveness (Global Initiative for Asthma, 1995). The latest revision of these GINA guidelines in 2006 emphasizes more on the diagnosis and the maintaining of asthma control, rather than on the definition of asthma, however they describe asthma as: a chronic inflammatory disorder defined by its clinical, physiological, and pathological characteristics. The predominant feature of the clinical history is episodic shortness of breath, particularly at night, often accompanied by cough. These episodes are usually associated with widespread, but variable, airflow obstruction within the lung that is often reversible either spontaneously or with treatment. Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. Diagnosing asthma in children of 5 years and younger, presents a particularly difficult problem, because episodic wheezing and cough are also common in children who do not have asthma. Particularly in those under the age of 3, wheezing is usually associated with a viral respiratory illness. Three categories of wheezing in children of 5 years and younger have been described:

- *Transient early wheezing*, which has been associated with prematurity and parental smoking and often disappears in the first 3 years of life.
- *Persistent early onset wheezing*, with a set-off before 3 year, associated with recurrent acute viral infections and in the absence of allergies and/or a family history regarding allergies.
- *Late onset wheezing asthma*, symptoms often persist throughout childhood and into adult life. An allergic/atopic background including eczema, upper airway inflammation in patients and/or family histories may be observed.

Alternative causes of recurrent wheezing (also in the adult) must be excluded, these include:

- chronic rhino-sinusitis
- gastro-oesophageal reflux
- recurrent viral lower respiratory tract infections
- cystic fibrosis
- broncho-pulmonary dysplasia
- tuberculosis
- congenital malformation causing narrowing of the intra-thoracic airways
- foreign body aspiration
- primary ciliary dyskinesia syndrome
- immune deficiency
- congenital heart disease

The inflammation in asthmatics also causes an associated increase in airway responsiveness to a variety of stimuli. The structural and inflammatory changes of COPD and asthma are described in detail elsewhere.

II. REVERSIBILITY TESTING

Reversibility tests to bronchodilators are recommended at all stages of obstructive airways diseases. They are helpful in differentiating patients with COPD with those of asthma. Many patients with COPD and even those with severe airflow obstruction can demonstrate (partial) reversibility. Patients with a positive bronchodilator response i.e. reversibility are more likely to respond to a trial of oral or inhaled corticosteroids.

Although a variety of interpretations have been issued, reversibility to bronchodilators is considered to be present when the FEV_1 increases by 200 ml and 12% of the pre-bronchodilator value. Although in the latest GINA guidelines this issue is no longer addressed, the same criteria have been used for evaluation of the response to corticosteroids. A corticosteroid trial compared spirometric tests before and at the end of oral prednisolone (e.g. 30 mg/d) taken for two weeks or a course of inhaled steroid (e.g. beclomethasone 500 μg twice daily or equivalent) taken for six weeks. A positive response to corticosteroids justified prescription of regular inhaled steroid. Subjective improvement as a single efficacy parameter is not considered to be a satisfactory end point. Objective improvement is seen in 10–20% of patients with COPD.

A systematic review of six trials involving a total of 55 people concludes that caffeine appears to improve airways function modestly in people with asthma for up to four hours. People may need to avoid caffeine for at least four hours prior to lung function testing.

III. GENERAL PRINCIPLES OF PHARMACOTHERAPY

Medications for obstructive pulmonary disease are used to reverse and prevent symptoms and airflow

limitation and include controllers and relievers (Tables 1 and 2). *Controllers* or *long-term control medications* are taken daily on a long-term basis to achieve and maintain control of chronic airways disease. *Relievers* or *quick-relief medications* are taken to provide prompt reversal of acute airflow obstruc-

Table 1. Long-term control medications (modification of National Institutes of Health, 1997)

Drugs	Indications/Mechanisms	Potential adverse effects
ICS (Inhaled Corticosteroids) (glucocorticoids) Beclomethasone Dipropionate Budesonide Ciclesonide Flunisolide Fluticasone propionate Mometasone Triamcinolone acetonide	Indications • long-term prevention of symptoms • suppression, control, and reversal of inflammation Mechanisms • anti-infalammatory: block late reaction to allergen, reduce hyper-responsiveness • inhibit microvascular leakage reduce need for oral corticosteroid	Cough, dysphonia, oral thrush (candidiasis) in high doses, systemic effects may occur: adrenal suppression, osteoporosis, cataract skin thinning and bruising Anti-inflammatory: block late reaction to allergen growth suppression
Cromones Cromolyn sodium Nedocromil	Indications • long-term prevention of symptoms may modify inflammation • preventive treatment to exercise or provocative/known allergen Mechanisms • anti-inflammatory: block early and late reaction to allergen; interfere with chloride channel function, stabilize mastcell membrane inhibit release of mediators from eosinophils and epithelial cells • inhibit acute response to exercise, cold air and SO_2	Unpleasant taste (nedocromil)
LAβA (Long-acting β_2-agonist) Inhaled: Formoterol Salmeterol (single or in combination with inhaled corticosteroids)	Indications • long-term prevention of symptoms, especially nocturnal symptoms, added to anti-inflammatory therapy prevention of exercise-induced bronchospasm Mechanisms • bronchodilation: smooth muscle relaxation *in vitro*: inhibit cell mediator release, decrease vascular permeability, increase mucociliary clearance and long duration of bronchodilation (>8–10–12 h)	Tachycardia Skeletal muscle tremor Hypokalemia Prolongation of QT_c interval in overdose Diminished bronchoprotective effect during chronic therapy (clinical significance unclear)
LAACh (Long-acting anti-cholinergics) Thiotropium	Indications • long-term prevention of symptoms, • especially nocturnal symptoms, Mechanisms • competitive inhibition of muscarinic cholinergic receptors, reduces intrinsic vagal tone to the airways • may decrease gland secretion, may block reflex broncho-constriction secondary to irritants or to reflux esophagitis	

Table 1. (Continued)

Drugs	Indications/Mechanisms	Potential adverse effects
Leukotrien Modifiers Montelukast Zafirlukast Zileuton	Indications • long-term control and prevention of symptoms in mild persistent asthma Mechanisms • 5-lipogenase inhibition or leukotrien receptor antagonist	No specific adverse effects relation to Churg–Strauss syndrome Elevation of liver enzymes
Methylxanthines Theophylline (sustained release tablets and capsules)	Indications • long-term control and prevention of symptoms, nocturnal symptoms Mechanisms • bronchodilation; smooth muscle relaxation inhibition of eosinophilic infiltration decrease of T-lymphocyte numbers in epithelium increase of diaphragm contractility and mucociliary clearance	Dose-related acute toxicities include tachycardia, nausea, vomiting, tachyarythmias (SVT) CNS stimulation, headache, seizures, hematemesis, hyperglycaemia Adverse effects at usual therapeutic doses include insomnia gastric upset, 30 possibly from phosphor-diesterase inhibiton aggravation of ulcer or reflux

tion and relief of accompanying bronchoconstriction.

III.a. Route of Administration

Medications for the treatment of obstructive airways diseases can be administered either by inhaled or systemic routes. Systemic routes are oral (ingested) or parenteral (subcutaneous, intramuscular, or intravenous). The advantage of delivering drugs directly into the airways via inhalation is that high concentrations can be delivered more effectively to the airways, and systemic side effects are avoided or minimized. In addition, some of the drugs in obstructive airways diseases can only be used via inhalation because they are not absorbed when given orally. Generally, the onset of action of bronchodilators given via inhalation is substantially shorter than when administered orally.

Aerosolized medications are available as pressurized or breath-actuated metered-dose inhalers (MDIs), dry powder inhalers (DPIs), and nebulized or wet aerosols. Most inhaled medications currently used are available as metered-dose inhalers (Table 3). For the patient who has difficulty to coordinate activation of a MDI, a spacer improves delivery. Spacers reduce deposition of the drug in the mouth and the oropharynx. In the case of inhaled corticosteroids, spacers have been shown to decrease the systemic bioavailability and the risk for systemic side effects.

DPIs do not utilize Freon propellants, but use either with or without lactose as vehiculum. These devices have a clinical efficacy similar to standard metered-dose inhalers, but may be easier to use in selected patients, since a minimal inspiratory flow rate is necessary to inhale from a DPI. Therefore, the DPI may be difficult for patients with an insufficient inspiratory flow rate, which occurs in children, the elderly, people with severe COPD shared with diaphragm dysfunction, and during an exacerbation. The inspiratory flow rate is associated with the internal resistance of the device used. For instance the turbuhalor has a significant internal resistance and its delivered dose is dependent from the inspiratory flow rate.

Nebulized or wet aerosols generated by an air compressor are particularly useful for children under 5 years of age and in the treatment of acute severe bronchus constriction, in which ventilatory insufficiency could impair inhalation from a MDI or DPI.

MDI technology has utilized chlorofluorocarbons (CFCs) as propellants. CFC-containing MDIs

Table 2. Quick-relief medications (modification of National Institutes of Health, 1997)

Drugs	Indications/Mechanisms	Potential adverse effects
SAβA (Short acting β_2-agonists) Albuterol (salbutamol) Bitolterol Fenoterol Pirbuterol Terbutaline	Indications • relief of acute symptoms • preventive treatment prior to exercise for exercise-induced bronchospasm Mechanisms • bronchodilation: smooth muscle relaxation	Tachycardia, skeletal muscle tremor, hypokalemia, increased hyperglycemia Lactic acid production, headache
SAACh (Short-acting anti-cholinergics) Ipratropium bromide Oxitropium bromide	Indications • relief of acute bronchospasm Mechanisms • bronchodilation: competetive inhibition of muscarinic cholinergic receptors reduces intrinsic vagal bronchotonus • may block cholinergic receptorsreflex bronchoconstriction secondary to irritants or to reflux esophagitis may decrease gland secretion	Drying of mouth and respiratory secretions increased wheezing in some individuals
Combination SAβA & SAACh Berodual (Ipratropium + salbutamol) Combivent (Ipratropium + fenoterol)		

have proved to be a low-cost, effective and reliable means to treat respiratory diseases. At the end of the nineties some 500 million MDIs were used annually worldwide, resulting in the use and emission of around 10,000 tons CFCs per year.

CFCs released to the atmosphere eventually find their way up to the stratosphere where they destroy the ozone layer which protects the Earth's surface from harmful ultra-violet radiation. During the last decades, the ozone layer has been severely depleted, both over the Antarctic region where the ozone hole now appears annually, but also over the northern hemisphere. Ozone depletion up to 40% has been recorded in each of the last three years over Northern Europe.

In order to prevent the destruction of the Earth's ozone layer, the international community has agreed upon restrictions during a convention (The Vienna Convention, 1985) and a protocol was written (The Montreal Protocol, 1987). The Montreal Protocol requires the progressive phase-out of the production and consumption of substances which destroy the ozone layer. The production of CFCs has been banned by more than 100 signatory countries of the Montreal Protocol.

Hydrofluoroalkane (HFA)-134a (CF_3CH_2F, norflurane) is an alternative to the CFCs that does not contain chlorine and so has no potential to destroy ozone. The safety of HFA-134a as a pharmaceutical propellant was established by the pharmaceutical consortium, International Pharmaceutical Aerosol Consortium for Toxicological Testing of HFA-134a (IPACT-1) and HFA-134a has now been globally accepted as a safe alternative for CFCs, in both pharmaceutical and industrial applications.

CFC-based metered-dose therapeutic aerosols are in the process of being reformulated with HFA-134a. HFA-formulations of salbutamol (= albuterol) and fluticasone propionate have been shown to be as effective and well tolerated as CFC products at equivalent doses.

Table 3. Aerosol delivery devices (modification of National Institutes of Health, 1997)

Device/Drug	Population	Optimal technique	Therapeutic issues
MDI (Metered-Dose Inhaler) SAACh LAβA & SAβA ICS Cromones	>5 years	Actuation during a *slow* (30 l/min or 3–5 s) deep inhalation, followed by 10 sec breath holding. Open mouth technique: holding MDI 2 inches away from open mouth, is comparable to closed-mouth technique (closing lips around MDI mouthpiece)	Slow inhalation may be difficult. Difficulty in coordination of actuation and inhalation in children and elderly, 80% of dose may deposit in oropharynx. Mouth washing effective in reducing systemic absorption
MDI, breath actuated SAβA ICS	>5 years	*Slow* (30 l/min or 3–5 s) inhalation followed by 10 s breath-holding	Indicated for patients unable to coordinate Inhalation and actuation. May be particularly useful in elderly. Requires more rapid inspiration to activate than is optimal for deposition.
Soft Mist Inhalor LAACh SAACh/SAACh combined		Actuation during a *slow* (30 l/min or 3–5 s) deep inhalation, followed by 10 s breath holding. Open mouth technique: holding MDI 2 inches away from open mouth, is comparable to closed-mouth technique (closing lips around MDI mouthpiece)	May be particularly useful in elderly. Relatively high lung deposition requires lower doses per actuation
DPI (Dry Powder Inhaler) SAACh & LAACh LAβA & SAβA ICS	>5 years	Actuation during a *rapid* ($\geqslant$60 l/min or 1–2 s) deep inhalation followed by 10 s breath holding. Minimally effective inspiratory flow is device dependent	Dose lost if patient exhales through device Most appear to have similar delivery efficiency as MDI either with or without SHC but some may have delivery >MDI (e.g. Turbuhaler).
SHC (Spacer/Holding Chamber)	>4 years	Slow (30 l/min or 3–5 s) inhalation or *tidal* breathing Immediately following actuation	Easier to use than MDI alone. With a face mask: enables MDI to be used with small children. Simple tubes do not obviate coordinating actuation The effect of a SHC on output from a MDI is dependent on both MDI and spacer type; thus the rate from one combination should not be extrapolated to all others. SHCs decrease oro-pharyngeal deposition and will reduce potential systemic absorption of ICS preparations with higher bioavailability. SHCs are recommended for all patients on medium or high doses of ICS. May be as effective as nebulizer delivering high doses of β_2-agonists during severe exacerbations
	$\leqslant$4 years	Actuation only once into spacer/holding chamber and per inhalation. If face mask is used, allow 3–5 inhalations per actuation.	

Similarly, beclomethasone propionate (BDP) has now been reformulated using the new HFA propellant. In contrast to current CFC-products this new formulation is a solution, rather than a suspension, of BDP in propellant. This HFA-BDP solution delivers an aerosol with a much smaller mean particle size ± mass median aerodynamic diameter (MMAD) 1.1 μm than that of aerosols generated by conventional CFC-based MDIs of BDP (MMAD 3.5 to 4 μm). Due to this particle size, HFA-BDP extra-finer aerosol changes the standard pattern of drug deposition seen with CFC-BDP formulations, delivering most of the inhaled dose to the airways and depositing a much smaller proportion in the oropharynx. Results of direct radio-labeled deposition studies in both healthy volunteers and patients with asthma show ex-actuator lung deposition to be up to 51% with HFA-BDP compared with lung deposition of <10% for CFC-BDP. The extent of lung deposition is known to be a major determinant of the therapeutic efficacy of inhaled corticosteroids, so these improved delivery characteristics are likely to provide several important clinical benefits. In particular, the improved lung deposition of HFA-BDP extra-fine aerosol compared with CFC-BDP suggests that lower doses of HFA-BDP may be needed to provide equivalent asthma control. Indeed, comparative studies showed that equivalent asthma control can be maintained at a significantly lower total daily dose with HFA-BDP than with CFC-BDP. Currently, a dose comparability ratio CFC-BDP vs. HFA-BDP of 2–2.5 : 1 is favored.

A further advantage is the potential for reduced systemic side effects of the HFA-BDP as a result of both reduced oropharyngeal deposition and thus less gastrointestinal absorption from swallowed BDP and the lower total ex-actuator dose needed to achieve comparable efficacy.

Another potential advantage of extra-fine corticosteroid aerosols is their apparently greater accessibility to peripheral airways (⩽ mm in diameter) which appear to be poorly penetrated by conventional CFC-based aerosols. Recent data indicate that airway inflammation is present in both large and small airways, as well as alveolar tissue, and that airway wall remodeling occurs in small airways. The clinical significance of small airways involvement in asthma, its contribution to fatal asthma or to the accelerated rate of decline in lung function with age that occurs in asthma, and the consequences of treating the small airways component are as yet unclear. Using extra-fine HFA-BDP it may be possible to address these unsolved issues. From a systematic Cochrane review including 2066 children and 614 adults in 25 trials from emergency room and community settings and in addition, six trials on in-patients with acute asthma (213 children and 28 adults) it was concluded that metered-dose inhalers with holding chamber produced outcomes that were at least equivalent to nebulizer delivery. Holding chambers may have some advantages compared to nebulizer for children with acute asthma.

IV. CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

COPD is a chronic, slowly progressive disorder characterized by airways obstruction ($FEV_1 < 80\%$ predicted; FEV_1/VC ratio $< 70\%$) which does not change markedly over several months. The airways obstruction is largely fixed but may be partially reversible by bronchodilator therapy. Unlike asthma, airflow limitation in COPD can never be returned to normal values. The diagnosis of COPD is usually suggested by symptoms. A firm diagnosis can only be made by objective measurement of airways obstruction with spirometric tests, which may be enhanced by radio diagnostic techniques (Table 4).

Several guidelines for the management of COPD have been published in the last years, for instance those of the American Thoracic Society (ATS), the European Respiratory Society (ERS), and the British Thoracic Society (BTS). In analogy to asthma, a large panel of international experts, under the auspices of the National Heart, Lung and Blood Institute (NIH) and the World Health Organization (WHO) developed a global initiative for recommendations for the management of COPD. These "GOLD"-guidelines were released in 2004 and updated in 2005.

Most guidelines state that the main aim of COPD management is to achieve and maintain control of the disease. This includes:

- improvement of symptoms and quality of life
- reduction the frequency and severity of exacerbations
- improvement of lung function (if achievable)
- reduction the accelerated decline in lung function
- prevention and effective treatment of complications

Table 4. A summary of characteristics and recommended treatment at each stage of COPD (from American Thoracic Society/European Respiratory Society, 2005). Therapy at each stage of COPD

Old staging	0: At risk	I: Mild	II: Moderate IIA	IIB	III: Severe
New staging	0: At risk	I: Mild	II: Moderate	III: Severe	IV: Very Severe
Characteristics	Chronic symptoms Exposure to risk factors Normal spirometry	$FEV_1/FVC < 70\%$ $FEV_1 \geqslant 80\%_{pred}$ With or without symptoms	FEV_1/FVC $50 < FEV_1 < 80\%_{pred}$	FEV_1/FVC $30 \leqslant FEV_1 < 50\%_{pred}$	FEV_1/FVC $FEV_1 < 30\%_{pred}$ OR $FEV_1 < 50\%_{pred}$ + chron. resp. failure
	Avoidance of riskfactor(s); influenza vaccination				
		Add short acting bronchodilators when needed			
			Add regular treatment with one or more long-acting bronchodilators *Add* rehabilitation		
				Add inhaled glucocorticoids if repeated exacerbations	
					Add longterm oxygen if chron. respir. failure consider surgical treatments

- reduction of mortality
- avoidance of treatment-related side effects.

Table 4, adapted from the GOLD citeria, summarizes the range of therapies available for the treatment of COPD and the stage in the illness, also adapted from these guidelines, when they may be introduced. The only treatment options that have been proved to achieve the aims of treatment are smoking cessation and long-term oxygen therapy in severe COPD. The step up-regimen involves increasing doses and frequency of administration and adding drugs to reach and maintain the patient's personal best. The step down-strategy involves the use of maximal therapy at the beginning with full doses of all available bronchodilators, followed by decreasing doses and frequency of administration and the number of drugs to achieve the best response on the lowest therapeutic regimen. Although several large studies have already been performed, this clinically important topic still needs further adequate studies.

IV.a. Bronchodilation

Bronchodilators play an important role in the long-term control of symptoms, but they do not alter the progression of COPD. In all current guidelines there is consensus that bronchodilators are the cornerstone of the pharmacotherapy of stable COPD. This recommendation is despite the fact that by definition COPD-patients show only limited bronchus dilatation. The usefulness of a particular bronchodilator for any patient can only be assessed by a therapeutic trial, accepting either increase of lung function values or subjective improvement as efficacy parameters.

Short-acting β_2-adrenoceptor agonists are recommended for use "as required" for symptom relief. Salbutamol (= albuterol) or related drugs should be used up to a maximum of three to four times a day or as prophylaxis before exercise, in case of exercise induced bronchus constriction.

Anti-cholinergic drugs are at least as efficacious as β_2-agonists in COPD. These drugs have a slower onset and a longer duration of action than short-acting β_2-agonists and thus are less suitable for use on an "as needed"-basis. The combination of an anticholinergic and a β_2-agonist may enhance exercise capability more than can be achieved by either drug alone. The use of a combination in the same metered-dose inhaler may help simplify therapy.

IV.a.1. Long-Acting β_2-Agonists

According to the BTS guidelines from 1997, the value of long-acting inhaled β_2-agonists such as formoterol and salmeterol was considered limited and

these agents were to be considered only if objective evidence of improvement was available. However, several novel studies showed that long-acting inhaled β_2-agonists are effective as short acting symptomatic relievers in asthma and COPD, resulting in a significant decrease in dyspnea, an improved quality of life, and appear to have steroid sparing influence. Long-acting oral β_2-agonists such as bambuterol have a high incidence of systemic side effects and are not recommended unless patients are unable to use inhaled therapy.

A Cochrane systematic review including twenty-three published and unpublished studies (6061 participants) concludes that treatment of patients with COPD with long acting β_2-agonists produces only modest increases in FEV1. However, there was a consistent reduction in exacerbations. The size of improvement in airways function does not appear to reflect the symptomatic improvement that can occur in some patients with salmeterol in COPD.

IV.a.2. Theophylline

This xanthine derivative is an only a modest bronchodilator in COPD, and because of its narrow therapeutic range, frequently seen adverse effect and drug interactions, it is becoming less frequently used, some patients experience side effects even within the therapeutic range. The non-bronchodilator effects of theophylline such as systemic and pulmonary vascular dilatation, central nervous system stimulation, improvement of the strength and effectiveness of respiratory muscles and possibly anti-inflammatory effects are of disputed clinical significance at usual therapeutic levels.

Sustained-release formulations can produce stable serum concentrations with once or twice daily dosage. Therapeutic effects occur at blood levels > 5 mg/l, and side effects increase considerably at levels > 15 mg/l. Smoking, alcohol, anticonvulsants, and rifampicin induce the drug-metabolizing enzyme system in liver and reduce the half-life of theophylline. On the other hand, heart and liver failure, sustained fever, old age and drugs such as cimetidine, ciprofloxacin, and oral contraceptives reduce theophylline clearance and thereby increase serum concentrations.

In addition, a change in the type of theophylline preparation may affect serum concentration, even if the dose is unchanged. Due to these potential problems, in most cases a trial of theophylline is no longer recommended. A meta-analysis of randomized trials, concerning treatments with methylxanthines for exacerbations of chronic obstructive pulmonary disease, did not support the use of methylxanthines for the treatment of exacerbations of chronic obstructive pulmonary disease. Potential benefits of methylxanthines for lung function and symptoms were generally not confirmed at standard levels of significance, whereas the potentially important adverse events of nausea and vomiting were significantly increased in patients receiving methylxanthines.

IV.b. Anti-inflammatory Agents

The role of anti-inflammatory agents in the management of COPD is still under debate. Up to now, there is little evidence that inhaled corticosteroids (ICS) are beneficial in COPD. It is estimated that about 10% and up to 20% of COPD patients may have some response to steroids. These patients should probably be regarded as having concomitant asthma. Several longer-term trials on ICS in COPD have recently been completed. Some trials have demonstrated beneficial effects on lung function, symptoms or frequency of exacerbations. However, no overall effect of ICS on the accelerated decline in lung function could be demonstrated in any of these studies (Table 5). Despite these findings ICS seem to prevent modestly exacerbations and according to the latest GOLD guidelines should be given in certain stages of COPD (Table 4).

Presently, inhaled steroids (up to the equivalent of BDP 1000 µg/d, budesonide 800 µg/d, fluticasone 500 µg/d) should be given to patients who show an objective response to either oral or inhaled steroids (s. corticosteroid reversibility testing). For those patients who experience no symptomatic relief, the currently available evidence does not support the use of ICS for alteration of the natural history of the disease. Nevertheless, corticosteroids are effective in treating acute exacerbations in COPD and taking patients of off their ICS regimen may lead to deterioration. Oral corticosteroids (e.g. 40 mg prednisolone for ten days) are recommended for exacerbations, if

- the patient is already on oral steroids
- there is a previously documented response to oral CS
- the airflow obstruction fails to respond to an increase in bronchodilator dose
- this is the first presentation of airflow obstruction.

Table 5. Randomized placebo controlled trials on inhaled corticosteroids in COPD

Authors	Regimen	Duration	Nr	Results	Conclusion
Bourbeau, 1998	Budesonide 1.6 mg/d	6 months	$n = 79$	No effect on lung function, quality of life, symptoms, or exercise capacity (only non-responder to oral steroids)	No benefit
Burge, 1999	Fluticasone 1 mg/d (ISOLDE)	36 months	$n = 990$	Decrease in number of exacerbations reduction of symptoms, no effect on FEV_1 decline	Benefit
Nishimura, 1999	BDP 3 mg/d	4 weeks	$n = 30$	Responder, improvement of symptoms ($n = 5$)	Modest benefit
Paggiaro, 1998	Fluticasone 1 mg/d	6 months	$n = 281$	Significant improvements: moderate/severe exacerbations; lung function; cough; exercise capacity	Benefit
Pauwels, 1999	Budesonide 0.8 mg/d (EUROSCOP)	36 months	$n = 1277$	No effect on FEV_1 decline (small initial effect)	No benefit
Renkema, 1996	Budesonide (1.6 mg/d) or budesonide + prednisolone 5 mg	24 months	$n = 58$	FEV_1 decline (ml/yr.): placebo 60, BUD + PRED 40, BUD 30 (not significant)	No benefit
Vestbo, 1999	Budesonide 1.2 (0.8) mg/d	36 months	$n = 290$	No effect on FEV_1 decline no effect on exacerbations	No benefit

ISOLDE: Inhaled Steroids in Chronic Obstructive Lung Disease in Europe; EUROSCOP: European Respiratory Society Study on Chronic Obstructive Pulmonary Disease; BUD = budesonide; PRED = prednisolone.

Recent studies suggest, that repetitive "short course regimens" with oral CS may be harmful with respect to inducing CS induced osteoporosis at cumulative doses that exceed 1000 mg, while in continuous low dose regiments such a cumulative dose relationship was not found.

IV.c. Antibiotic Therapy

The major precipitants of exacerbations of COPD are acute airways infections. The role of bacteria in precipitating exacerbations is controversial. Bacteria may have a primary role in the development of an exacerbation or represent a secondary superinfection of an initial viral process. The major bacterial organisms that have been associated with exacerbations are Haemophilus influenzae, Streptococcus pneumoniae, and Moraxella (Branhamella) catarrhalis. Mycoplasma pneumoniae and Chlamydia pneumoniae may play a part. In COPD patients with a $FEV_1 < 35\%$ predicted gram-negative bacteria, especially Enterobacteriaceae and *Pseudomonas* spp. play an important part in acute exacerbations.

The effects of antibiotics also suggest an etiological role for bacteria in exacerbations in some patients. A meta-analysis of nine studies showed a small overall benefit with antibiotic treatment for COPD exacerbations. Therefore, in exacerbation treatment with antibiotics is justified when the patient has at least two of three features of increased dyspnea, increased sputum volume, and sputum purulence. Antibiotic choice will depend on local experience derived from local bacteriological sensitivity data. Older, less costly compounds such as tetracycline, doxycycline, amoxicillin, erythromycin, cefaclor etc. are often as effective as newer, more expensive ones. If resistant organisms are suspected or when the severity of the patients' clinical condition puts them at high-risk of treatment failure, a second or third generation cephalosporin, fluoroquinolone, newer macrolide or broad-spectrum penicillin may be preferred. In cases of recurrent infection prolonged courses of antibiotics continuous or intermittent, may be useful.

While the treatment of infections can be of benefit in COPD patients a Cochrane systematic review concludes that bronchodilators produce only modest short-term improvement in clinical scores in patients with bronchitis. This small benefit must be weighed against the costs of these agents.

IV.d. Vaccination

Immunization with influenza and pneumococcal vaccines is done to prevent infectious complications

involving the respiratory tract. All COPD guidelines recommend yearly influenza vaccination. Outcomes of recent studies on the efficacy of pneumococcal vaccination in COPD are not unanimous. For this reason, pneumococcal vaccination cannot be formally recommended. If given, vaccination should be repeated every 5–10 years.

IV.e. Other Pharmacologic Agents

α_1-Antitrypsin augmentation therapy is appropriate in non-smoking, younger patients with severe α_1-antitrypsin (AAT) deficiency and associated emphysema. Such therapy is not indicated in the common form of COPD.

Respiratory stimulants are not recommended. Side effects have precluded the use of drugs such as almitrine.

There is no role for other anti-inflammatory drugs such as sodium cromoglycate, nedocromil, ketotifen, leukotriene antagonists or antihistamines in COPD.

Mucolytic drugs such as acetylcysteine and ambroxol are given to improve sputum clearance. However, trials of their effectiveness have produced variable results. There is no evidence to support prescription of these agents in acute exacerbations.

A Cochrane Review of 20 randomised controlled trials involving 280 participants, showed that 4 mg, of nedocromil sodium inhaled 15–60 minutes prior to exercise significantly reduces the severity and duration of exercise-induced bronchus constriction in both adults and children, when compared to placebo. This effect appears to be more pronounced in people with severe exercise-induced bronchoconstriction.

IV.e.1. Antioxidant Agents

Based on accumulating evidence that oxidants/free radicals play an important part in the pathogenesis of COPD, gaining more insight on the mechanisms, that encompass the pulmonary antioxidant capacity might be of potential therapeutic benefit. Possible interventions could be directed towards the reduction of recruitment or the activation of inflammatory cells in the lungs that are mediating this process, thereby limiting the production of reactive oxygen intermediates. Another possibility could be the stimulation of endogenous antioxidant enzyme production, so limit the generation of free radicals, or application of non-enzymatic antioxidants which can detoxify reactive oxygen species once they are formed. N-acetylcystein (NAC) is the most widely investigated drug with antioxidant properties. It is a thiol-containing compound that may act as an antioxidant by providing cysteine intracellular for the enhanced production of glutathione (GSH). A favorable effect of prolonged NAC therapy on FEV_1 decline in COPD was observed, however more recent data were not conclusive in this matter, and it is debatable whether an antioxidant therapy with NAC in COPD should be recommended.

IV.e.2. New Drug Developments

There is an increasing need for the development of new drugs for the treatment of COPD. Several new drugs are now in development that may be useful in COPD. These include leukotriene B_4 antagonists, 5-lipoxygenase inhibitors, phosphordiesterase (PDE4) inhibitors, new antioxidants, neutrophil elastase and matrix metalloproteinase (MMP) inhibitors. As pointed out, it will be difficult to demonstrate the efficacy of such treatments as determination of the effect of any drug on the rate of decline in lung function will require large studies over at least two years.

IV.f. Smoking Cessation

There is worldwide consensus that smoking cessation is essential at all stages of COPD. This can be achieved by physician intervention, strong support, behavioral modification, and pharmacological intervention. Well-implemented programs in a specialist setting result in a 20–30% success rate in 1 year and in an improvement in FEV_1. The arsenal of pharmacological agents available for smoking cessation has expanded in the last few years. Nicotine-replacement therapy is available in gum, patch, nasal spray, or inhaler. Therapy with the antidepressant bupropion sustains smoking cessation through dopaminergic activity and enhancement of central noradrenergic activity. As recently shown, treatment with sustained-release bupropion alone or in combination with a nicotine patch resulted in significantly higher long-term rates of smoking cessation than use of either the nicotine patch alone or placebo. Abstinence rates with combination therapy may be higher than with bupropion alone. The latest drug available to support smoking cessation is varenicline, a selective $\alpha_4\beta_2$ nicotinic acetylcholine receptor partial agonist.

V. ASTHMA

Asthma is considered as a chronic inflammatory disorder of the airways. This inflammation causes recurrent episodes of symptoms, variable airflow limitation, and increased airway responsiveness. Prevention of asthma involves both the prevention of the initial development of asthma (= primary prevention) and the prevention of exacerbation in patients with asthma (= secondary prevention). Primary prevention methods include reducing exposure to indoor allergens, particularly domestic mites, avoidance of passive smoking, especially by infants, and avoidance of vehicle emission pollutants, largely from incomplete combustion of petrol by car engines.

The most effective management of asthma is to prevent the asthmatic inflammation by eliminating the causal factors. In principle, it should be realized that although asthma can be controlled effectively in most patients, it cannot be cured. On the other hand, the major factors contributing to asthma morbidity and mortality are under diagnosis and inappropriate treatment. Many attempts have been made to produce guidelines, aiming for a more effective diagnosis and treatment, leading to the Global Initiative for Asthma (GINA) guidelines in 1995, which has recently been updated.

The classification of asthma by the level of control has been suggested in these Guidelines, and is stated in Table 6.

According to these guidelines asthma can be effectively treated and most patients can achieve good control of their disease, which enables patients to:

- avoid troublesome symptoms night and day
- use little or no reliever medication
- have productive, physically active lives
- have (near) normal lung function
- avoid serious attacks.

Avoidance or control of triggers can prevent exacerbations and reduce symptoms and requirements for medications and thus is considered non-pharmacological secondary prevention. Environmental control measures include avoidance of indoor allergens (domestic mites, animal allergens, cockroach allergen, fungi) and of outdoor allergens (allergens from plants and fungi). In addition, exposure to indoor air pollutants (mainly passive and active smoking) and outdoor air pollutants (ozone, nitrogen oxides, acidic aerosols) should re reduced as much as possible.

Acetyl salicylic acid and related non-steroidal anti-inflammatory agents can cause severe asthma exacerbations and should be avoided in patients with a history of reacting to these agents. β-adrenoreceptor antagonists (beta blockers) orally administered and even in eye drops may provoke bronchospasm.

V.a. Therapy

There is still ongoing debate on the long term treatment options for persistent asthma which is most effectively controlled with daily long-term control medication, in particular anti-inflammatory therapy. However, 'how much is too much' is the comprehensive title of a recently published paper which reviewed ten large studies during the episode 1998–2007. The overall conclusion of this paper suggests that low doses of ICS, i.e. 400 μg Beclomethasone di-propionate or equivalent, can often provide an ideal asthma control and reduce the risk of exacerbations in both children and adults with mild persistent asthma and showed to have higher effectiveness compared to ICS as needed regimens. There is still no convincing evidence that regular use of a combination therapy with ICS and LAβA provides any additional benefit. So far only a few studies have shown promise in an as needed regimen in the latter. In order to achieve this control, the stepwise approach, in which the dose and number of medications and frequency of administration are increased as necessary and decreased when possible, is emphasized in all current guidelines (Tables 6 and 7). Therapy should be initiated at a higher level than the patient's step of severity at the onset to establish prompt control and then stepped down (A "start high" "go low" strategy). Inhaled corticosteroids (ICS) are established as first-line therapy for patients with persistent asthma. ICS are the only currently available asthma therapy that suppresses inflammation in asthmatic airways in a highly effective manner. They inhibit almost every aspect of the inflammatory process in asthma. Their equipotent dosages are mentioned in Fig. 1. The relevant effects of ICS in asthma are as follows:

- control symptoms
- improve quality of life
- improve lung function
- prevent exacerbations
- reduce mortality (probably)
- prevent irreversible airways changes
- alter natural history of asthma (?).

Inhaled steroids are effective in most patients with asthma, irrespective of age or asthma severity. ICS

Table 6. Classification of asthma by level of control (see O'Byrne P et al., 2006). Levels of asthma control

Characteristics	Controlled: All of the following	Partly controlled: Any measure present in any week	Uncontrolled
Daytime symptoms	None ($\leqslant 2\times$/week)	$>2\times$/week	$\geqslant 3$ features of partly controlled asthma present in any week
Limitations of activities	None	Any	
Nocturnal symptoms	None	Any	
Need for reliever/ rescue treatment	None ($\leqslant 2\times$/week)	>2/week	
Lung function (PEF or FEV_1)[a]	None	<80% predicted or personal best (if known)	
Exacerbations	None	One or more/year[b]	One in any week[c]

[a] Lung function testing is not reliable for children 5 years and younger.
[b] Any exacerbation should prompt review of maintenance treatment to ensure that it is adequate.
[c] By definition an exacerbation in any week makes that an uncontrolled asthma week.

are recommended as first-line therapy for all patients with persistent symptoms. The steroids should be started in any patient who needs to use a β_2-agonists inhaler for symptom control more than twice weekly. Indications and dosages of conventional asthma medications are summarized in Tables 7 and 8. Once asthma control is achieved, the dose of inhaled corticosteroid should be reduced in a step-wise manner to the lowest dose needed for optimal control. It may take as long as 3 months to reach a plateau in response, and any change in dose should be made at intervals of 3 months or more. In the latest GINA guidelines therapy strategies are deducted from the level of control in asthma (Tables 6 and 7).

Several inhaled corticosteroids are currently prescribed in asthma, although their availability varies between countries (Table 8). There are relatively few studies comparing efficacy of the different inhaled steroids. There appear to be some differences between inhaled corticosteroids in terms of their systemic effects at comparable anti-asthma doses. There is evidence, that all of the inhaled steroids are absorbed to some extent from the lung and hence will have some systemic activity. It is recommended, therefore, in all guidelines to give the lowest dose of inhaled steroid compatible with asthma control.

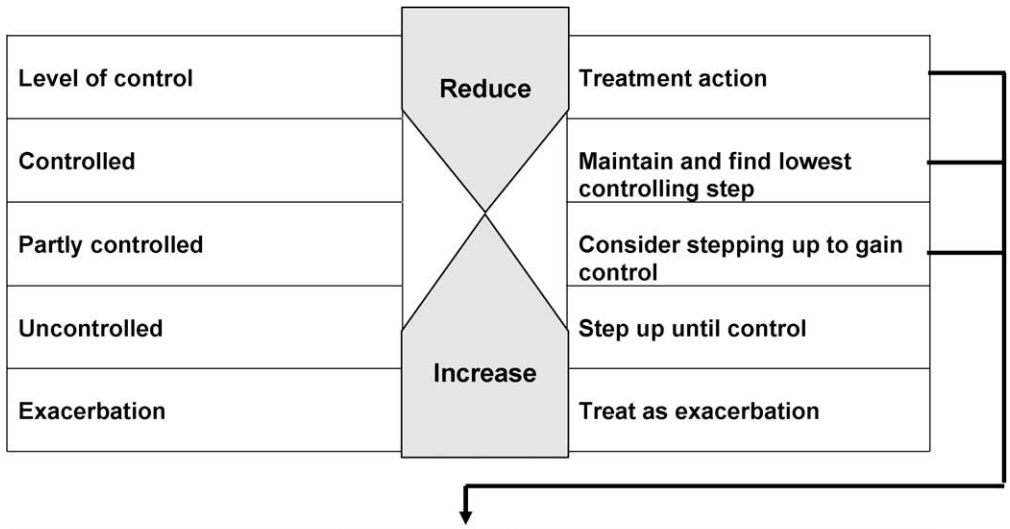
A Cochrane Review of 7 studies concludes that a short course of corticosteroids following assessment for an acute exacerbation of asthma significantly reduces the number of relapses to additional care and decreases beta-agonist use without an apparent increase in side effects. Intramuscular corticosteroids appear as effective as oral agents.

Another review of nine trials including a total of 344 adult patients concludes that no differences can be identified among the different doses of corticosteroids in acute asthma requiring hospital admission. Low dose corticosteroids ($\leqslant$80 mg/day of methyl-prednisolone or $\leqslant$400 mg/day of hydrocortisone) appear to be adequate in the initial management of these adult patients. Higher doses do not appear to offer a therapeutic advantage.

V.a.1. Combination of Drugs

If asthma control is not optimal, conventional advice was to increase the ICS dose. However, it is now apparent, that the dose–response effect of ICS is rather flat, so that there is little improvement in lung function after doubling the dose of inhaled steroid. An alternative strategy is to add some other class of controller drug. Several studies have shown that the combination of ICS and salmeterol or formoterol was more effective than increasing the dose of inhaled corticosteroid in terms of lung function improvement, rescue β_2-agonist use, symptom control, and frequency of mild and severe asthma exacerbations.

Table 7. Management approach based on control (see O'Byrne P et al., 2006)



Step 1	Step 2	Step 3	Step 4	Step 5
Asthma education Environmental control				
As needed SAβ_2A	As needed SAβ_2A			
Controller options	Select one	Select one	Add one or more	Add one or both
	Low dose ICS	Low dose ICS & LAβ_2A	Medium or high dose ICS & LAβ_2A	Oral glucocorticosteroid
	Leukotriene modifier	Medium or high dose ICS	Leukotriene modifier	Anti-IgE treatment
		Low dose ICS & Leukotriene modifier	Sustained release Theophylline	
		Low dose ICS & sustained release Theophylline		

Leukotriene modifier: either receptor antagonist or synthesis inhibitor. Alternative reliever treatments include anticholinergics, short acting oral β_2-agonists, and short acting theophylline. Regular dosing with short and long acting β_2-agonists is not advised unless accompanied by regular use of ICS.

A fixed combination of ICS plus long-acting β_2-agonist, such as fluticasone/salmeterol or budesonide/formoterol, is available and may simplify therapy. However, new insights in treating patients with these combinations on an as needed regimen in combination with a daily low dose maintenance therapy, is still debated.

Stages in severity of asthma are mentioned in Table 9. Older studies have already shown that addition of low doses of theophylline in worsening asthma (giving serum concentrations < 10 mg/l) was more effective than doubling the dose of the inhaled corticosteroid. Similar data are now emerging with anti-leukotrienes. The reason why a combination ther-

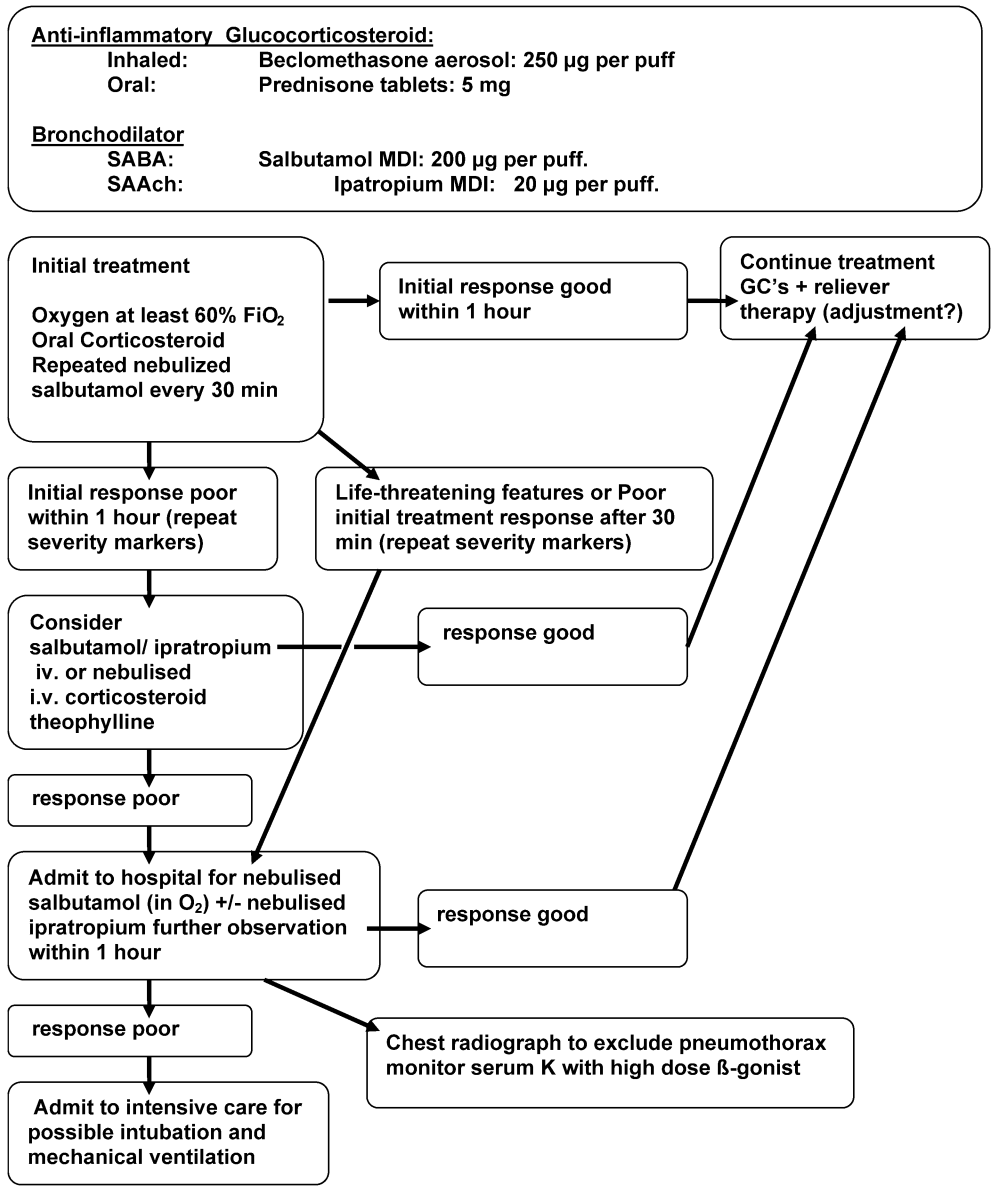


Fig. 1. Guide for management of asthma in low income countries (adapted and modified from IUATLD, 2007).

apy is more effective than monotherapy with ICS remains to be elucidated. It has been postulated that a reversible component of asthma that may not be steroid-sensitive inflammation. The addition of another class of therapy may therefore be preferable to increasing the dose of inhaled corticosteroids in patients with moderate-to-severe asthma.

From a systematic review of six trials involving 321 infants in three different settings which at the time of writing was present in the Cochrane data base it was concluded that there is not enough evidence to support the uncritical use of anti-cholinergic therapy for wheezing infants, although parents using it at home were able to identify benefits. However another Cochrane review concludes that adding multiple doses of anticholinergics to β_2-agonists in children with acute sever asthma improves lung function and would avoid hospital admission in 1 of 12 such treated patients (see Plotnick et al., 2000). There is no associated increase in adverse effects. There is no

Table 8. Estimated equipotent doses of inhaled glucocorticosteroids (see O'Byrne P et al., 2006)

Drug	Adults, daily dose (μg)[a]			Children, daily dose (μg)		
	Low	Medium	High[b]	Low	Medium	High
Beclomethason dipropionaat	200–500	>500–1000	>1000–2000	100–200	>200–400	>400
Budesonide	200–400	>400–800	>800–1600	100–200	>200–400	>400
Budesonide-Neb inhalation suspension (children only)				250–500	>500–1000	>1000
Ciclesonide	80–160	>160–320	>320–1280	80–160	>160–320	>320
Flunisolide	500–1000	>1000–2000	>2000	500–750	>750–1250	>1250
Fluticasone	100–250	>250–500	>500–1000	100–200	>200–500	>500
Momethasone furoate[c]	200–400	>400–800	>800–1200	100–200	>200–400	>400
Triamcinolone acetonide	400–1000	>1000–2000	>2000	400–800	>800–1200	>1200

[a]Comparison based on efficacy data.

[b]Patients considered for high doses except for short periods should be referred to a specialist for assessment to consider alternative combinations of controllers. Maximum recommended doses are arbitrary but with prolonged use are associated with increase risk of systemic side effects.

[c]Approved for once daily dosing in mild patients.

Additional notes:

- The most important determinant of appropriate dosing is clinician's judgment of the patients' response to therapy the clinician must monitor the patients' response in terms of clinical control and adjust the dose accordingly. Once control of asthma is achieved, the dose medication should be carefully titrated to the minimum dose required to maintain control, thus reducing the potential for adverse effects.
- Designation of low, medium, and high doses is provided from manufactures' recommendations where possible. Clear demonstration of dose response relationships is seldom provided or available. The principal is therefore to establish the minimum controlling dose in each patient as higher doses may not be more effective and are likely to be associated with greater potential for adverse effects.
- As CFC preparations are taken from the market, medication inserts with HFA preparations should be carefully reviewed by the clinician for the equivalent corrected dosage.

conclusive evidence for using multiple doses of anti-cholinergics in children with mild or moderate exacerbations. Single doses of anti-cholinergics may improve lung function in children with severe asthma, but do not appear to reduce hospital admission.

V.a.2. Specific Immunotherapy

The role of specific immunotherapy in asthma management is under continual investigation. It used to be given as subcutaneous injections and is directed at treating the underlying allergy, by inducing the forming of IgE blocking immunoglobulins. It has been demonstrated to be effective in asthma caused by grass pollen, domestic mites, animal dander or Alternaria allergy. Specific immunotherapy may be considered when avoiding allergens is not possible and when appropriate medication is not available or fails to control asthma symptoms. This type of therapy can be hazardous and should only be performed by health care professionals specifically trained for this form of treatment. Lately a new variant of this immunotherapy has been launched. Instead of the subcutaneous immunotherapy (SCIT) sublingual immunotherapy (SLIT) is being developed. Recent debate is ongoing on the efficacy of this patient friendly immunotherapy. A review of 22 trials showed insufficient evidence in favor of SLIT; moreover a large randomized double blind placebo controlled trial strongly suggests SLIT with grass pollens so far being ineffective. Further studies are needed to obtain more insights on efficacy and safety of this new immunotherapy modality.

Table 9. Severity of asthma exacerbations (see O'Byrne P et al., 2006)

Parameter	Mild	Moderate	Severe	Respiratory arrest imminent
Breathless	Walking can lie down	Talking infant softer, shorter cry, difficulty feeding prefer sitting	At rest infant stops feeding hunched forward	
Talks in	sentences	phrases		
Alertness	may be agitated	usually agitated	usually agitated	drowsy or confused
Respiratory rate	increased	increased	often > 30/min	

Normal rates of breathing in awake children

Age: 2–12 months	Normal rate: <60/min
<2 months	<50/min
1–5 years	<40/min
6–8 years	<30/min

Accessory muscles and supra-sternal retractions	Usually not	Usually	Usually	Paradoxical thoracoabdominal movements
Wheeze	Moderate often only and expiratory	Loud	Usually loud	Absence of wheeze
Pulse/min	<100	100–120	>120	Bradycardia

Guide to limits of normal pulse rates in children

2–12 month	Normal rate: <160/min
1–2 years	<120/min
2–8 years	<110/min

Pulsus paradoxus	Absent <10 mmHg (1.3 kPa)	May be present 10–25 mmHg (1.3–3.3 kPa)	Often present >10 mmHg (Adult) 20–40 mmHg (Child)	Absence suggests respiratory muscle fatigue
PEF after initial bronchodilatator % predicted or % personal best	>80%	±60–80%	<60 % predicted or personal best <100 l/min (adults) or response lasts <2 hours	
PaO_2 (on air) and/or	Normal (test usually not necessary)	>60 mmHg (8 kPa)	<60 mmHg (8 kPa) possible cyanosis	
$PaCO_2$	<45 mmHg (6 kPa)	<45 mmHg (6 kPa)	>45 mmHg (6 kPa) possible respiratory failure	
SaO_2 (on air)	>95%	91–95%	<90%	

Hypercapnia (hypoventilation) develops more readily in young children than in adults and adolescents

Note: The presence of several parameters, but not necessarily all indicates the general classification of the exacerbation. Kilopascals are also used internationally, conversion would be appropriate in this regard (1 kPa = 7.5 mmHg).

V.a.3. Alternative Medicine

Alternative healing methods are not substitutes for recommended pharmaco-therapy. Although alternative healing methods may be popular with selected patients and of some interest to investigators, their scientific basis has not been established.

V.a.4. Oral Corticosteroid-Sparing Therapy

In patients who have serious side effects with main-

tenance oral corticosteroid therapy, there are several treatments that may reduce corticosteroid requirements. Immunosuppressive agents including methotrexate, oral gold, and cyclosporin A have been shown to have oral corticosteroid-sparing effects. These therapies all have side effects that may be more troublesome than those of oral corticosteroids and are therefore only indicated as an additional therapy to reduce the requirements of oral corticosteroids. There are occasional patients with a good response. Because of the potential side effects, treatments with immunosuppressants cannot be considered as a way to reduce the dosages of inhaled corticosteroids. Other therapies such as azathioprine, dapsone, and hydroxychloroquine, have not found to be beneficial. Little therapeutic gain is achieved with the macrolide troleandomycin, which has steroid-sparing effects due to reduced metabolism of methylprednisolone.

V.a.5. Asthma Management in Developing Countries

Asthma increases with the level of urbanization and industrialization. It is expected that asthma will increase in developing countries in the future because a high proportion of the population is young in those parts of the world where urbanization and industrialization are rapidly occurring. It is estimated that asthma affects up to 200 million people in developing countries, with 40,000–50,000 deaths per year. In the USA the costs of asthma are estimated as high as about 13 billion dollars per year, which is twice as high as in 1990. The International Union Against Tuberculosis and Lung Disease (IUATLD) developed a model for health services delivery in low income countries. Its model for the National Tuberculosis Program has been evaluated by the World Bank as among the most cost-efficient of any health intervention in low income countries and has been adopted by the World Health Organization as the basis of their Global Tuberculosis Program. The IUATLD has used the framework of this model for the development of guidelines for the management of asthma in adults in low-income countries. In these guidelines recommend the most effective and least costly diagnostic methods and essential drugs to manage asthma. In this respect it should be emphasized that inhale steroids are extremely expensive and the majority of developing countries do not have access to these drugs or even any treatment. For example in certain African countries costs of one year treatment would reach up to 3–5 month salary of a local nurse. IUATLD proposes methods of organizing the management of asthma patients within the general health services and recommends an information management system to evaluate patient treatment (Table 10 and Fig. 1).

Using these medications, a stepwise approach for the long-term management of asthma is recommended, which is similar to those recommendations in other asthma guidelines (Tables 6–9).

V.a.6. Management of Asthma Exacerbations

The staging and drug treatment for acute severe asthma has changed over the past three decades, comprising primarily of bronchodilators, corticosteroids, and oxygen. A summary flow chart for the

Table 10. Guide for management of asthma in low-income countries (adapted and modified from IUATLD, 2007)

	Clinical signs and severity markers	Life-threatening features	Blood gas severity markers
General	Unable to complete sentences	Exhaustion, confusion, or coma	
Circulatory	Pulse >110/min,	Bradycardia or hypotension	
Respiratory	Respiratory rate >25/min $SpO_2 < 92\%$	Cyanosis	$PaCO_2 > 6$ kPa (45 mmHg) $PaO_2 < 8$ kPa (60 mmHg) $SaO_2 < 92\%$ pH < 7.35
Ventilatory	PEF < 60% predicted or best	PEF < 30% predicted or pers best Silent chest feeble ventilatory effort	

treatment of acute severe asthma is shown in Tables 6, 7 and 9. In fact again therapy is based upon the severity of the exacerbation as is being suggested in the GINA guidelines.

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Chapter 37

Disorders of Connective Tissue, Bone and Joints

John Darmawan

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I. INTRODUCTION

Rheumatic disease is defined as "disease of connective tissue and medical disorders of the musculoskeletal system". The medical discipline concerned with these diseases is referred to as rheumatology. The majority of rheumatic diseases are: soft tissue rheumatism and nonspecific low back pain (LBP), autoimmune inflammatory rheumatic diseases, osteoarthritis (OA), osteoporosis, crystal-deposition disease and infectious arthritis.

The etiologies of the autoimmune inflammatory diseases, OA, osteoporosis and crystal-deposition disease are still not known in exact details. This is in contrast with impressive molecular insights gained recently. However, there is consensus that manifestations of autoimmune diseases are precipitated by either acute and/or chronic interactions of genetic and environmental risk factors.

I.a. Therapeutic Options

Therapeutic options in rheumatic disease consist of general, physical, and medical measures. General measures comprise general and local rest of the affected joints and local supports such as splints, corsets, and neck collars. Adjustment of life-style and protection against acute physical trauma and/or chronic overuse of affected joints are included in the general measures. Physical measures include physiotherapy and occupational therapy.

The most important medical measures are mainly pharmaceutical therapies in early stages to terminate progression and achieve remission of the disease. In late stages of the disease orthopedic interventions are required to improve function when irreversible joint damage has occurred. Analgesics used for rheumatic pains are paracetamol, tramadol, COX1 and COX2 non-steroidal anti-inflammatory drugs (NSAIDs). However, gastrointestinal, renal, hepatic, and cardiovascular toxicities limit the use of COX1 and COX 2 NSAIDs as analgesics and anti-inflammatory agents.

Chondroitin Sulfate and Glucosamine in OA therapy have efficacy comparable to placebo as showed by a National Institute of Health study. Intraarticular hyaluronic acid for pain relief is inferior compared to intraarticular corticosteroids. Temporary crepitus reduction or eradication may last several years in radiological stages I and II Knee OA with intraarticular hyaluronic acid.

Clinical treatment recommendations for low back pain based, on 5 international guidelines and on information in the Cochrane database of systematic reviews, can be summarized as follows: there remains a lack of consensus regarding reported efficacy of spinal manipulative therapy for the treatment

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of non-specific LBP, guidelines reviewed have not changed significantly with respect to treatment recommendations for non-specific LBP since the original review and there is inconsistency between the guidelines regarding optimal time to introduce spinal manipulation to treat non-specific LBP. So, in general the treatment recommendations for nonspecific LBP, particularly spinal manipulation, remain inconclusive.

Unfortunately, a substantial proportion of patients with autoimmune inflammatory diseases have become refractory to NSAIDs, and/or oral or intravenous Disease Modifying Anti Rheumatic Drugs (DMARDs). However, oral combinations of DMARDs generate better outcomes compared to single drug therapy in autoimmune disease. Even autoimmune diseases can become refractory to oral DMARD combinations.

With the advent of biological-DMARD combinations with Methotrexate (MTX) a new era of therapy in autoimmune disease is introduced. DMARD-refractory autoimmune diseases are treated with combinations of a biological with MTX with achievement of improvements of ACR 20 and ASAS 20 in the majority of patients. A small minority of around 20% obtains improvements of ACR 70 and ASAS 70. ACR responses are American College of Rheumatology response criteria and ASAS stands for *ASsessment in Ankylosing Spondylitis*. ACR and ASAS 20, 50 or 70 scores are exactly defined improvements of respectively 20%, 50% or 70%.

The introduction of intravenous DMARD combinations provides a less expensive alternative than the use of biologicals in DMARDs refractory autoimmune disease in developing countries. The regimen of Step-down Bridge Combination of 5 immunosuppressants (SBC-5-IMNs, see below) obtained better results than single biological DMARDs or biological DMARDs in combination with MTX.

II. SOFT TISSUE RHEUMATISM

Soft tissue rheumatism can be one of the many manifestations of an underlying specific autoimmune disease. Secondary fibromyalgia and enthesitis are the consequences of long-term inadequately treated autoimmune diseases. When no specific underlying causes can be detected, the disorder is called non-specific soft tissue rheumatism. The major manifestations of soft tissue rheumatism are non-specific LBP, stiff shoulder, epicondylitis and tendonitis. In soft tissue rheumatism pain at rest and/or during activity, stiffness, tenderness, and disability are the predominant features. Physical deformities are minimal but disabilities are major problems.

Non-specific (without an underlying specific disease) LBP is the second most prevalent disorder worldwide after common cold. Based on the duration of pain, LBP can be classified into:

- acute LBP lasts 0–7 days, which is pain free before the onset of LBP;
- acute pain on chronic LBP, which is significant exacerbation from existing chronic LBP;
- sub-acute LBP lasts more than 7 days to 3 months;
- chronic LBP with duration of more than 3 months;
- intractable LBP, which fails conservative therapy;
- chronic LBP syndrome, which is psychological and is the social consequences of chronic LBP influencing behavior.

II.a. Therapy of Soft Tissue Rheumatism

Medical non-pharmaceutical therapy of soft tissue rheumatism includes general and local rest, often physiotherapy, occupational therapy, and early mobilization. The pharmaceutical therapy of soft tissue rheumatism comprises analgesics and NSAIDs, the latter when inflammatory components are present.

Most nonspecific LBP settles within 2 weeks. Almost 90% of patients are relieved from pain within 6 months. Only 1–2% of patients eventually require surgery. Of the patients with LBP in combination with sciatica due to a herniated disc 70–93% is relieved of symptoms between 2 and 8 weeks without surgery. Before the pain settles, analgesics, minimum rest, appropriate physiotherapy, and early mobilization are required. Recurrence of LBP can be effectively prevented by endurance exercises.

Acceptable levels of comfortable living, tolerable levels of drug side effects and the limit of maximum exercise are decided by patients with LBP. Symptomatic, pharmaceutical and supportive therapies combined with endurance exercises are the mainstay of patients with LBP. The financial and social and psychological burdens of LBP are enormous on a personal, national, and global scale.

II.b. Treatment of Chronic Low Back Pain Syndrome

Every LBP sufferer who does not improve in 3 months should be sent to a multidisciplinary team.

This team must be skilled in handling the complex origin of disability. Risk factors for the disease to become chronic are often of a psychosocial and not a physical nature. Primary targets of treatment should be physical fitness and the self-management of problems by the patient. Awareness of the psychosocial factors, which can disturb occupational reintegration, should be developed. Rehabilitation is based on measures to modify patient's beliefs and fitness. The prescribed treatment should aim to relieve pain, correct disability, prevent relapses, inform and educate the patient.

III. AUTOIMMUNE INFLAMMATORY DISEASES

The autoimmune rheumatic diseases consists of: Rheumatoid Arthritis (RA), Spondylarthritis (SpA), Systemic Lupus Erythematosus (SLE), Polymyositis, Dermatomyositis, Polymyalgia Rheumatica, Acute Temporal Arteritis, Giant Cell Arteritis, Behcet's Disease, Sjorgren's Syndrome, Felty's Syndrome and Mixed Connective Tissue Disease (MCTD). Spondylarthritis (SpA) can be subdivided in: Reactive Arthritis (ReA), Ankylosing Spondylitis (AS), Psoriatic Arthritis (PsA), Arthritis associated with the inflammatory bowel diseases are Crohn's disease and Ulcerative Colitis (IBD), Undifferentiated SpA (UspA) and Sacro-ilitis, Juvenile SpA and Acute Anterior Uveitis (AAU).

Autoimmune diseases may have an acute or a chronic insidious onset with a chronic progressive course with varying periods of severe or mild disease activity and spontaneous remissions in a minority of patients. Inherent to the initially chronic progression, reversible autoimmune inflammation and disability are susceptible to effective therapy when still no irreversible organ damage has occurred. Nowadays these reversible joint or organ changes in autoimmune arthritis and autoimmune nephritis can be normalized with novel treatment modalities.

Initial manifestations of inflammation are acute episodes of joint pain, stiffness, swelling, warmth, and redness. This set of symptoms and signs is incompletely or completely present in RA and SpA. Malaise and general fatigue may precede or accompany the arthritis.

Initially, autoimmune-induced and corticosteroids-induced osteoporosis affect the bones of joints and later generalized osteoporosis may occur. Subsequently, progressive erosion, subchondrial sclerosis, resorption and ultimately ankylosis of the joint margins follow. Progressive damage is inflicted to joint cartilage up to total denudement, and there is damage to ligaments, joint capsules, tendons, muscles and the peripheral and central nervous system. These progressive changes are cumulative and cause variable degrees of permanent disability and joint deformities with consequent a lower health-related quality of life.

Extra-articular manifestations of autoimmune inflammatory disorders indicate severe disease. These manifestations may occur in the: eye, neurocerebral and cardiovascular system, kidney, hematopoietic system and hepato-gastrointestinal organs. The systemic extra-articular progression of autoimmune inflammation shortens a patient's life in SLE, SpA, and RA.

III.a. Therapeutic Principles of Autoimmune Diseases

In terms of molecular biology, the attachment of Antigen Presenting Cells (APC) to T-cells can at this moment not be prevented. So a cure for chronic progressive autoimmune inflammatory disease is not feasible yet. Sooner or later disease in remission relapses when APC attach to T-cells with induction of Co-stimulatory pathways. The current therapeutic principles are to stop or slow down disease progression. This is achieved by elimination or at least a reduction of the pool of existing autoantibodies and of cytokines in the upstream systemic and downstream local interleukin independent and dependent pathways.

Moderate to severe autoimmune inflammation requires immunosuppression to minimize or stop progression of early disease. There now is consensus that autoimmune inflammation should be totally suppressed at an early stage when there is maximum susceptibility to immune-suppression with single or combination drugs therapy. In early stages of the disease changes are reversible with no consequent disability and joint deformity.

The most important prognostic factors in autoimmune inflammatory disease are, disease duration, the degree of disease activity-dependent radiological erosion, previous drug therapy and previous exposure to immunosuppressants (IMN), i.e. IMN naivety. Early autoimmune inflammation can be totally eradicated, irreversible disability and damages can be prevented when adequate treatment has been initiated.

Mechanical pain and disability due to permanent joint deformities require joint orthosis. Long-term relief of pain and improvements of function have been achieved with total hip, knee, shoulder, wrist and multiple joint replacements.

Outcome measurements used in the evaluation of the outcome of treatment of RA with sulfasalazine, parenteral gold salts, D-penicillamine, hydroxychloroquine, prednisolone, MTX, cyclophosphamide (CyC), and azathioprine in single drug therapy cannot be compared with endpoints used in SBC-5-IMNs and biological-DMARDs combined with MTX.

III.b. Biomolecular Pathogenesis

III.b.1. Biomolecular Rationale for SBC-5-IMNs in RA

The phase of Intravenous Therapy (IVT) of the SBC-5-IMNs regimen suppresses activated T-cells and indirectly B-cells and macrophages. This inhibits up-stream systemic cytokine dependent and independent pathways of the production of interleukin-1 (IL-1), IL-6 and TNF-α by macrophages and production of immunoglobulin G (IgG) and immunoglobulin M (IgM) by B-cells. Concomitant weekly polyarticular injections/intralesional infiltration (PA) inhibits down-stream local cytokine dependent and independent pathways of macrophages production of interleukin-1 (IL-1), IL-6, tumor necrotizing factor- α (TNF-α) and B-cells production of IgG, IgM, and auto antibodies. This inhibits local activation of articular osteoclasts, synovial fibroblasts, and chondrocytes.

The simultaneous administration of IVT + PA terminates the molecular biologic progression at early and late stages of the disease.

PA is defined when concomitant weekly polyarticular corticosteroids injections together with corticosteroids injections into trigger points of secondary fibromyalgia and inflammation of attachments of skeletal muscles to bone (enthesitis) are administered.

The pool of upstream systemic IL-1, IL-6, TNF-α and IgG, IgM, including autoantibodies is bigger than the pool of local down-stream ones in early disease. In late disease the pool of local cytokines, TNF-α, and autoantibodies is bigger than the pool of the upstream ones. This happens when symmetrical poly-arthritis, trigger points of enthesitis, and secondary fibromyalgia have developed. That is why weekly PA is as important as IVT in late stages of the disease.

III.b.2. Biological-DMARDs

Based on the bio-molecular pathogenesis, novel therapeutic agents have been developed since 1998 for the treatment of DMARDs refractory autoimmune diseases. These biological-DMARDs include infliximab, etanercept, adalimumab, rituximab and abatacept. The biological-DMARDs anti TNF-α were first approved for therapy of refractory RA, followed by Crohn's disease, AS, and PsA. Scores of other biological DMARDs in Phase I, II, and III clinical trials in autoimmune diseases indicate that the number of these biological agents may ultimately become equal to the number of NSAIDs introduced over the last 50 years.

Biological DMARDs are indicated when autoimmune inflammatory diseases are refractory to therapy with single traditional DMARDs or with combinations of oral or IV traditional DMARDs. Improvements of ACR 20 and ASAS 20 in over 70% of patients with refractory RA and AS do not mean much to the patients in terms of pain relief, improvement of function and health-related quality of life. The present biological DMARDs combined with MTX still cannot fully address the problems of the majority of patients with DMARDs refractory chronic progressive autoimmune inflammatory diseases. Those who are refractory to MTX + biological DMARDs respond well to SBC-5-IMNs in over 80% of cases.

There is comparative effectiveness of anti TNF-α modalities in the treatment of patients with RA and AS (see Canete et al., 2004). This would apply to all the disease entities of SpA such as, PsA, ReA, Crohn's disease, Ulcerative Colitis, Acute Anterior Uveitis (AAU), and Undifferentiated Spondylarthritis (UspA).

The application of the present biological DMARDs in RA in the Third World will not be feasible for reasons of treatment costs which range from $15,000 to $25,000 per patient per year.

III.c. Step-Down Bridge Combination Therapy of Five Immunosuppressants (SBC-5-IMNs)

III.c.1. Indication for SBC-5-IMNs in Disease States Refractory to Conventional DMARDs

The main criteria for this indication are: (1) erythrocyte sedimentation rate (ESR) > 40 mm (ESR of knee OA very rarely exceeds 40 mm) and (2) pain with a Visual Analog Score (VAS) > 40 mm.

Less than 5% of patients with RA in the community at large have an indication for treatment with SBC-5-IMNs.

In RA the disease-activity dependent degree of erosion and IMNs naivety or non-naivety determine the achievement of Remission with Oral Drugs (RworalDs) and Remission without Drug (RwD). SBC-5-IMNs uses for endpoints the ACR Remission Criteria Plus.

Prospective observational studies with SBC-5-IMNs in 3 international centers indicated over 80–90% remission in early as well as late RA. These findings need to be supported by prospective double blind controlled trials. The RworalDs and RwD achieved can be maintained by immediate suppression of early flare. Even grade $\geqslant 2$ erosions of joints can be healed when treated adequately.

III.c.2. Application of SBC-5-IMNs in 4 Phases

III.c.2.1. The rationale for combination therapy. Combining different IMNs with common receptor sites enhances efficacy, low dosages avoid dose-dependent hematological adverse effects because of the different receptor sites for side effects and finally, cyclosporin (CyS) may block oxidation of MTX to its relatively inactive metabolite, 7-OH-MTX, thereby potentiating MTX efficacy.

III.c.2.2. Intravenous versus oral therapy. Intravenous therapy (IVT) generates maximum, fast, and long lasting efficacy with minimum adverse effects while the efficacy of oral therapy is less, slow and short lasting with more potential for adverse effects.

With IV CyC + 5FU + MTX it cannot be established which IMN in the combination is effective and which induces adverse effects. Immediate allergic reactions arising during IV drips may indicate the IMN concerned. Drug interactions among 5FU, MTX and CyC by IVT and oral CyS, MMF, and MTX have not been studied. It has been established however that quinolone antibiotics may interact with IMNs.

III.c.2.3. Daily dosages of IV IMMs with concomitant weekly polyarticular injections/intralesional infiltration (PA).

Phase 1. Mostly standard dosage of 1.5 mg/kg/day of CyC 5 times per week, 1.5 mg/kg/day 5FU 5 times per week and 0.2 mg/kg/day of MTX once weekly are given. Dose-dependent hematological adverse effects are not encountered when weekly dosages of 25–100 mg CyC and of 5FU 5 times per week and weekly 5–12.5 mg MTX are used.

Concomitant weekly PA is given with triamcynolone acetonide (TA) + dexamethasone (DxM) + lignocain (LNC) in ratio's of 60–20–20% until the mean local VAS is <10 mm (scale 0–100 mm). The rationale of this mixture is: instant anesthesia for up to 4 hours by LNC, efficacy of DxM commencing after 4 hours and lasting for 4 days and effects of TA which start after 4 days and last for <6 days. Efficacy of PA lasts at least for 10–14 days unless the joint becomes refractory to local corticosteroids. Weekly PA is effective in RA (see Darmawan et al., 2003) and AS (see Darmawan et al., 2006) and is equally effective in musculoskeletal manifestations of LN (see Darmawan et al., 1999).

Phase 2. Oral mycophenolate mofetil (MMF), combined with cyclosporin (CyS) if needed, is prescribed when the ESR becomes <20 mm while the daily 5 times weekly IVT + PA continues until ESR is <10 mm. The purpose of Phase 2 oral therapy is to maintain remissions achieved by IVT + PA for at least 2 years. Dosages of oral therapy are 250–500 mg MMF bid/tid, or 250–500 mg MMF + 25–50 mg CyS bid/tid or 250–500 mg MMF + 25–50 mg CyS bid/tid and weekly MTX 5–12.5 mg.

The wide-ranging dosages of IVT and Oral Therapy are determined by the history of gastrointestinal (GI) symptoms:

- If no history of GI symptoms is present daily 1.5 mg/kg/BW of CyC + 5FU and weekly 0.2 mg/kg/BW of MTX, or the maximum dosages tolerated, are given. When GI symptoms appear, they are treated and subsequently each IV session is preceded by giving a proton pump inhibitor and/or anti-emetics and/or spasmolytics.
- In the presence of GI symptoms the regimen is started with daily 25 mg CyC + 5FU + weekly 5 mg MTX with weekly increments of 25 mg CyC + 5FU and 2.5 mg MTX. These increments are applied if the response is unsatisfactory or the reduction of the ESR after monitoring for 2 weeks is <1 mm. Each IV session is again preceded by giving a proton pump inhibitor and/or anti-emetics and/or spasmolytics to prevent GI symptoms.

Phase 3. When ESR $<$ 10 mm is obtained IVT + PA are tapered off and remission is maintained with oral drugs for at least 2 years (RworalDs). This includes incidental suppression of early flare with IVT + PA.

Phase 4. Monitoring and immediate suppression of early flare with IVT + PA for maintenance of ESR < 10 mm during RworalDs and RwD is required.

The combination of 5 IMNs is only continued if the ESR is between $\leqslant$20 mm to $\leqslant$10 mm and then during 17 weeks of tapering off the IVT sessions. The 5 IMNs combination is administered over a period of <5 months. Generally in less than 6 months Remission with Oral Drugs (RworalDs) is achieved.

III.c.2.4. Contra-indications. The contra-indications for the application of single or combined drug therapy with IMNs are obvious. The inserted leaflets in the package of CyC, 5FU, MTX, and Oral MMF, and CyS are self-explanatory.

III.c.2.5. Adverse effects. A high frequency of GI adverse effects is generally seen and gastrointestinal adverse effects may occur in up to 55.5% of the cases. GI adverse effects include anorexia, nausea, vomiting, diarrhea, gastritis, GI ulcers and bleeds. The shared receptor sites for intravenous CyC, 5FU, and MTX maximize GI adverse effects. These GI adverse effects can be avoided, prevented, and treated with anti-emetics for nausea and vomiting, spasmolytics for diarrhea, proton pump inhibitors to prevent and treat gastrointestinal gastritis, ulcers, and bleeds. Maximal protection with these agents can reduce GI adverse effects to less than 5%.

Monitoring of hematogenic, hepatogenic, and renal adverse effects should be carried out once monthly during daily 5 × weekly IVT sessions. When indicated anytime during IVT.

III.c.2.6. Prevention of dropouts because of allergy. A history of previous allergy or allergy becoming manifest during IVT to any of the drugs applied must be suppressed. Preceding intravenous drips with a dilution of 0.1–0.5 CC epinephrine in 100–300 CC 0.9% NaCl prevents such allergies. All the contraindications and safety precautions must be observed before the administration of intravenous epinephrine. The infusion rate depends on the appearance of tachycardia and discomfort of the patients. Palpitations can be treated and then prevented by giving a β blocker.

III.c.2.7. Co-morbidity. Co-morbidity or associated conditions such as hypertension, diabetes mellitus, cardiovascular and cerebrovascular atherosclerosis, neuropathy, osteoporosis, etc., must be treated simultaneously.

III.c.2.8. Cost effectiveness of SBC-5-IMNs. The application of SBC-5-IMNs is cost-effective therapy because it is required intermittently and only when autoimmune disease is active. Application of IVT + PA is 6 months and oral therapy is 2 years compared with the long-term or lifetime disease course.

III.d. Rheumatoid Arthritis

Rheumatoid Arthritis (RA) is defined as a chronic progressive autoimmune inflammatory disease with articular and extra-articular manifestations. The former induce pain and disabilities and a lowered health-related quality of life while the latter may shortened life expectancy. However, RA is also a disease of which the chronic progressive course can be stopped or slowed. Long-term remissions can be achieved and maintained with oral drugs (RworalDs) or sustained without drug (RwD), including radiological normalization. These long-term RworalDs and RwD in RA have been achieved by an immediate and total suppression of relapses with IVT + PA.

With the current modified ACR remission criteria only a retarded radiological progression of RA is achieved. The ultimate therapeutic goal in RA therapy should be sustained termination of radiological progression and sustained clinical remission with or without drugs. Therefore, the Modified ACR Remission Criteria Plus should be used for long lasting clinical and radiological remissions.

These ambitious primary and secondary endpoints can only be obtained depending on the grades of erosion and on naivety to SBC-5-IMNs. Similar primary and secondary endpoints are reached in DMARDs and SBC-5-IMNs refractory RA with the combination of SBC-5-IMNs + 100 mg infliximab at week 0, 2 and 6.

III.d.1. Treatment of Rheumatoid Arthritis

With the combination of traditional DMARDs complete remissions are obtained in 30% of early RA over a period of 5 years. These remissions last on average less than 10 months. After 5 years only half of the patients continue with MTX and less than 25% stay on other DMARDs. After 5 years non-compliance is mostly due to adverse effects and lack of efficacy of NSAIDs, hydroxychloroquine, sulfasalazine, prednisone, d-penicillamine, azathioprine, and gold salts. Only MTX retains some efficacy. With these therapeutic modalities joint erosions progress to permanent joint destruction, deformities and disability.

The combination of MTX + biological DMARDs, achieves ACR 20 in over 60% of patients with RA. ACR 70 is acquired by a minority (circa 20%) of RA patients. Even ACR 50 improvements were seen in less than 50% of the patients. More than 50–70% of patients who did not achieved ACR 70 or ACR 50 suffer from progression of the disease. Since the arrival of biological DMARDs the paradigms of RA therapy have changed dramatically. Combinations of MTX + biological DMARDs often have to be given long-term or for life as cessation of treatment induces relapses in almost all cases.

The indications for therapy with SBC-5-IMNs in DMARD-Refractory RA are ESR > 40 mm (ESR of knee OA very rarely exceeds 40 mm) and VAS > 4. Patients are considered to have DMARD-Refractory RA (DR-RA) if optimal dosages of single and combined oral DMARDs (corticosteroids, hydroxychloroquine, sulphasalazine, and MTX) have been used for 2 months without lowering of the ESR with 1 mm or more, with a decrease of the swollen and tender joint count of less than 1 and the VAS still above 10 (scale 0–100) at month 1 and 2 compared with baseline.

When SBC-5-IMNs is endangered 3–4 times by non-compliance to the execution of its 4 fixed schedule phases then the disease becomes refractory. Depending on the level of the ESR when patients drop out relapses occur after several months to several years. The majority of patients acquire remission in 2 months again with IVT + PA and 100 mg infliximab at week 0–2–6 added to this. After tapering off IVT + PA guided by the ESR levels after induction of remission, oral IMNs will maintain remission and thus avoid the need for long-term use of biological DMARDs.

III.e. Spondylarthritis

Seronegative SpA is a group of heterogeneous and closely related diseases without rheumatoid factor (see the beginning of Section III). These diseases all share some genetic, serological, articular, extra-articular, radiological, and therapeutic characteristics. The SBC-5-IMNs has shown efficacy in the treatment of DMARD refractory Spondylarthritis such as Ankylosing Spondylitis and Crohn's disease.

Some general principles for the treatment of Seronegative Spondylarthritis can be summarized as follows. Mild cases of SpA are controlled with physiotherapy and NSAIDs, paying attention to GI, renal, cardiovascular, hypertensive and hepatic risk factors. However the gold standard of SpA therapy with physiotherapy and NSAIDs cannot always stop the course of the disease. Nowadays a progressive course of NSAIDs refractory SpA can be stopped by SBC-5-IMNs and/or slowed down by biological DMARDs combined with MTX.

The use of traditional DMARDs can be disappointing in moderate or severe SpA cases and also with biological DMARDs ASAS 70 was achieved in a minority (circa 20%) of patients with SpA. The majority, around 70% of the patients, reached an ASAS 20 response and less than 50% acquired ASAS 50. The high costs and long-term administration of biologic-DMARDs prohibit their use in the Third World. With inefficacy of traditional DMARDs and biologic-DMARDs being unaffordable, the SBC-5-IMNs approach is an attractive alternative.

III.e.1. Reactive Arthritis

Reactive arthritis (ReA) develops 1–3 weeks after a bacterial infection in the intestinal tract (diarrhea) and/or urethra (urethritis) or elsewhere due to immune responses. HLA-B27 positive individuals may develop ReA. ReA is an autoimmune disease and consists of sterile axial and/or peripheral articular inflammation, enthesitis and extra-articular manifestations.

The causative bacteria in the intestinal tract may be: *Salmonella typhimurium*, *Shigella flexneri*, *Shigella sonnei*, *Campylobacter jejuni*, *Campylobacter lari*, *Chlamidia trachomatis*, *Yersinia enterocolitica*, *Staphylococcus aureus*, *Hafnia alvei* or the protozoan pathogen cryptosporidium.

A history of urethritis and prostatitis in men or of cervicitis and cystitis in women is common in patients with ReA. The disease has been called HLA-B27 associated ReA and includes classical Reiter's disease with arthritis, urethritis and conjunctivitis. Presenting symptoms and signs are mostly asymmetrical axial and/or peripheral arthritis. Determining the B27 status of an individual patient with ReA is irrelevant to therapy. Diagnosis usually can be made by clinical examination and history.

ReA refractory to NSAIDs, DMARDs and physiotherapy can be treated with SBC-5-IMNs. When also refractory to SBC-5-IMNs then add on infliximab at week 0–2–6 combined with IVT + PA. Corticosteroids and dilating eye drops are used to suppress ocular inflammation to prevent scaring and alleviate pain. When required to prevent blindness, corticosteroids are injected into the eye.

III.e.2. Ankylosing Spondylitis

Ankylosing spondylitis, also known as Bechterew's disease, is a chronic progressive autoimmune inflammatory disease with mostly symmetrical axial and to a lesser extent peripheral arthritis. Presenting symptoms and signs are characteristic nocturnal spinal pain, enthesitis, secondary fibromyalgia, and ankylosis of joints in long-term disease. Ankylosis appears after 4–12 years after disease onset if progression of the initial course is not stopped by pharmaceutical treatment. Onset can be acute or insidious with or without fever. After 3 decades progressive calcification of the spine leads to complete fusion of the vertebrae. In completed ankylosis spinal pain disappears because autoimmune inflammation of axial joints is terminated, but osteoporosis continues.

The most important prognostic factor in AS is: early treatment, disease duration, IMN naivety and disease activity as scored with the Bath Ankylosing Spondylitis Radiology Index for the spine (BASRI-s) and the Bath Ankylosing Spondylitis Radiology Index for the hip (BASRI-h). The importance of IMNs naivety and a BASRI $\geqslant 2$ cannot be underestimated. Remission without Drug (RwD) cannot be achieved with IMNs non-naivety and BASRI $\geqslant 2$. When treatment is inadequate ESR and C-reactive protein (CRP) are not normalized and remission cannot be acquired. The disease progresses to irreversible axial and/or peripheral joint damage, ankylosis and ultimately vital organ involvement with early mortality.

NSAID-refractory-AS is defined when after treatment with at least 2 different NSAID over a period of at least 2 months, ASAS 20 is not obtained, and ESR, CRP, and the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score do not improve, or worsens versus baseline. Indications for therapy with SBC-5-IMNs are in NSAID-refractory AS with ESR $>$ 40 mm and a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) > 4. Less than 5% of patients with NSAID-refractory AS in the community at large fulfill these conditions. Remission is defined when ESR and VAS have declined to $\leqslant$10 mm (men $\leqslant$5 mm) and the disease activity scores are $<$1 (scale 0–10). Remission with oral drugs is defined when remission is maintained with oral drugs for at least 2 years. Remission without drugs is defined when remission without drugs is sustained without relapse for at least 2 years.

The 4 phases of SBC-5-IMNs can achieve primary and secondary endpoints of ASAS 20, ASAS 50 and ASAS 70 in circa 80% of the patients.

III.e.3. Psoriatic Arthritis

Psoriasis is a chronic skin and nail disease. About 10% of patients with psoriasis develop arthritis (PsA). Psoriasis may precede arthritis or vice versa. The diagnosis of PsA is based on finding psoriasis along with arthritis.

Treatment of refractory PsA is comparable to therapy in other SpA without psoriasis. In this disease entity SBC-5-IMNs contains IV MTX + oral CyS, which is the ideal combination for therapy of psoriasis, besides other IMNs.

III.e.4. Arthritis of Chronic Inflammatory Bowel Disease (IBD)

Arthritis of IBD comprises rheumatic syndromes associated with IBD. Inflammatory bowel disease consists of Crohn's disease and Ulcerative Colitis. Gut inflammation is common in patients with SpA. Around 25% of patients with chronic SpA have early features of Crohn's disease.

Treatment of refractory arthritis-IBD is similar to therapy of other SpA disease categories. Outcomes are similar to AS therapy with SBC-5-IMNs.

III.e.5. Undifferentiated Spondylarthritis and Sacro-iliitis

In long-term observational studies Undifferentiated SpA (UspA) mostly developed into mild AS and some into ReA, PsA, arthritis of IBD or remained as UspA. Only 14% were in functional class III.

If ESR is $>$ 40 mm, SBC-5-IMNs should be applied to the few cases that develop into moderate to severe AS, ReA, PsA, and arthritis of IBD.

Spondylarthritis can manifest itself as sacroileitis without the involvement of other joints.

III.f. Systemic Lupus Erythematosus

The spectrum of Systemic Lupus Erythematosus (SLE) includes latent lupus, discoid lupus, drug-induced lupus, neonatal lupus, lupus profundus, neuropsychiatric lupus, lupus vasculitis, pulmonary lupus, etc. The disease course is characterized by unpredictable exacerbations, drug-induced remissions and spontaneous remissions. SLE is characterized by a wide range of variable individual clinical manifestations which are controllable at early stages.

There is predisposition for the clinical involvement of skin, joints, muscles, peripheral and central nervous system, GI tract, kidneys, hearth, serosa and

lungs. Lupus is not necessary a chronic progressive, lifelong and potentially fatal autoimmune disease. Adequate therapy can achieve RworalDs and RwD when no irreversible changes have occurred in vital organs such as renal damage. Long-term RwD can be maintained if incidental early flare is immediately suppressed with adequate immunosuppression.

Notwithstanding DMARDs therapy (NSAIDs and/or prednisolone and/or hydroxychloroquine and/or azathioprine) lupus nephritis still develops in 48% of patients with SLE. Of these 40% develop into End Stage Renal Disease and subsequent mortality mostly due to infections.

III.f.1. Therapy of Systemic Lupus Erythematosus

Lupus nephritis is the most common manifestation of inadequately treated SLE. Its therapy serves as a module for treatment of other lupus manifestations.

Single drug therapy is mostly adequate in lupus nephritis (LN) classified as *renal biopsy WHO Class I and II*. Single drug therapy in lupus nephritis Class III–V, and in particular Class VI is less or not effective. One immunosuppressant cannot suppress all aspects of autoimmune inflammation in the more serious forms of the disease. The SBC-5-IMNs is not required in Class I, II, and also not in Class VI. In Class VI nothing helps, except renal dialysis or renal transplantation.

Renal disease as a complication of severe SLE still causes major morbidity and mortality and therefore, the application of the SBC-5-IMNs is justified in LN Class III–V. With this therapy of LN Remission with Oral Drugs (RworalDs) and also Remission without Drug (RwD) can be achieved.

The underlying rationale for early application of SBC-5-IMNs in LN is that once renal damage occurs, progressive damage will follow if the disease activity remains high (Systemic Lupus Activity Measure or SLAM score $\geqslant 4$). Indications for therapy with SBC-5-IMNs in DMARD-Refractory LN (DR-LN) include:

- ESR > 40 mm;
- SLAM score $\geqslant 2$ (any of the 6 validated lupus outcome measures is applicable);
- Biopsy WHO Class III–V;
- Nephrotic syndrome.

Lupus Nephritis is considered DMARD-Refractory if after 2 consecutive monthly evaluations of single DMARD or combination DMARDs therapy response is unsatisfactory with ESR > 40 mm and SLAM-R scores that are not reduced compared to baseline. When patients with clinical and/or biopsy-proven LN fulfill the indications then the 4 phases of SBC-5-IMNs should be started.

DMARD Refractory Lupus Nephritis is considered to be in remission when the SLAM-R Score is suppressed to zero, ESR is suppressed to 10 mm (male 5 mm) and 24 hours Micro-albuminuria is suppressed to <30 mg (normal <30 mg). Remission with oral drugs (RworalDs) is defined when Remission is maintained with MMF and/or CyS for at least 2 years and remission without drug (RwD) when after 2 years therapy, oral drugs are tapered off with a sustained remission for at least 2 years.

IV. OSTEOARTHRITIS

Osteoarthritis is the most frequent arthritis encountered in medical practice. That is why 5 times more NSAIDs are prescribed for OA than for all other arthritides together. However, this therapeutic situation will change when more knowledge in the pathogenesis of OA is acquired by molecular research.

Osteoarthritis is defined by the American College of Rheumatology as a: “heterogeneous group of conditions that leads to joint symptoms and signs. These are associated with defective integrity of articular cartilage, in addition to related changes in the underlying bone at the joint margins”. Its prevalence after the age of 65 years is about 60% in men and 70% in women.

Osteoarthritis is not a single disease entity because the different locations are exposed to different risk factors. Outcomes of OA vary among patients but are also variable in each individual patient. This depends on the joints involved, duration of disease, and the frequency the active inflammatory process is switched on and off.

Osteoarthritis proves to be a more complex disease than autoimmune disease, with multiple variable manifestations like knee, hip, hand, DIP, elbow, shoulder, and spinal joints OA, which have different risk factors. The etiology of OA is multifactorial with inflammatory, metabolic and mechanical causes. A number of personal and environmental risk factors, such as obesity, occupation, and trauma, may initiate various pathological pathways. OA comprises degeneration of articular cartilage together with changes in subchondral bone of the joint margins and mild intraarticular inflammation.

The pathophysiology involves a combination of cellular, biochemical, and mechanical processes.

The interaction of these processes leads to changes in the composition and mechanical properties of the articular cartilage. Cartilage is composed of water, collagen, and proteoglycans. In healthy cartilage, continual internal remodeling occurs as the chondrocytes replace macromolecules lost through degradation. This process becomes disrupted in OA, leading to increased degenerative changes and an abnormal repair response. There is evidence of thickening of the lining layer, increased vascularity, and inflammatory cell infiltration in synovial membranes from patients with all grades of OA.

The aim of therapy is to terminate the inflammation and subsequent degenerative and reparative pathways in early OA. The principal treatment objectives in late OA are to eradicate inflammation, control pain adequately, improve function and reduce disability.

IV.a. Therapy of Osteoarthritis

NSAIDs were never able to stop the different processes of inflammation, degradation, and reparation of OA. Intra-articular injection of hyaluronic acid has also not been able to stop the destruction of affected joint cartilage over time. The National Institute of Health (USA) has showed that glucosamine or chondroitin sulfate have comparative efficacy with placebo.

Eradicating the inflammatory aspect in radiological stage I and II Knee OA will prevent, terminate or slow the degradation and reparation process. In radiological stage III and IV knee OA, mechanical imbalance will continue to maintain low-grade inflammation. The degenerative process will continue to total denudement of cartilage and development of genu varus or valgus by the reparative process. Quadriceps and other knee joint muscles including joint capsule and ligaments are subject to fast atrophy in knee OA.

The current trend is to treat OA as a low-grade autoimmune inflammatory disease as indicated by activated cytokine dependent pathways with the presence of IL-6β, IL-1α, TNF-β, abnormal ESR and CRP. ESR ($<$40 mm) and CRP are mildly elevated and suppression to normal can be achieved with a few weekly IVT and PA sessions from SBC-5-IMNs. Early diagnosis of relapses and suppression of inflammation is the key to prevent radiological stage III and IV knee OA.

V. OSTEOPOROSIS

Osteoporosis is a metabolic bone disease characterized by low bone mass and micro-architectural deterioration of bone tissue. This will lead to bone fragility and consequent increase in bone fracture risk. Mean bone mineral density (BMD) is measured with dual X-ray absorptiometry (DEXA) and expressed in Tsc (Tscore). WHO standards are: a Tsc that is 1 standard deviation (SD) below mean BMD is graded as normal bone, Tsc between 1 and 1.5 SD below mean BMD is graded as osteopenia and a Tsc of more than 2.5 SD below mean BMD is graded as osteoporosis. When the Tsc is below 1.5 SD mean BMD prevention of osteoporosis must be initiated. Primary osteoporosis is caused mainly by hormone deficiency in both women and men. Secondary osteoporosis may result from endocrine, metabolic, nutritional and autoimmune causes or from immobility because of trauma. Also the use of medicaments such as corticosteroids may be contributing.

V.a. Therapy of Osteoporosis

Disease-induced, drug-induced, old age-induced, immobility-induced and menopause-induced osteoporosis is all relatively cheap to prevent but become very expensive and difficult to treat as soon as a fractures occur. Oral calcium, vitamin D, biphosphonates, hormone replacement and parenteral calcitonin in post-menopausal women, achieved annual BMD increases of 0.5–1.5%. Limited efficacy of less than 0.5% annual BMD increase, adverse effects, and high costs have restricted the large scale use of calcitonin.

Non-compliance is a serious problem in the prevention of osteoporosis and osteoporotic fractures. This is due to adverse effects, lack of noticeable benefit and ignorance. It is difficult to convince regular intake of oral calcium, biphosphonates, vitamin D and in post-menopausal women hormone replacement. Long-term compliance to hormone replacement is worse in developing countries. The most cost-effective therapy for osteoporosis is primary prevention.

In post-menopausal women with osteoporosis oral biphosphonate treatment is associated with an increase of BMD and a more than 40% reduced risk of hip fracture. To increase compliance once monthly 150 mg oral ibandronate is introduced, which is equally effective as an oral dose of 2.5 mg once daily. Intravenous drips of ibandronate 2–3 mg

every 2–3 months are at least as effective as oral daily 2.5 mg. Optimal increase of BMD in post-menopausal women occurs when IV biphosphonates are combined with oral calcium, vitamin D and the selective estrogen receptor modulator raloxyphene.

VI. CRYSTAL-DEPOSITION DISEASE

Arthropathies associated with crystals deposition are acute gouty arthritis, chronic gout and chronic tophaceous gout due to monosodium urate crystals. Then there is acute pseudogout and chronic pyrophosphate arthropathy caused by calcium pyrophosphate dehydrate crystals. Acute calcific periarthritis, acute hydroxylapatite arthritis and chronic hydroxyapatite arthritis including Milwaukee-shoulder–knee syndrome are due to basic calcium-phosphate–hydroxyapatite crystals.

VI.a. Gout and Hyperuricemia

Gouty arthritis is an inflammatory response to the deposition of monosodium urate monohydrate crystals secondary to hyperuricemia. It is called monosodium urate crystal deposition disease. Hyperuricemia is a serum urate concentration > 7 mg% in males and >6 mg% in females. Hyperuricemia results from overproduction (10–15% of individuals) or a renal excretion of urate lower than 400 mg uric acid/24 hours (85–90% of individuals). The urate under-excretors have a urate clearance of <6 ml/min or a urate to creatinine clearance ratio of $<6\%$. The combination of a relative excess of dietary purine consumption together with urate under-excretion is often the basis for hyperuricemia.

In the last 2 decades increasing prevalence and clinical complexities of gout and hyperuricemia are encountered. The principal factors underlying these are increased longevity of the population, high prevalence of hypertension, increased alcohol consumption, increased prevalence of obesity and metabolic syndrome and in Third World countries trends towards Western diet habits. Regrettably these factors were not balanced by an equivalent development of uric acid lowering drugs.

Hyperuricemia-associated medical problems are: clinical manifestations of gout by recurrent attacks of inflammatory arthritis, chronic tophaceous gout, uric acid urolithiasis, renal impairment, end stage renal disease and early mortality. These manifestations are due to precipitation of urate crystals into joints, tissues, renal tubules and parenchyma.

Gouty arthritis, chronic gout, and chronic tophaceous gout is easily treatable and controllable compared with autoimmune arthritis or OA. Chronic tophaceous gout requires lifetime urate lowering drugs and to a lesser extent restriction of purine-rich food.

Estrogen is uricosuric and that is most probably the reason why premenopausal women do not have primary gout. Estrogen hormone replacement therapy in post-menopausal women lowered serum uric acid (SUA). Consequently, the prevalence of primary gout in these subjects is similar to what is seen in pre-menopausal women.

VI.a.1. Therapy of Gout

Number and changes in tophi size during uric acid-lowering therapy is measured with magnetic resonance imaging (MRI) or ultrasonography (USG). MRI or USG for imaging unsuspected tophi in both large and small joints and in the urinary-genital tract for urolithiasis determines therapeutic options. Long-term or even lifetime uric acid lowering drugs are indicated when tophi and urolithiasis are evidently present.

Acute gouty arthritis interferes seriously with work, recreational activities and mobility. Between flare and intercritical gout 25% of patients still report pain most of the time for unexplained reasons. Therefore, maintaining low levels of serum uric acid (SUA) in chronic gout is important to prevent flare of acute gouty arthritis.

Pharmaceutical therapy of acute arthritis of crystal-deposition disease is effective, in particular for gout and hyperuricemia. Treatment is directed towards termination of acute arthritis, prevention of recurring attacks and prophylaxis and reversal of complications of chronic gout. Such complications include tophi, urolithiasis, nephropathy and with hyperuricemia associated medical problems that can be prevented, inhibited, and sometimes reversed.

To treat hyperuricemia associated medical problems the following steps are recommended: life-style corrections by restriction of purine-rich nutrition, prevention and reduction of obesity, bloodpressure control, limitation of alcohol consumption and control of hyperlipidemia.

Gout can be best managed by general medical practitioners and family physicians. When hyperuricemia associated medical problems are serious,

then consultation or guidance is required from a specialist or a rheumatologist.

The gold standard for the treatment of acute gouty arthritis with colchicine and/or NSAIDs are initially effective. With recurrent acute attacks of chronic gout or chronic tophaceous gout, arthritis may become refractory to these 2 treatment modalities. Colchicine effectively functions as a 'mitotic poison', thereby reducing the production of purines and thus of uric acid. It should be used with extreme caution in chronic renal or hepatic failure in particular hepatorenal failure. Colchicine should not be used in patients on chronic hemodialysis because it is not dialyzed. Intravenous colchicine is not used because of serious adverse effects. NSAIDs are superior in terms of speed of onset of action and efficacy compared with colchicine. NSAIDs dosage used to treat acute gouty arthritis tends to be maximum or more than the usual therapeutic range. Cardiovascular, renal, hepatic, and gastrointestinal risks for adverse effects dictate extreme caution in the application of maximum therapeutic dosage of NSAIDs. Parenteral NSAIDs speed up and maximize efficacy, but the aforementioned risk factors for adverse effects limit this option.

Parenteral corticosteroids may be used effectively when colchicine and NSAIDs are contraindicated or in patients with gout that is refractory to colchicine and NSAIDs. Combined intramuscular injections of dexamethasone 20 mg and 40 mg Triamcynolone Acetonide (TA) is the regimen of choice. The rationale is that DxM starts to suppress acute gouty arthritis after 4 hours and lasts for 4 days. Triamcynolone acetonide depo efficacy starts after 4 days and last 6 days. The combined fast acting and slow acting corticosteroids relieve pain and swelling within 1 day and prevent flare over 0.5–1.0 month. Gastric hyperacidity and irritations by high dose corticosteroids can be prevented with proton pump inhibitors.

Persistent chronic gouty arthritis resistant to systemic therapy with colchicine and/or NSAIDs and/or corticosteroids is relieved by intraarticular corticosteroids.

VI.a.2. Therapy of Hyperuricemia

Correctable Environmental causes of hyperuricemia should be minimized or eliminated concomitantly with pharmaceutical therapy. Drugs effective in controlling acute gouty arthritis are of no value in controlling hyperuricemia. The number of currently available primary uric acid-lowering drugs is limited. Primary uric acid-lowering drugs contemporary in use are allopurinol and the uricosurics probenecid, sulfinpyrasone, and benzbromarone (the latter is withdrawn from the market in some countries because of fatal liver injury).

Allopurinol is an xanthine oxidase inhibitor. It reduces urate production and is used in primary and secondary urate overproduction. Therapy of hyperuricemia prevents recurring attacks of acute gouty arthritis. Allopurinol dosages are 300 mg/day for serum creatinine $\leqslant$ 1.5 mg/dl and 100 mg/day for serum creatinine between 1.6–2.0 mg/dl. Reduction of tophi is slow with allopurinol, particularly in patients with giant tophi and renal insufficiency where drug dosage is limited.

Major limitations of the use of allopurinol are allergy, hypersensitivity syndromes, hepatotoxicity, bone marrow suppression, nonspecific central nervous system and gastrointestinal side effects. Skin rash occurs in 2% and Steven–Johnson syndrome, although rare, may occur. The latter can cause life-threatening major organ system failure.

Uricosurics like probenecid, sulfinpyrasone and benzbromaron increase urate clearance and fractional excretion of filtered urate. They are used in underexcretors of urate. Uricosurics benefit patients with hyperuricemia, intact renal function and no history of nephrolithiasis. In tropical and subtropical climates where most of the Third World countries are situated, the prevalence of urolithiasis is $>$40%. The use of uricosurics is contraindicated in patients with a history of urolithiasis as the number and size of stones will be increased. Without an history of urolithiasis, uricosurics still should be applied with caution where the risk for dehydration is high.

Secondary uric acid-lowering drugs such as fenofibrate, atorvastatin and losartan all are mild-to-moderate uricosurics.

Febuxostat is also an inhibitor of xanthine oxidase and seems to be most promising in difficult to treat chronic tophaceous gout. It can replace allopurinol when allopurinol is not tolerated and there is history of urolithiasis.

VII. INFECTIOUS ARTHRITIS

Infectious Arthritis comprises viral, bacterial, and fungal joint infection. Bacterial infectious arthritis should be considered an emergency for the patient

and joint concerned. The disease is acute and may very quickly progress to irreversible joint destruction and sepsis if not adequately controlled. Certain bacteria like gram-negative gonococcus can cause irreversible joint destruction within 24 hours and bacterial sepsis.

The risk for infectious arthritis is high in patients with autoimmune diseases with compromised immunity. Acute bacterial arthritis mostly results from hematogenous spread in the elderly and in the less than 15 years. Acute monarthritis should raise a high index of suspicion of joint infection.

Viral arthritis is rather common and usually self-limited within a few weeks. The most common pathophysiological mechanism is not a direct virus invasion in the synovium but deposition of immune complexes. Viral infections frequently involve multiple joints and produce inflammation without suppuration. The typical clinical presentation is a peripheral and symmetrical polyarthritis, undistinguishable from other inflammatory arthritis. Virtually all viruses can cause arthritis. There is no specific treatment and simple symptomatic measures are sufficient.

Incidence of fungal bone and joint disease is increasing with the increase in the prevalence of factors predisposing to fungal arthritis. These are the use of central venous catheters, broad-spectrum antibiotics, immunosuppresives and abdominal surgery.

Chronic tuberculous arthritis is not at all rare in developing countries. Mycobacterial tuberculosis can directly or indirectly affect the musculoskeletal system. Most commonly there is a direct musculoskeletal involvement of M. tuberculosis which may lead to spondylitis, osteomyelitis, septic arthritis and tenosynovitis. M. tuberculosis has become an important pathogen in rheumatic diseases since the use of anti-TNF-α biopharmaceuticals was introduced.

VII.a. Therapy of Infectious Arthritis

While waiting for the results of bacterial culture and sensitivity tests, intravenous broad-spectrum antibiotics must be administered immediately, to be replaced by a specific antibiotic as soon as results of biopsy or aspirate cultures are known. Skin infection in the proximity of joints should be treated with antibiotics to prevent joint infection in immune compromised patients.

Drainage, debridement, and large volume irrigation by 3-directional arthroscopic surgery may become standard treatment for septic arthritis of the hip with concomitant intravenous antibiotics for at least 3 weeks followed by oral antibiotics for at least another 3 weeks. After infectious arthritis is eradicated a follow-up period of 1–4 years is advised.

To eradicate tubercle bacilli longer courses of combinations of tuberculostatics are required in joint tuberculosis compared to treatments of pulmonary tuberculosis. Similar to the therapy of other forms of arthritis, local rest and protection of the joint are required to support recovery.

Therapy of fungal arthritis consists of amphotericin B in combination with surgical debridement. Azole antifungal agents including itraconazole, fluconazole, voriconazole, and posaconazole, are promising in the therapy of fungal arthritis.

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Chapter 38

Treatment of Psychiatric Disorders

David Healy, Nicholas Moore

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I. INTRODUCTION

Psychiatric diseases and their treatment have come a long way since the time when these disorders were ascribed to possession by demons and treatment was restricted to community care (the village idiot or mumbler) or in-patient detention. This progress has been on several fronts, with the understanding of the social, personal and developmental aspects of clinical cases, following Sigmund Freud, on one hand and the development of psychotropic drugs. Since the 1950s, neuropsychopharmacology has identified multiple receptors and neural connections, and the pharmacology of the mostly empirically found drugs has been refined, but we are still very far from understanding exactly how the drugs treat or impact on psychiatric disorders.

As a consequence, the choice of pharmacological treatment for any given disease should rely not on theoretical grounds based on neurochemistry or hypothetical mechanisms of action, but on sound science and clinical evaluation. This is true for any disease, but all the more in psychiatry, where there is lots of fine histochemical knowledge, many operational theories, but few hard links between theory and effect.

In practice, the drugs are evaluated using psychometric scales for anxiety, depression or other symptoms, scales that have usually been derived in the Western hemisphere, and need to be carefully validated in different sociocultural settings (for example, the CAGE four-question test for the detection of alcoholism includes one question on drinking before noon: this may be a sign of severe alcoholism in Northern Europe, but not in Southern Europe where the 'apéritif' is a way of life). Furthermore while the drugs show some benefits on these rating scales, for the most part there is no evidence for any reduction in mortality or morbidity.

The part of the international classification of diseases (ICD 10) concerning psychiatric disorders identifies over 500 different diagnoses or classification terms, divided into 10 main chapters and 100 categories, including classification and diagnostic criteria. These ten main chapters will not all be covered here, because clinical trials and approval data usually do not allow such discrimination. Additionally, some of these categories, such as dementia (code F00-09) can be covered more appropriately under neurological diseases rather than in a chapter on psychiatric diseases.

We will try to give indications of therapeutic drug use in the main categories, without being exhaustive to the point of giving actual doses, which can be found in the marketing approval summary of product characteristics or other such therapeutic infor-

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mation, but to try to summarize whatever information is currently available on these drugs and their use. The indications given rely as far as possible on evidence-based data as covered in Cochrane Collaboration Reviews. In this treatment area, there really have been few major changes over the last 45–50 years since the discovery of the three main classes of psychotropics. Since we are not really closer to understanding the basic pathophysiology or mechanism of psychiatric diseases, 'designer' drugs will probably not appear in the near future. But then again, science and medicine have a way of surprising predictions ....

Finally, psychiatric diseases are a complex area, with a high degree of comorbidity and intermediate states, which all merit attention and treatment. In addition, as in every disease state but perhaps even more so, personal and social therapy or intervention are invaluable adjuncts to medicinal therapy. Drugs alone do not cure or treat psychiatric diseases, but they can often help.

II. ORGANIC, INCLUDING SYMPTOMATIC, MENTAL DISORDERS (ICD 10 CODES F00–F09)

These codes cover dementia of the Alzheimer type, and other organic disorders. The treatment of the diseases within this group is discussed in more detail in Chapter 39.

Alzheimer's disease is a major focus of the efforts of the drug industry, considering the growing age of the population, and the social and financial benefits that could derive from preventing the disease or retarding its consequences. To date, the drugs that have been developed and marketed are inhibitors of cholinesterase. Some are marketed (e.g., donepezil, rivastigmine), many others are still in a development phase. Identification and development of candidate drugs is made difficult by the lack of experimental or laboratory models of the disease, and by the very long latency before the disease becomes symptomatic. Possible treatments are divided into two main categories. The first are agents such as the cholinergic agents, which oppose the effects of the disease, but not its evolution. The second category would act on the disease itself, interrupting or slowing its evolution. It may take many years before the efficacy of such a drug can be proven or disproved, maybe explaining why all the drugs on the market are of the first kind.

The treatment of other dementias is that of the underlying disease. The treatment or prevention of ischemic brain disease by various drugs (gingko extracts, ergot derivatives, anti-oxidants, vasodilators, 'oxygenators', etc.) has never been clearly demonstrated as being of real value. There are ongoing trials of the use of drugs used to treat Alzheimer's disease for ischemic or vascular dementia in the hope of also obtaining symptomatic if temporary improvement.

III. MENTAL AND BEHAVIOURAL DISORDERS DUE TO PSYCHOACTIVE SUBSTANCE USE (ICD 10 CODES F10–F19)

Within this field, most of the research and results have been focused on the effects of drug therapy on the disorders induced by alcohol, and by the abuse of opiates. For a broader discussion of substance abuse see Chapter 18. In all instances of alcohol or drug abuse the first objective is to wean the patients from the addictive substance, treating or preventing the effects of withdrawal for those substances which cause physical dependence (alcohol, nicotine, opiates, caffeine, certain psychotropic agents such as benzodiazepines, possibly antidepressants). The second phase is the prevention of recurrence or relapse, which relies on a combination of social support, psychotherapy, and pharmacotherapy where available. In this respect, alcoholism is exemplary.

III.a. Alcohol Abuse

Alcohol abuse and dependence, widely known as alcoholism, is a major cause of morbidity and mortality. Its acute and chronic toxicity spreads across multiple systems and organs, from child abuse to domestic or public violence to traffic accidents and from cirrhosis to hypertension. Mean life expectancy of alcohol abusers is around 55 years. Alcohol seems involved in several hundred thousand deaths each year in Europe, with considerable added social and health care costs. This is in clear contrast with the little attention paid to the treatment of alcohol dependence and abuse. On the other hand, much is made of the "French Paradox", the "J curve" and the demonstrated cardiovascular benefits of regular moderate wine intake.

Alcoholism, beyond treating the physical consequences related to nervous or hepatic toxicity or associated psychiatric or social comorbidity, offers two

distinct fields for drug therapy: withdrawing from alcohol, and maintaining abstinence.

III.b. Withdrawal from Alcohol

The main risk is that of the occurrence of delirium tremens (DT) and its risk of somatic damage by convulsions, aggravated by dehydration. Symptoms of DT include restlessness, heavy sweating, tremor, severe anxiety, delirium, and hyperthermia. It is treated or better still prevented by a calm environment, adequate (but not excessive) hydration, and careful monitoring, with the adjunction of anticonvulsive/sedative agents, mainly benzodiazepines. The preventive effects of benzodiazepines on withdrawal morbidity has been clearly demonstrated. There do not seem to be major differences between benzodiazepines, such as chlordiazepoxide or diazepam or others. Because of the abuse potential in these highly susceptible patients, these should be rapidly weaned, and proper prevention of relapse instituted.

III.c. Prevention of Relapse

The aims of treatment are to maintain total abstinence, avoid the cognitive and social consequences of alcoholism, or possibly allow a return to the 'normal' social use of alcohol. The latter is rarely obtained, probably because of long-term neuroadaptation to dependence, which makes alcoholism a life-long disease, at least in the present state of knowledge and treatment. Disulfiram and other acetaldehyde dehydrogenase inhibitors cause reactions (antabuse) when alcohol is ingested, forming the basis of aversive therapy associated with behavioural intervention, which with support groups and psychosocial intervention has long been the mainstay of therapy. Prevention of alcoholic relapse has been demonstrated with two drugs, acamprosate and naltrexone, which act through two very different mechanisms not involving aversion. Naltrexone is essentially an opioid antagonist, whereas acamprosate probably acts through GABA receptors. Both have been approved for this indication in several countries. They have been shown to decrease relapse rates, improve short and medium term prognosis, improve compliance to medication and treatment, and possibly, perhaps in some ill defined patient subtypes actually decrease or modify the craving for alcohol. Though at least six months of treatment seem necessary, to obtain even minimal benefits, the effects of long-term treatment, and the optimal duration of treatment are not known. Much work remains to be done in this field, and the emergence of pharmacological tools may provide for a better understanding of possible subtypes, either psychochemical or treatment-related.

It can be hoped that the commercial success of a drug in this field will lead to further development of what in most respects is still an 'orphan' field.

III.d. Opioid Abuse

The treatment of opioid abuse and dependence aims also at preventing the social complications of abuse, especially infections linked to parenteral administration (HIV and HepB). It relies on the use of substitutive drugs that can be either pure agonists, or partial agonist-antagonists (methadone, buprenorphine, naltrexone), with the objective of limiting receptor desensitization and the development of tolerance. Any success in the treatment of opiate dependence may stem as much from the re-establishment of healthcare contact and social reinsertion as from any treatment induced decrease in the abuse behaviour itself.

Systematic reviews from the Cochrane database indicate that at present the available trials do not allow a final evaluation of these maintenance treatments. A trend in favour of treatment with naltrexone has been observed for certain target groups (see Minozzi et al., 2006).

III.e. Treatment of Craving

Most psychoactive substance use problems are characterized by dependence and tolerance. Dependence may be "physical" or "psychic", though the substratum of the latter, often also called craving (as opposed to the purely physical need to avoid or treat withdrawal symptoms) is largely unknown, there are indications that there is a common pathway involving dopamine. There have been some trials of various drugs (other than the substance itself or congeners, e.g. nicotine gums or patches, or methadone substitution) to treat craving, with unclear success, applied to alcohol, opiate or other abuses such as cocaine. Drugs that have shown some activity are clonidine, lithium carbonate, and bromocriptine, but there is no consensus in this area.

IV. SCHIZOPHRENIA, SCHIZOTYPAL AND DELUSIONAL DISORDERS (ICD 10 CODES F20–F29)

This section covers, along with the more severe of the mood disorders, what are usually called psy-

choses. Schizophrenic diseases can generally be considered as an alteration of the relationship with the outside world, either in excess (delusional type or positive symptoms), or by default (autistic, or negative), traits of both of which can be combined in individual patients. The most common instrument used to measure drug effects is the PANSS (Positive and negative symptoms score).

These diseases are associated with considerable comorbidity, both psychiatric and non-psychiatric, resulting in a high mortality rate (2–10 times that of age-corrected general population), particularly in elderly patients. Suicide is a major cause of death, along with cardiovascular disorders, related in part to associated behavioural disorders resulting in extremely high nicotine and other drug use, frequent alcoholism, overeating with obesity and diabetes, but also to pharmacotherapy. Life expectancy falls in proportion to the number of antipsychotics used. Having made this point, psychotic illnesses entail considerable social non-insertion, and up to half the homeless may be schizophrenic, and these factors illustrate that treatment must involve a careful assessment of hazards and benefits.

The families of drugs primarily used to treat these diseases are the neuroleptics or antipsychotics, which share common characteristics, essentially that of acting as dopamine receptor antagonists. Since there is no appropriate animal disease model, potential neuroleptics are identified by the existence of other signs of dopamine antagonism such as parkinsonism, or extrapyramidal symptoms (EPS). The original drugs in this area such as chlorpromazine had a multiplicity of actions on diverse physiological systems and hence a large range of side effects. Subsequent agents such as haloperidol, perphenazine and flupenthixol progressively eliminated many of the accessory side effects, leaving EPS as the most significant set of side effects.

Some drugs giving less EPS were discovered serendipitously, such as metoclopramide, first used to treat gastro-intestinal disorders, led to the development of a series of related drugs for psychosis such as sulpiride, sultopride, and amisulpride.

In the late 1980s, clozapine a chlorpromazine like compound with a multiplicity of effects was rediscovered and termed an "atypical" neuroleptic. It appears to be the only genuinely atypical agent – that is an agent with significant beneficial treatment effects in the absence of EPS (see Wahlbeck et al., 1999). A second generation of antipsychotics have succeeded clozapine been marketed as being atypical. This group includes risperidone, quetiapine, olanzapine, ziprasidone, and aripiprazole. But all these agents cause dose-related EPS and appear in general more likely to cause diabetes and other metabolic problems than some of the older drugs (see Duggan et al., 2005).

Because of multiple receptor actions, which occur at different concentrations, different neuroleptics have different action profiles. There are many classifications for neuroleptic drugs, the least useful of which is probably based on their chemical structure. Other classifications include linear classifications based on the propensity to cause EPS, or multidimensional ones such as the "Liège star" which combines information on three positive effects (antiautistic, antiproductive, antipsychotic), and three negative (hypotensive, extrapyramidal, sedative). In a general way, the more sedative neuroleptics such as levomepromazine, used more to treat acute agitation states, cause more hypotension related to alpha blockade, whereas those that act best on delirium (productive states) such as haloperidol tend to cause more EPS.

Considering the large number of drugs available and the wide spectrum of psychotic or schizophrenic disorders, there is no immediate choice in a given situation. Drugs such as, perphenazine, flupentixol, sulpiride or haloperidol have a good all-round profile making them possible drugs of first choice. In cases of severe EPS or treatment resistance, clozapine may be useful. Clozapine has been shown to be more effective than typical neuroleptics in reducing symptoms of schizophrenia, producing clinically meaningful improvements and postponing relapse, at least, but this may be only in patients who have an adverse response to typical neuroleptics. However, clozapine carries a risk of neutropenia and agranulocytosis (0.5% of treated patients) which warrants careful monitoring.

Other newer agents were claimed to provide the benefits of clozapine without the drawback of potentially lethal agranulocytosis, but recent studies indicate that older agents like perphenazine and sulpiride when used in sensitive dose regimens provide as good an outcome as any other drugs.

Most trials of the antipsychotic drugs are short term and consider only psychiatric outcomes. There is still a need for longer trials, and for the study of other variables such as patient and family quality of life and preference, or economic outcomes. Additionally, though newer neuroleptics and especially

clozapine may be more effective than haloperidol on negative symptoms, there is little indication for treatment preference concerning positive symptoms.

There is a further problem in that it has been known from the mid-1950s that many patients with schizophrenia do not respond to antipsychotics. However clinical trials that apparently prove antipsychotics work make it all but impossible not to give these drugs to all patients, even when they show minimal or no response. This raises difficulties in that there is no benefit other than perhaps some diminution of agitation that is likely to be set against the very real hazards of treatment. In such patients benzodiazepines or other sedatives may be preferable.

Among the difficulties in pharmacological treatment is the frequent non-compliance. The biggest determinant of compliance is the quality of a patient's relationship with his doctor. But a further way to handle the issue has involved the development of long acting products (depot neuroleptics), even though their effectiveness in the absolute or compared to oral preparations has not been adequately explored. The most commonly used depot agents are fluphenazine and haloperidol decanoate (see David et al., 2004).

The duration of treatment is a complex issue. Up to 20% of psychoses are acute and transient and do not need ongoing treatment. Up to 30% are enduring schizophrenias which show minimal responses to treatment. The real beneficiaries of treatment lie in the middle and in these cases care is probably best driven by consulting with patients as to whether they can perceive a benefit of the prescription. There have been no convincing long-term trials of different drug regimens, maybe because of the extreme difficulty of running long-term trials in these patients, due to high drop-out rates, related to the disease itself, to varying drug efficacy, or to side effects. Stopping drugs in the short term is advisable in acute and transient psychoses. In more enduring disorders, it is likely to be associated with relapse, but in a proportion of these relapses it is possible that clinical deterioration will stem from the fact that antipsychotics can lead to a physical dependence and this dependence may give rise to difficulties on withdrawal.

The more disagreeable and troubling side-effect of long-term neuroleptic treatment is tardive dyskinesia. This occurs after variable duration of treatment, and may be precipitated by changing doses, and repetitive stopping and starting drugs. Its mechanism is not well known, and it may improve when neuroleptics are stopped, or when doses are increased. There is no clear proof that tardive dyskinesia is less associated with some neuroleptics. There is no clear indication that either giving or stopping anticholinergic medication will improve the symptoms of tardive dyskinesia, nor that cholinergic medication is of any help. Benzodiazepines were not clearly useful, or other miscellaneous agents.

There are many other non-psychiatric side-effects to the use of neuroleptics: acute movement disorders (acute dyskinesia), extrapyramidal syndrome, hypotension, hyposalivation (or hypersalivation with clozapine), weight gain (olanzapine), constipation (anticholinergic effect), hyperprolactinemia (galactorrhoea – amenorrhoea), sexual disorders (impotence and frigidity), cholestatic jaundice (chlorpromazine). A disturbance of central temperature control is common, resulting in hypo- or hyperthermia, leading to a risk of heatstroke. One of the more severe disturbances of temperature regulation is neuroleptic malignant syndrome, with extremely high temperature resulting from excessive peripheral production of heat due to muscle energetic uncoupling combined with central disturbance of the body thermostat. Though rare, this syndrome which has links to catatonia can be fatal. It is now treated with high dose benzodiazepines, and if these fail with electroconvulsive therapy (ECT). Arrhythmias have also been described with most neuroleptics, at normal or increased doses.

In addition to the somatic side-effects of neuroleptics, there are a number of important psychiatric side-effects, such as demotivation or indifference (a direct effect of most drugs, actually part of the definition of the neuroleptic effect). This may mimic the negative features of the illness and may lead to prescriptions of an antidepressant when a reduction in dose or change of antipsychotic may be more appropriate. A second key problem is anxious activation or akathisia. This dose-dependent dysphoric state may lead to an apparent worsening in the clinical picture and accordingly an increase in antipsychotic dose rather than decrease and may be so intolerable as to lead on to suicide.

V. MOOD [AFFECTIVE] DISORDERS (ICD 10 CODES F30–F39)

This section covers changes in mood, which can be increased (mania) or decreased (depression, melan-

cholia). These mood swings can be part of the bipolar disorder manic-depressive illness (MDI), manifest as swings between mania and depression, or as manifestations in mainly or only one direction. The frequency of the episodes can also vary from a single episode of mania or depression to severe frequently recurrent illness. Depression can also be a manifestation of other diseases, or secondary to external factors, though the exact role of endogenous and exogenous disorders is not always easy to discern.

A distinction between idiopathic depression and bipolar disorder is not always easy at the first episode, and it is important to determine when another episode of depression occurs whether it is relapse of recurrence. Relapse is defined as the reappearance of signs or symptoms of depression within the same treated episode, often when treatment is stopped prematurely. Recurrence is defined as the reappearance of signs of depression after a symptom-free and treatment-free period. This distinction is important because MDI warrants specific long-term preventive treatment whereas simple depression does not. Treatment can be envisioned for manic episodes, for depression, and for MDI (including recurrent unipolar disease).

Antidepressants belong to three broad categories according to mechanism of action: the monoamine reuptake inhibitors; the monoamine oxidase inhibitors; and the stimulants. Reuptake inhibitors include the classical tricyclic antidepressants such as imipramine, desipramine, and amitriptyline to cite the best known. These are generally non-specific inhibitors of monoamine reuptake, and will inhibit reuptake of serotonin, dopamine and noradrenaline to varying degrees. They also have activity on other receptors, especially on alpha-adrenergic, histaminic and cholinergic receptors. Their antidepressant activity is generally ascribed to the inhibition of uptake, though the precise mechanism by which uptake inhibition acts on depression remains a matter of conjecture.

Serotonin-specific inhibitors (SSRI) include fluoxetine, paroxetine, sertraline, citalopram and others. They are not more effective than the tricyclic antidepressants but may suit some patients better and are generally safer in overdose (see Geddes et al., 1999). While the SSRIs are devoid of the cardiac effects (membrane stabilisation, inhibition of conduction) of the tricyclics in overdose, they increase the risk of hemorrhage into the gut or brain.

Stimulants such as dexamphetamine and methylphenidate have also been used to treat depression. They are not widely used. They may have a faster onset of action and have been proposed to initiate treatment, during the time before the other antidepressants become effective.

Monoamine oxidase inhibitors (MAOIs) are as non-specific as the tricyclic uptake inhibitors but act through a different mechanism, with possibly the same final result – increasing neurotransmitter concentration in the synapse. Whether the final antidepressant effect is related to increased post-synaptic transmission or to post-synaptic receptor desensitization, or to other reasons is much discussed. MAOIs, by decreasing monoamine metabolism, increase the risk of severe hyperadrenergic (pseudophaeochromocytoma) or hyperserotoninergic (the serotonin syndrome) states, which can be fatal. This is more likely when they are given with drugs that modify monoaminergic metabolism, synaptic release or uptake, such as the classical or SSRI antidepressants, but also with beta-2 agonists, or other indirect adrenergic agonists that increase epinephrine release (e.g., nasal vasoconstrictors, ephedrine), or with tyramine-rich foods (fish, cheese, wines). Because of this severe risk of interaction, non-selective irreversible or long-acting MAOIs have been generally abandoned. More recent MAO-A selective drugs such as moclobemide seem safer, but there are published cases of interactions, especially when they are given too early after SSRIs such as fluoxetine, whose active metabolites have very long elimination half-lives. Extreme caution must be exercised when switching patients from one category of drugs to another, in both directions, or when associating other drugs to MAOI.

All placebo controlled studies of antidepressants have recently been reviewed (see Lima et al., 2005). The United States Food and Drug Administration (FDA) reports that 5 out of 10 subjects show a response to active treatment on rating scale measures, where 4 out of 10 show a response to placebo. The evidence suggests then that 80% of responders are responding to placebo factors. These placebo responses probably stem from the fact that the majority of subjects entered into antidepressant trials have a self-limiting condition that lasts on average 12–16 weeks, and can furthermore be helped by sensible advice as regards matters of lifestyle and diet, and simple problem solving of pertinent work related or domestic issues.

In trials of hospitalized patients tricyclic antidepressants have generally been more efficacious than selective serotonin reuptake inhibitors (SSRIs). Otherwise there are no overall differences between the drugs in terms of tolerability or efficacy in primary care settings. After reviewing 15 trials it was concluded that drugs are effective in the treatment of dysthymia with no differences between and within class of drugs. Tricyclic antidepressants are more likely to cause adverse events and dropouts. As dysthymia is a chronic condition, there remains little information on quality of life and medium or long-term outcome.

V.a. Manic Episodes

These are usually treated with sedative neuroleptics (as for schizophrenia, above). Treatment must also aim to support the patient socially including for instance advising on legal protection from the financial or other consequences of mania. One of the risks of treatment is the sudden mood swing at the end of the manic episode, with acute depression possibly triggered by the neuroleptics. Because of the concern for the manic episode and symptoms, return to normal is viewed with relief, and the downswing may go un-noticed, with the concomitant suicidal risk.

V.b. Depression

The major risk of severe depression is suicide, greatest during the downward mood swing or at the beginning of the upward swing during treatment. During the most severe period of depression, the risk is less because of intense motor and psychic inhibition preventing an active attempt on life. This risk also exists to a lesser degree in reactive depression, where the effects of depression are more manifest on social and professional functioning. Endogenous (MDI) depression is rare compared to reactive depression, whose range of symptoms can go from the "I'm feeling down today" to symptoms of full-blown major depression. Depression is rated on scales, the most used of which are the Hamilton depression rating scale (HDRS), and the Montgomery–Asberg Depression Rating Scale (MADRS). Though these are systematically used in clinical trials, they are rarely used in routine practice making it difficult to extrapolate to clinical practice.

Treatment of depression should follow a certain number of basic rules and concepts:

- The onset of treatment effect is slow. The reason for this is not known, and it contrasts with the quasi-immediate effect of the drugs on reuptake. The effect of the drugs presently available therefore cannot be judged before at least three weeks of treatment.
- The optimal duration of treatment is not firmly established. In isolated or primary care cases of depression treatment may not need to last any more than 3–6 months but in more severe or recurrent illnesses it may need to last longer if not indefinitely.
- On cessation, treatment should be tapered slowly. A proportion of patients have significant withdrawal symptoms to antidepressants on tapering that respond to the reinstitution of treatment. At present there is no known treatment for the physical dependence linked to antidepressants when severe other than gradual tapering.
- Because depression is often accompanied by anxiety, and antidepressant drugs often increase the anxiety, it is common to co-prescribe benzodiazepines at the beginning of antidepressant treatment. This has also the reputation of decreasing the early risk of suicide. This adjunct therapy usually does not need to be pursued more than 4–8 weeks, with careful tapering to avoid withdrawal symptoms that are a cause for benzodiazepine dependence or unjustified continued use.
- Because of the risk of suicide, patients should be carefully assessed for suicidal ideation and risk from the beginning of treatment. Most suicide attempts occur within 2 months of beginning of treatment. This justifies the use of drugs that carry a low risk in overdose, since most patients attempt suicide with their own medication in patients who are already suicidal. But some of these same drugs may lead to the emergence of agitation and suicidality in patients who at baseline appeared well.

V.c. Bipolar or Recurrent Disorders

Bipolar disease, or recurrent unipolar disease may be manic-depressive illness. This disease can manifest as typical bipolar disease, with alternating depressive and manic episodes, or as recurrent depression (or more rarely recurrent mania). The age of onset and frequency of recurrence may be highly variable, with at best a single episode, where the disease may be suspected from family history. The intensity of individual episodes may vary from the maximal intensities of depression, also called melancholia, or mania justifying rapid hospitalisation to barely pathological mood swings, where it is an alternation and

recurrence of mood changes that suggests mild underlying disease.

Treatment of MDI includes treatment of individual episodes, and preventive long-term treatment.

Treatment of individual episodes is described above. The treatment or monitoring of individual episodes of mania or depression should also take into account the risk of a swing to the opposite polarity induced by the treatment of the current episode (i.e., depression triggered by neuroleptic treatment of manic episode, or mania following antidepressant treatment). The speed of such a swing may take unwary physicians by surprise.

Long-term preventive treatment is based on drugs that prevent the occurrence of both depressive and manic episodes. The best known of these drugs is lithium though other drugs, such as valproate and more recently carbamazepine may have effects on the prevention of episodes. Lithium therapy is adjusted on serum lithium concentrations. Physicians should be aware of the more common adverse reactions, such as a fine distal trembling and multiple drug interactions (especially with diuretics), and of the risk of overdose, with potential renal, cardiac and neurological toxicity. Valproate is closely related to valproic acid, with the same advantages and inconveniences, and carbamazepine is an anti-epileptic drug that also has specific analgesic properties for facial neuralgia. All three drugs are old drugs that have been used long and widely for this or other indications, and are generally safe. Lithium is traditionally the drug of first choice, because the oldest and best known, though there have been no clear comparisons between the drugs that validate such an assumption.

Both lithium and valproate are teratogenic. In this case, women thinking of having children may be advised to switch to alternate treatments before the pregnancy.

In recent years second generation antipsychotics have been increasingly given as "mood-stabilizers". This is a largely marketing derived term. There is no difference between these second generation agents and older antipsychotics. The use of these drugs seems reasonable in very severe cases of manic-depressive illness but as bipolar disorders have become commoner and commoner, with increasing numbers of primary care patients likely to attract this diagnosis, the risks from these treatments seem disproportionate.

VI. NEUROTIC, STRESS-RELATED AND SOMATOFORM DISORDERS (ICD 10 CODES F40–F48)

This part of the classification covers many disorders, whose pharmacological treatment is not simple, clearly defined or univocal. Anxiety disorders may be alleviated by anti-anxiety drugs, or tranquillizers, the foremost of which are benzodiazepines. Although there have been concerns about the use of benzodiazepines, because of their effects on memory, and likely withdrawal symptoms, as well as abuse, these drugs remain among the most used of all drugs. It is probable that their use should not exceed a few weeks situational use, beyond which there is usually no longer any measurable effect, except that patients often have difficulties stopping them. They are also used for sedation and as hypnotics, and it is estimated that up to 30% of the older age groups use these drugs on a regular basis. They are not always recorded in medical charts, and the general practitioner may not be aware of their use, in that the user may not always be the person to whom the drugs are prescribed, especially in the elderly. In some studies, inadvertently stopping benzodiazepines at admission was the first cause for in-hospital seizures.

In recent years many of these primary care cases that would formerly have been seen as anxiety disorders have been portrayed as anxious-depressives and have led to treatment with antidepressants, in particular the more recent serotonin reuptake inhibitors. As part of this 'rebranding' a variety of states such as panic disorder, post-traumatic stress disorder, social phobia and generalized anxiety disorder have appeared, along with more traditional disorders such as obsessive compulsive disorder (OCD). Many of these diagnoses are likely to lead to prescriptions of an SSRI although the evidence for benefit from SSRIs is poor except for OCD.

As anxiolytics, benzodiazepines have faster onset of effect than SSRIs or antipsychotics. Their use is best limited to short-term situations, although there are likely to be comparable risks of dependence in these populations from all major classes of drugs.

VII. BEHAVIOURAL SYNDROMES ASSOCIATED WITH PHYSIOLOGICAL DISTURBANCES AND PHYSICAL FACTORS (ICD 10 CODES F50–F59)

This group of disorders covers many entities, from eating disorders, to sexual disorders, to otherwise

unspecified disorders or disorders related to other causes. Eating disorders include anorexia nervosa and bulimia nervosa. Weight maintenance in anorexia may be improved by fluoxetine, but drug therapy in this group is often compromized by the frequent use of voluntary vomiting and subsequent low drug compliance or absorption. Bulimia nervosa has been shown to be improved in several clinical trials by the use of antidepressant medication, independent of pre-existing depression. For most other disorders in this group it is impossible because of non-specificity to recommend or cite specific treatments other than that of an underlying disease when present.

VIII. OTHER ITEMS

Disorders of adult personality and behaviour (ICD 10 codes F60–F69), mental retardation (ICD 10 codes F70–F79), disorders of psychological development (ICD 10 codes F80–F89), behavioural and emotional disorders with onset usually occurring in childhood and adolescence (ICD 10 codes F90–F98) and unspecified mental disorder (ICD 10 code F99) are all often non-specific and/or cannot be treated with conventional psychopharmacological medicaments. For example, disorders of sexual behaviour have been treated with hormone therapies or antagonists and hyperkinetic disorders and other disruptive behaviour disorders in children have been treated with stimulants such as methylphenidate (Ritalin®).

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Chapter 39

Neurological Diseases*

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I. INTRODUCTION

Health care for patients with diseases of the central nervous system (CNS) has long suffered from its necessarily symptomatic approach. This situation greatly changed with the decade of the brain, inaugurated in 1990, when a large number of drugs emerged for use in a wide range of neurological diseases including dementia, migraine headache and multiple sclerosis. Such rapid progress in pharmacology has led to renewed interest in evidenced-based medicine for neurological diseases, using new therapeutic schemes with well-established risk/benefit ratios. Data from clinical trials, pharmacovigilance databases and pharmacoepidemiology studies are now available on drugs designed for neurological diseases, providing essential information for legislation and regulatory guidelines and reinforcing our opinion that these drugs and medical services offer practical contributions to patient care. This is the underlying concept of this chapter devoted to Neuropharmacology. For each disease, and for each therapeutic class, we will discuss indications, contraindications and differences in drug effects, guided by evidence-based decision making in the choice of each therapeutic regimen. In general, the drugs mentioned in this chapter are widely available in member countries of the European Union. Most all of the therapeutic strategies proposed are based on broad consensus or documented opinions. There remain of course differences in the reimbursement systems of the different countries.

II. EPILEPSY

II.a. Background

Epilepsy is a chronic often progressive disorder of the central nervous system (CNS). Periodic and unpredictable epileptic seizures caused by the abnormal electrical discharge of neurones in various anatomic structures of the CNS is the characteristic feature. This is an approximate definition based on international classifications of seizures and syndromes which take into account the extremely variable clinical and electroencephalographic expression of the disease. The annual incidence of epilepsy is an estimated 20–70 cases per 100,000 inhabitants with a prevalence of 0.4–0.8%. Globally, incidence is higher during childhood, remaining rather stable

* This chapter is dedicated to the memory of Prof. Hervé Allain who died on November 2006. Hervé cowrote this chapter for the first edition of this book. We miss him a lot.

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from 15 to 65 years then increasing again in elderly subjects. A neurological or systemic cause can be identified in 30% of all epilepsies; idiopathic or cryptogenic epilepsy is a general term applied to the other 70%. Approximately 5% of the general population will experience an epileptic seizure during their lifetime; 5% of all children will have a fever-induced convulsion. Schematically, seizures can be divided into two major categories, partial seizures (localized focus) and generalized seizures (bilateral, synchronous neuronal electrical discharges). Partial seizures can be further divided into two categories depending on progression or not to generalized seizures.

Likewise, generalized seizures are subdivided into absence (petit mal) and myoclonic, clonic, tonic, tonic–clonic and atonic seizures. A focus can be identified in 60% of all epilepsies (focal or partial epilepsies) with neuroimaging techniques, implantation of deep electrodes (stereoencephalography, SEEG) or magnetoencephalography (MEG). The choice of an anticonvulsant is based first on its proven efficacy in specific types of seizure or epileptic syndromes (40 distinct syndromes have been identified). A rich pharmacological armamentarium is available: most of the antiepileptic drugs (AEDs) achieved marketing approval before the seventies (first generation AEDs). A second series of AEDs became available in the nineties (second generation AEDs). A third generation (stiripentol, eterobarb, zonizamide) should lead to the ideal antiepileptic drug capable of preventing and treating epilepsy, completely freeing the patient from seizures and maintaining, or even improving, normal brain function in the interictal periods. These future products should reduce the number of drug-resistant patients (25%) who, in case of partial seizures, are currently candidates for epilepsy surgery.

II.b. Pathophysiology

According to the experimental model of psychomotor epilepsy, the fire which eventually triggers focal seizures kindles in the limbic system. This kindling circuit leads to exaggerated sensitivity to electrical stimulation. On the cellular level the kindling circuit is maintained by receptor hypersensitivity (particularly NMDA receptors) to excitatory amino acids (glutamate, aspartate) in the hippocampus (pyramidal cells in zone CA3). In parallel, gamma amino butyric acid (GABA) mediated transmission is diminished, particularly in circuits projecting to the pyramidal neurones of the hippocampus. Exaggerated glutaminergic neurotransmission appears as a marker of epileptogenesis and would explain the cell loss observed in chronic epilepsy as well as the abnormal dendritic sprouting observed in the temporal lobe of epileptics. The ion channels controlling chlorine ion flow in the CA1 and CA4 regions of the hippocampus, normally stimulated by GABA and benzodiazepine binding sites, are abnormal, producing what is termed channelopathies. In 20% of all epilepsies, identified neurochemical perturbations have a genetic basis: certain "abnormal" genes coding for ion channels cause benign familial neonatal seizures (potassium channel: chromosomes 20q13-3 and 8a24) or fever A seizure syndrome (sodium channel, CNS1B).

II.c. Principles of Treatment

Four main mechanisms of action underlie the beneficial pharmaceutical effect of AED: (1) blockade of the voltage-dependent sodium channels; (2) increased GABAergic inhibition of neurotransmission; (3) blockade of glutaminergic transmission; (4) blockade of type T calcium channels. AEDs are thus classed according to their known predominant effect:

- Sodium channel blockers: oxcarbazepine, carbamazepine, felbamate, valproic acid
- GABAergic drugs: vigabatrin, gabapentin, tiagabine, benzodiazepines, pregabalin
- Glutaminergic drugs: lamotrigine, topiramate
- Calcium channel inhibitors: ethosuximide, zonisamide.

For several reasons, this classification and the underlying theories of treatment are necessarily artificial: (1) All of these drugs have several neurochemical effects. (2) No one mechanism of action is strictly correlated with an anti-seizure activity. (3) The older drugs (e.g. barbiturates) have not necessarily been reevaluated in light of the more recent neurobiological data. (4) Products under development may act on other, different targets (e.g. cromakalim analogues affect the opening frequency of ATP-dependent potassium channels) and the precise mechanism(s) by which levetiracetam exerts its antiepileptic effect is unknown.

Theoretically, the ideal AED would act on the brain during seizures (and the very short-lived neurochemical correlate) (e.g. agents affecting ion channels) and protect against the long-term deleterious effects of excitatory neurotransmission (e.g.

AMP/Kainate and glutamate NMDA receptor blockers which have a neurocytoprotector effect). Theoretically, a substance with multiple actions should be effective against many types of seizure and, most importantly, allow a single-drug regimen and thus avoid the risks of drug–drug interactions.

II.d. Therapeutic Benefits

II.d.1. Preliminary Comments

There is a large body of literature on assessment of the therapeutic benefit of AEDs, mostly composed of comparative clinical trials. A few meta-analyses have been performed. For any given AED, it is sometimes difficult to formulate an opinion due to the different methodologies used for assessment: tested alone or as an add-on drug, wide range of dosages, different types of seizures or epileptic syndromes. Classifications of indications and recommendations for use vary accordingly.

II.d.2. Therapeutic Efficacy

The efficacy of the main AEDs providing a recognized therapeutic benefit can be best presented in a table. Table 1 can be used as a guide for choosing a drug for a given type of seizure. It summarizes the numerous clinical trials focusing precisely on certain types of seizures or syndromes. Table 2 gives more detailed information on some newer anticonvulsants. A systematic review of four trials with a total of 750 randomized patients that can be found in the Cochrane database concludes: "Gabapentin has efficacy as an add-on treatment in patients with drug resistant partial epilepsy. However, trials reviewed were of relatively short duration, and provide no evidence for the long term efficacy of gabapentin. Results cannot be extrapolated to monotherapy or patients with other epilepsy types".

An other Cochrane review of nine trials representing 1049 randomized patients concludes: "Topiramate has efficacy as an add-on treatment in patients with drug resistant partial epilepsy. However, trials reviewed were of relatively short duration, and provide no evidence for the long term efficacy of topiramate. Results cannot be extrapolated to monotherapy or patients with other epilepsy types".

Finally, a systematic review of ten trials including 2036 patients dealing with the prevention of seizures after brain injury concludes: "Prophylactic anti-epileptics are effective in reducing early seizures, but there is no evidence that treatment with prophylactic anti-epileptics reduces the occurrence of late seizures, or has any effect on death and neurological disability. Insufficient evidence is available to establish the net benefit of prophylactic treatment at any time after injury".

II.e. Therapeutic Risks

II.e.1. Background

Both first and later generation antiepileptic drugs must be carefully monitored due to the large number of patients on long-duration treatment regimens

Table 1. Treatments for epilepsy

Partial seizures	Tonic–clonic generalized seizures	Complex partial seizures	Absence	Generalized seizures: Status epilepticus
Phenytoin	Phenytoin	Phenytoin	Valproic acid	Phenytoin
Carbamazepine	Carbamazepine	Carbamazepine	Ethosuximide	Fos-phenytoin
Oxcarbazepine	Oxcarbazepine	Phenobarbital	Clonazepam	Phenobarbital
Phenobarbital	Phenobarbital	Primidone		Diazepam
Pregabalin	Primidone			Lorazepam
Primidone	Valproic acid			
Gabapentine	Gabapentine			
Vigabatrin	Vigabatrin			
Levetiracetam	Felbamate			
Lamotrigine	Zonisamide			
Topiramate	Nitrazepam			
Clobazam	Tiagabine			
Zonisamide				
Nitrazepam				
Tiagabine				

Table 2. Some newer antiepileptic agents

	Zonisamide 2000–2005*	Levetiracetam 1999–2000	Lamotrigine 1994–1995	Tiagabine 1997–1998	Topiramate 1995–1996	Oxcarbazepine 2000	Pregabalin 2004
Child (mg/kg/day)	3–30	20-60	5–15			10–40	
Adult (mg/day)	100–400	1000–500	200–500	30–60	200–1000	600–3000	150–300
Half-life Monotherapy (h)	60	7 (4–12 y: 5)	30	6	20	8–10	5–7
Protein binding (%)	40	0	55	96	15	40	0
Numbers of drug intakes	1 or 2	2	2	3	2	2 or 3	2 or 3
Elimination	Kidney	Mainly kidney	Liver	Liver	Liver + kidney	Liver	Kidney
Hepatic enzyme induction	0	0	0	0	Weak	Moderate	0
Tablets formulations	100 mg (capsules)	250–1000 mg (also oral solution 100 mg/ml)	25, 100 mg	5, 10, 15 mg	100 mg	300 mg	25–300 mg (capsules)

*Marketing approval in US, UK and/or France.

and to the frequency of adverse effects which modulate patient compliance, treatment continuation and dose titration.

- The adverse effects of AED are perfect examples of the principles of pharmacovigilance and pharmacoepidemiology. They are of variable gravity (from weigh gain to Stevens–Johnson syndrome), classed *type* A (sedation and fatigue for barbiturates and benzodiazepines, sexual and libido disorders) or *type* B (medullary aplasia for felbamate, kidney stones for zonisamide, alopecia for valproic acid), develop early after treatment onset (sedation for primidone, nystagmus for cabamazepine) or late (cerebellar syndrome for phenytoin, leukopenia for ethosuximide or valproic acid, Dupuytren's disease for barbiturates), are dose-dependent (gingival hyperplasia for phenytoin, initial skin rash for lamotrigine), or finally mimic the disease itself (aggravation of the epilepsy).
- In all programs for the development of new AEDs, special attention must be given to the serious questions of impact on cognition, neuropsychologic effects and intellectual development (AEDs appear to have no significant effect on cognition).
- In accordance with these general points, all adverse effects must be reported to the nearest Pharmacovigilance Center. This Center makes the causality assessment and may initiate any necessary national surveys (e.g. concentric narrowing of the visual field with vigabatrin in 30% of cases) for guiding new regulatory measures (e.g. very strict laboratory monitoring is required when using felbamate for Lennox–Gastaut syndrome due to the risk of medullary aplasia and hepatotoxicity).
- Risk assessment for a given drug is highly dependent on the methodology used and in all cases must not rely solely on an analysis of data from clinical trials. It must be recalled that for AED, underreporting of adverse effects appears to be a chronic defect. In addition, it can sometimes be difficult to attribute cause to a specific drug due to the frequency of comedications and the absence of the habitual mechanistic explanation of the observed phenomena.

II.e.2. Facts

II.e.2.1. Early events. Central nervous system:

(1) tolerable sedation and tiredness occur with most of the first generation AEDs;
(2) vertigo, motor incoordination, diplopia, and nystagmus are observed with phenytoin and carbamazepine;
(3) sedation and ataxia occur with zonisamide; diplopia, visual disorders, headache and somnolence with lamotrigine;
(4) coma is exceptionally reported with valproic acid and bigabatrin.

Gastrointestinal tract:

(1) anorexia, nausea, vomiting, and gastric pain are often reported in patients given primidone, ethosuximide, zonisamide and valproic acid;

(2) elevated gamma-GT occurs with phenobarbital, phenytoin and carbamazepine;
(3) liver toxicity is exceptional with valproic acid (genetic metabolic anomaly) but is a crucial problem with felbamate;
(4) pancreatitis has been reported with valproic acid.

Skin and mucosa:
(1) skin rash is a frequent adverse effect and requires drug discontinuation;
(2) severe reactions have been reported including epidermolysis, Stevens–Johnson syndrome, polymorphous erythema; almost all AEDs may be incriminated with the exception of gabapentin, felbamate and vigabatrin;
(3) with lamotrigine, skin rash occurs early and is dose-dependent; it is more frequent in combination regimens with valproic acid.

II.e.2.2. Late events. Central nervous system:
(1) sedation, tiredness, daytime somnolence, and vertigo occur with the majority of the AEDs but are generally tolerated;
(2) with vigabatrin, sedation is transitory but with zonisamide it remains a persistent problem (associated with headache);
(3) chronic encephalopathy has been reported with phenytoin;
(4) involuntary movements of all types occur with phenobarbital, carbamazepine and valproic acid;
(5) cerebellar syndromes occur with phenytoin;
(6) neurocognitive disorders including irritability, aggressiveness and memory disorders are reported for vigabatrin, as well as depression for phenobarbital and even vigabatrin;
(7) psychotic episodes may occur in patients taking ethosuximide or vigabatrin.

Peripheral nervous system: peripheral axonal neuropathy with phenytoin, carbamazepine and phenobarbital.

Hematopoietic system:
(1) leukopenia is generally benign with the older drugs;
(2) medullary aplasia may occur with carbamazepine, and especially felbamate;
(3) thrombocytopenia occurs with valproic acid;
(4) folate deficiency is observed with phenobarbital, phenytoin and carbamazepine.

Metabolic disorders:
(1) vitamin D3 deficiency (osteomalacia) with phenobarbital, primidone, phenytoin;
(2) hyponatremia and water retention may be observed with carbamazepine and oxcarbazepine;
(3) patients gain weight with valproic acid, vigabatrin and gabapentin.

Other systems:
(1) kidney stones occur with zonisamide; urinary lithiasis with topiramate;
(2) vigabatrin may cause narrowing of the visual field;
(3) cardiac conduction disorders are observed with phenytoin and carbamazepine, particularly in elderly subjects;
(4) hirsutism is reported with phenytoin;
(5) systemic lupus erythematosus has been observed with first generation AEDs;
(6) the antiseizure effect may wear off with benzodiazepines and perhaps vigabatrin.

II.e.3. Specific Clinical Conditions

- Children: paradoxical agitation is a possible adverse effect of all AEDs.
- Pregnancy: the exact cause of malformations is difficult to establish as epilepsy itself may cause foetal malformations (neural tube, clef palate . . .). Folate supplementation is considered to have a preventive effect.
- Elderly: no data specifically concerning the elderly is available for second generation AEDs; adverse effects with first generation AEDs result from kinetic alterations; carbamazepine is often poorly tolerated.
- Depression and bipolar states: viagabatrin is contraindicated.

II.e.4. Seizure-Inducing Drugs

The list of drugs capable of inducing epileptic seizures is impressively long. A drug cause should always be suspected.

AEDs themselves may contribute to the expression of seizure due to:
(1) overdosage (e.g. carbamazepine may trigger negative myoclonia and phenytoin may cause progressive myoclonic epilepsy) or
(2) sudden withdrawal (real risk of status epilepticus, lamotigine and refractory absences).

In normal dosages juvenile myoclonic epilepsy may be induced with lamotrigine.

Tolerance may occur which means that the effect of some AEDs may wear off with time (benzodiazepines, barbiturates, vigabatrin). There are exceptional cases where refractory epilepsy escapes

drug control (Lennox–Gastaut syndrome, severe myoclonic epilepsy in infants).

An inappropriate drug choice may be responsible. In children with generalized epilepsy, carbamazepine may induce tonic–clonic seizures; vigabatrin can exacerbate myoclonal tonic–clonic seizures and absence. Schematically, typical absences and generalized seizures are aggravated by tiagabine, vigabatrin, gabapentin and carbamazepine. GABAergic drugs should be avoided for patients with myoclonia.

II.e.5. Drug Interactions

II.e.5.1. Background. The most important drug interactions result from pharmacokinetic (PK) phenomena. Pharmacodynamic (PD) interactions are poorly understood in humans (receptor level interaction; potentiation of effect by action on different targets). Classically, PK interactions occur at the enzyme level. Careful attention to this factor should help limit the incidence of adverse effects, make it easier to maintain plasma levels within the therapeutic range, and demonstrate the benefit of certain therapeutic combinations. Clinical trials on add-on regimens are needed. It should be noted that the clinical relevance of certain PK interactions remains to be established.

Unlike first generation AEDs which present numerous PK interactions (metabolism, protein binding) and PD interactions (sedation, cognitive disorders), the newer AEDs do not have these drawbacks. Observations include: (1) elevated gabapentin plasma levels with cimetidine, likewise for tiagabine given with erythromycin; (2) reduced digoxin levels in patients taking topiramate; (3) accelerated metabolism of lamotrigine with paracetamol.

II.e.5.2. Interactions between first and second generation AEDs. Felbamate raises plasma concentrations of phenytoin, valproic acid and carbamazepine. Clearance of tiagabine, topiramate and zonisamide is increased in the presence of an enzyme inducer. Vigabatrin reduces phenytoin concentrations after 4–5 weeks of comedication (via an unknown mechanism). For tiagabine, the elimination half-life may be reduced by 2–3 hours in the presence of an enzyme-induction AED. Lamotrigine elimination is slower if given with valproic acid. Topiramate reduces elimination of phenytoin.

To date, there are few data demonstrating PK interactions between second generation AEDs. Felbamate has been found to increase plasma concentrations of lamortrigine.

II.e.5.3. Interactions with oestroprogestogens. Very schematically it can be said that all first generation AEDs are enzyme inducers and interact with oestroprogestogens. High-dose contraceptives must be used.

With the exception of topiramate (which also requires a high-dose oestroprogestogen), second generation AEDs are not considered to interfere with oestroprogestogen metabolism. The enzyme induction capacity of oxcarbazepine is much weaker than that of carbamazepine.

It should be noted however that to date we do not have enough follow-up and that all studies on interactions have tested doses generally lower than those recommended for therapy.

II.e.6. Monitoring Serum Levels

Serum levels of first generation AEDs should be monitored regularly (fasting sample drawn in the morning before drug administration to assess steady-state kinetics). Monitoring is particularly important when dosage is changed, a new drug is added, or in case of therapeutic escape.

There are four reasons for monitoring serum levels: dose titration; understand interactions; limit adverse effects; check compliance.

- Limitations of serum levels: pharmacokinetic parameters determined in blood are not closely indicative of the situation in the central compartment (here the CNS); serum levels are not correlated with activity (pharmacodynamics); in general, only the mother molecule is assayed although its metabolites may be active or toxic; the relationship between concentration (PK) and activity (PD) is often complex; assays of free forms would be more pertinent.
- For the time being, no guidelines for monitoring serum levels of second generation AEDs have been established.

II.f. Advice for Patients and Families

Currently available drugs can only offer symptom relief or a preventive effect. The advice of a specialist is generally needed to choose the appropriate drug, determine the right dosage, and assess the possible benefit of combination regimens. Cases of true drug resistance are very exceptional. The acceptability of the new AEDs is an major progress.

III. PARKINSON'S DISEASE

III.a. Background

Idiopathic Parkinson's disease is a neurodegenerative disease diagnosed clinically on the basis of typical signs (akinesia, rigidity, tremor) sometimes associated with sialorrhoea, orthostatic hypotension, depression, or even dementia, generally in the late stages of the disease. Estimated prevalence is 160 per 100,000 inhabitants, with an incidence of 20 cases per year per 100,000. Disease onset generally occurs in the fifth decade although very early and very late onset is also observed.

III.b. Pathophysiology

The characteristic histological feature of Parkinson's disease is the presence of Lewy bodies in dopaminergic neurones of the pars compacta of the brain stem locus niger. Cell death (apoptosis or necrosis) follows, explaining the fall in dopamine concentrations in the nigro-striate circuit and postsynaptic dopaminergic receptor sparing. Three etiological mechanisms have been put forward to explain this selective cell death: (1) oxidative stress on locus niger cells; (2) specific neurotoxicity similar to that provoked by MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine); (3) glutamate hyperactivity.

III.c. Principles of Treatment

III.c.1. Neuroprotection

The fact that no marker of disease progression has been identified in humans would explain in part why all attempts to demonstrate a cytoprotective effect have failed, or at best given inconclusive results. Among the proposed strategies, we can mention: use of antioxidants (alpha-tocopherol up to doses of 4,000 mg/d; ascorbic acid), monoamine oxidase B inhibitors (MAOI-B, predominantly selegiline), glutamate NMDA receptor inhibitors (only one non-selective inhibitor, amantadine, has been studied in Parkinson's disease). Likewise, as levodopa may be toxic and may aggravate oxidative stress, studies have been designed to examine the effect of low daily doses or abstention (replacement by dopaminergic agonists), at least during the first years of the disease, but have not demonstrated any convincing long-term effect. Finally, the potentially cytoprotective effect of dopaminergic agonists (bromocriptine, lisuride, piribedil) has only been demonstrated *in vivo* in animal models.

III.c.2. Symptomatic Treatment

Drugs currently used for the treatment of Parkinson's disease are essentially aimed at relieving the cardinal symptoms (akinesia, rigidity, tremor) but have no beneficial effect on certain associated signs: postural instability, dysarthria, dysphagia, ocular motility disorders, impaired independence. These drugs act via four mechanisms: (1) they limit cholinergic hyperactivity in the striatum secondary to disruption of dopaminergic inhibition (anticholinergic effect); (2) the dopamine precursor levodopa restores striatal dopamine concentration; (3) they inhibit catabolism of residual endogenous or levodopa-derived dopamine by inhibiting either the MAO-B pathway (MAOI, selegiline) or the catechol-methyl transferase pathway (COMTI: tolcapone, entacapone); (4) they stimulate postsynaptic receptors (direct dopaminergic agonists).

Other symptomatic therapeutic interventions are surgical procedures and deep brain simulation with three targets: ventral intermediate nucleus of thalamus, the internal segment of the globus pallidus and the subthalamic nucleus.

III.d. Therapeutic Benefits

III.d.1. Preliminary Comments

All of the more recent compounds have been tested in randomized double-blind clinical trials using the Unified Parkinson's Disease Rating Scale (UPDRS). We do not however have studies comparing the different drugs nor different treatment durations. In addition, the length of these trials is totally different from that of the natural disease course (20 years). It is paradoxical that levodopa, developed in the sixties, remains today the mainstay treatment for Parkinson's disease (levodopa is always associated with a peripheral decarboxylase inhibitor, either carbidopa or benzerazide).

III.d.2. Anticholinergic Drugs

These drugs were developed before levodopa which has largely replaced them, probably because of a lack of modern clinical research. Actually, the adverse effects of anticholinergic drugs (confusion, memory disorders, peripheral anticholinergic effects) and the interindividual variability of their effects considerably limit their use, particularly in subjects over 65 years of age. These compounds are considered to be effective against tremor and are

used as adjuvant treatment with levodopa in patients with motility fluctuations. The most widely used drugs are trihexyphenidyl (1 mg/d for 3 days, then 2 mg increments the following days to reach a maximum dose of 2 mg t.i.d.) and benztropine (beginning with 1 mg/d to reach a maximum dose of 6 mg/d in one week).

III.d.3. Amantadine

Amantadine is an old drug with several pharmacological properties warranting its (empirical) use in Parkinson's disease: facilitation of dopamine release, blockade of dopamine re-uptake, anticholinergic effect, blockade of NMDA receptors. Amantadine is usually employed early in the disease process (monotherapy, 100 mg b.i.d.) and most often in combination with levodopa in more advanced stage disease (anti-dyskinesia effect?).

III.d.4. Dopaminergic Agonists

The leading dopaminergic agonist is bromocriptine, followed by lisuride, ropinirol, cabergoline, pergolide, pramipexol, piribedil, and apomorphine. These compounds differ by their chemical structure (the older drugs are ergot derivatives), their pharmacokinetics, and most importantly by their impact on the receptors (e.g. ropinirol is a selective agonist of the dopaminergic D2 receptors, pramipexol and piribedil are selective for D2 and D3 receptors and apomorphine for D1 and D2 receptors). These elements explain the wide variation in daily dosages and administration routes (apomorphine is administered subcutaneously and has an effect which lasts no longer than 2 hours) and the pattern of adverse effects (particularly peripheral effects). All these drugs have an effect on the cardinal signs of Parkinson's disease (as evaluated on the UPDRS) either given alone (in early stages) or in combination with levodopa.

For all agonists, it is advisable to progressively increase the daily dose to reach optimal dose by plateaus. The optimal dose is titrated individually. In combination with levodopa, dopaminergic agonists lower the daily requirements for dopa and, after years of treatment, would prolong the duration of on phases and limit fluctuations in motricity and dyskinesia. Apomorphine is only indicated for patients with on–off swings, either via single-dose subcutaneous injections or a continuous infusion.

Two reviews with respect to the efficacy of pergolide for levodopa-induced motor complications can be found in the Cochrane data base. The reviewers of one single large multicentre study conclude: "Pergolide reduces 'off' time and improves impairment and disability due to Parkinson's disease whilst allowing a reduction in levodopa dose. This is at the expense of dopaminergic adverse events". Further trials are required to compare pergolide with the newer dopamine agonists. For the other review three short-term trials fulfilled the inclusion criteria. The reviewers conclusions are: "Although pergolide is superior to bromocriptine in reducing motor impairments and disability, no firm conclusions regarding levodopa-induced motor complications can be reached. Levodopa dose reduction, adverse events and withdrawals from treatment are similar for the two agonists. The small advantage of pergolide in efficacy does not take into account its additional cost compared with bromocriptine".

III.d.5. Enzyme Inhibitors

Selegiline is an irreversible inhibitor of type B monoamine oxidase (MAOI-B), an enzyme involved in the catabolism of endogenous and exogenous dopamine; this compound has several other properties and active metabolites including 2-phenylethylamine, L-amphetamine and L-metamphetamine. Selegiline is used either at the dose of 10 mg/d given morning and evening in a monotherapy regimen (usually in the early stage of the disease) or more often in combination with levodopa. A large-scale clinical trial conducted in North America in 1989 (DATATOP) was unable to clearly demonstrate in humans the cytoprotective effect suspected from *in vitro* and animal studies.

Rasagiline is a selective, potent irreversible inhibitor of MAO-B that possesses neuroprotective and anti-apoptotic properties in a variety of in vitro and *in vivo* animal models relevant to Parkinson's disease (PD). Several randomized controlled clinical trials have demonstrated the safety and efficacy of rasagiline as monotherapy in PD and as adjunctive therapy for patients receiving levodopa. Of greater interest is the potential neuroprotective effect of rasagiline and its major metabolite, 1(R)-aminoindan, which may have great utility in a wide variety of neurodegenerative disorders of aging.

Entacapone is a reversible inhibitor of peripheral catechol-O-methyltransferase (COMT). It is given at the dose of 200 mg with each dose of levodopa. It prolongs the action of levodopa and reduces synthesis of 3-O-methyldopa which is presumed to antagonize dopa passage through the blood–brain barrier.

Entacapone is indicated in combination with levodopa in patients with motility fluctuations (more than 1 hour gain in the 9–10 hour on phase). Marketing approval was awarded for entacapone just after tolcapone, a central and peripheral COMTI, was withdrawn from the market because of fulminant hepatitis.

III.d.6. Levodopa

Levodopa, the metabolic precursor of dopamine, is available in drug formulations in combination with a peripheral inhibitor of dopa-decarboxylase which limits peripheral synthesis of dopamine and favors central availability. This drug remains the mainstay treatment for Parkinson's disease despite the well-known variability of its effect, basically due to peripheral and central pharmacokinetics which vary as the disease progresses. As orally administered levodopa is mainly absorbed in the duodenum, any factor affecting stomach emptying affects the latency period and the motor response to levodopa (size of meal, hyperacidity, anticholinergic agents). Epithelial transport, both in the duodenum and at the blood–brain barrier, can be saturated as it depends on a mechanism shared by large neutral amino acids (LNAA) and 3-O-methyldopa (mentioned above). The plasma half life is short, explaining the need for 3–4 administrations per day. The duration of action does not exceed 3 hours. Pharmacokinetic-pharmacodynamic modelling and the rare studies using intravenous levodopa or subcutaneous apomorphine show that as the disease progresses, the pharmacokinetics of levodopa change with a trend towards longer but reduced action. As the effect of levodopa wears off, the dose–effect curve becomes steeper and the therapeutic window becomes narrower (lower threshold for the dyskinetogenic dose). The central pharmacokinetics of levodopa is considerably modified by the disease itself via changes in dopaminergic synaptic mechanisms during the disease course. This has led to considerable efforts in pharmacology to develop different forms of levodopa (controlled release formulations) or administration protocols avoiding the pharmacokinetic problems (continuous therapy, parenteral administration, duodenal infusion, effective mini-doses several times a day). Schematically, levodopa can be administered early in the disease course at daily doses not exceeding 300–500 mg (although the theoretical basis remains poorly established). As the disease progresses, smaller unit doses given at shorter intervals or controlled release formulations may be helpful but greatly depend on the skill of the prescriber. The addition of other agents (dopaminergic agonists, enzyme inhibitors) would, in theory, provide regular continuous stimulation of the dopaminergic receptors in the striatum. Likewise and although the theoretical arguments are weak, controlled release formulations given at bedtime would limit night-time symptoms and reduce early morning dystonia.

III.e. Therapeutic Risks

III.e.1. Type A Effects

Compounds which stimulate central and peripheral dopaminergic neurotransmission induce a common set of pharmacodynamic effects which, by definition, are dose-dependent and antagonized by any substance antagonizing dopaminergic receptors (e.g. neuroleptics). Classically, the worsening of clinical signs in patients given very low dose antiparkinsonian drugs is explained by a preferential stimulation of presynaptic dopaminergic receptors (D2 receptors) limiting release of endogenous dopamine. Typical type A effects include nausea, vomiting, and orthostatic hypotension which may respond to a transitory (1 month) regimen adding domperidone 3 times a day (30–60 mg/d). This antiemetic drug is not considered to cross the blood–brain barrier. True type A side effects concern the extrapyramidal motor pathways and are expressed clinically by dyskinesia or induced involuntary movements. These phenomena result from a complex pathophysiological mechanism implying small unit doses and optimal administration rhythm. Early introduction of dopaminergic agonists in single-drug regimens for long-term prevention of these complications is currently under clinical investigation. Finally, hallucinatory phenomena can produce dopaminergic psychosis which appears to be more related with age and the development of dementia than with the antiparkinsonian drug itself (levodopa would appear to be the safest compound, explaining its preferential indication in subjects over 70). Antipsychotic drugs are warranted in the case of dopaminergic psychosis. Atypical antipsychotics including clozapine, appear to be safe, having no effect on motor function unlike classical neuroleptics which are almost unusable in Parkinson's patients even at very low doses (risperidone $<$ 1 mg/d; tiapride $<$ 200 mg/d). Finally, it is important to recall briefly the major risk with anticholinergic

agents, especially in patients over 65 years of age. They can provoke confusion and cognitive disorders which are much worse than the usual anticholinergic type of manifestations (dry mouth, accommodation disorders, bladder atonia).

III.e.2. Type B Effects

Type B effects are rare but should be recognized. They include oedema of the lower limbs (bromocriptine, amantadine), livedo reticularis (amantadine), diarrhoea (tolcapone, entacapone), paroxysmal hypertension and dysregulation of blood pressure control (selegiline), narcoleptic phenomena (pramipexole), and insomnia (all dopaminergic agonists).

III.e.3. Drug Interactions

Antiparkinsonian drugs have a mutually potentiating effect, multiplying the risk and intensity of type A effects in combination regimens. A more serious problem, often the reason for consultation or hospitalization, is the risk of negative interaction, generally due to pharmacodynamic interaction between antiparkinsonian drugs and neuroleptics (haloperidol, thioridazine, benzamides) or other drugs (fluanarizine, cisapride). One should always keep in mind the risk of aggravating the disease in a formerly well controlled patient by adding a selective serotonin re-uptake inhibitor (SSRI) for depression. The same precaution must be taken when prescribing diltiazem, cordarone, or buspirone. Finally combining selegiline and an SSRI can produce a serious serotonergic syndrome (confusion, dysregulation of blood pressure control, myoclonia, diarrhoea).

III.f. Advice for Patients and Families

To date, the drugs proposed for the treatment of Parkinson's disease can only provide symptom relief. After a few years of treatment, dosages and drug combinations must be revisited regularly in a constant search for the best quality of life. Certain symptoms cannot be controlled by drugs. Levodopa remains the most well known and most manageable drug. Alternatives to drug therapy (foetal tissue grafts, neurostimulation of the subthalamic ganglia) are currently under investigation to determine their long-term effects and the pharmacological adjustments required. Stimulation of the subthalamic nucleus has been proved to be highly promising and many small and non-controlled studies seem to demonstrate that this intervention induces a major motor improvement and allows the reduction of levodopa complications (see Lang and Widner, 2002).

IV. ALZHEIMER'S DISEASE

IV.a. Background

The diagnosis of Alzheimer's disease (AD) is currently based on the criteria of the Diagnostic and Statistical Manual of Mental Disorders (fourth edition) (DSM IV-TR) and the National Institute of Neurological Disorders and Stroke–Alzheimer Disease and Related Disorders (NINCDS–ADRDA) work group. These criteria are fulfilled within a two-step diagnostic process where there is initial identification of a dementia syndrome and then the application of criteria based on the clinical features of the AD phenotype. The DSM IV criteria require the presence of both a memory disorder and impairment in a second cognitive domain, each of which is severe enough to interfere with social function or daily living activities. ADL impairment in turn has come to define the threshold for the diagnosis of dementia. The NINCDS–ADRDA clinical criteria of probable AD include the specification that the onset of AD is insidious and that there is a lack of other systemic or brain diseases that may account for the progressive memory and other cognitive deficits. In addition to cognitive symptoms, neuropsychiatric symptoms are prominent features in Alzheimer's disease because they are responsible for a large share of the suffering of patients and caregivers, and they strongly determine the patient's life-style and management. These symptoms occur at some point in the course of the illness in up to 90% of patients with Alzheimer's disease (AD), although there is a marked inter-individual variability.

This combination of criteria supports a probabilistic diagnosis of AD and a definite diagnosis of AD is only made when in addition to clinical criteria histopathological confirmation is obtained. Risk factors include age, familial cases, cardiovascular risk factors, marital status, apolipoprotein genotype E (APOE-4), mutation of certain genes (presenilin 1, presenilin 2, gene coding for the β-amyloid precursor protein (β-APP)). The prevalence of AD is an estimated 2% at the age of 65 years and reaches 30% at 80 years, with increasing incidence with age. The incidence is about 2:1000 between 65 and 69 years and reaches 70:1000 after 90 years with a predominance in Northern Europe. As the population ages in the European Union, the expected rise in the number of persons over 60 years of age explains the concerns of medical and political decision makers and the recent activation of pharmacological

research into a still poorly understood disease which causes major familial suffering (it is estimated that approximately 850,000 subjects currently have AD in France (in 2004) with an expected 1,300,000 in 2020). In the world it is estimated that approximately 24,300,000 subjects currently have AD with an expected 80,000,000 in 2040 (based on a Delphi consensus).

IV.b. Pathophysiology

There are three main histological features characteristic of Alzheimer's disease:

(1) diffuse neuron loss in the hippocampus and neocortex;
(2) accumulation of intracellular protein deposits (*tau* protein) leading to neurofibrillary degeneration (neurofibrillary tangles);
(3) an accumulation of extracellular protein deposits called senile plaques or amyloid plaques around abnormal nerve endings (dystrophic neuritis). One of the main constituents of these plaques is β-amyloid peptide (Aβ), a protein composed of 40–42 amino acids resulting from secretase mediated physiological cleavage of the Aβ precursor protein (APP). According to the amyloid theory, Aβ aggregates and accumulates as a result of genetic mutations and/or environmental factors. Genetic studies of the rare and genetically simple early onset have led to the identification of several single gene lesions in the amyloid precursor protein (APP) and in the presenilins. All of these mutations are near to site within APP that are normally cleaved by protease called the alpha, beta and gamma secretase.

All of the major neurotransmission systems are altered, either as a consequence or as a cause of the disease, and sometimes quite early in its course, explaining the wide range of clinical signs. The earliest and most intense lesions appear to occur in the cholinergic neurons of the nucleus basalis of Meynert. This is the basis of the cholinergic theory of AD; the fact that the post-synaptic cholinergic receptors (muscarinic and nicotinic receptors) remain intact has incited pharmacological work aimed at restoring this cholinergic neurotransmission.

Today AD can be easily recognized when memory and other cognitive and behavioural deficit are sufficiently severe to interfere with normal daily activities. Unfortunately, at this point in the patient's lifetime, the accumulation of amyloid plaques and neurofibrillary tangles in medial cortex has been started for decades and has irreversibly affected synapses and neurons viability.

This explain why an earlier identification of patients before symptoms develop at the earliest possible stage of the disease is desirable and would allow an effective intervention with antiamyloid drugs, which are currently being tested worldwide.

The rapid growth of knowledge around the potential pathogenic mechanisms of AD including the amyloidopathy and taupathy has spawned numerous experimental therapeutic approaches to enter into clinical trials. There is accruing evidence that years before the onset of clinical symptoms there is an AD process evolving along a predictable pattern of progression in the brain. The neurobiological advantage of earlier intervention within this cascade is clear and represents the underpinning of these disease modifying therapies that are now being investigated. Earlier intervention is likely to be more effective when there is a lower burden of amyloid and hyperphosphorylated tau as well as truncating the ill effects of secondary events due to inflammatory, oxidation, excitotoxicity and apoptosis. By the time there is clear functional disability, the disease process is significantly advanced and definitive intervention is likely to be elusive. Revised research criteria would allow diagnosis when symptoms first appear, prior to full-blown dementia, thus supporting earlier intervention. This explain why research of brain imaging and biological marker is one of the major research field at the moment.

According to the pathophysiology of the disease, several type of pharmacological treatment can be described:

- symptomatic treatment currently available
- disease modifying treatment in development.

IV.c. Symptomatic Treatment

IV.c.1. Cholinesterase Inhibitors

Donepezil, rivastigmine and galantamine are the three available cholinesterase inhibitor (ChEI) and all work by inhibiting the breakdown of acetylcholine, an important neurotransmitter associated with memory, by blocking the enzyme.

Randomized, double blind, placebo controlled trials (RCT) demonstrated that treatment for periods of 6 months and one year, with donepezil, galantamine or rivastigmine at the recommended dose for people with mild, moderate or severe dementia due

to Alzheimer's disease produced improvements in cognitive function measured with the ADAS-Cog scale on average −2.7 points.

Benefits of treatment were also seen on measures of activities of daily living and behavioural disturbances. Although there is less evidence for other than mild to moderate dementia. There is evidence of more adverse events in total in the patients treated with a ChEI than with placebo. Although many types of adverse event were reported, nausea, vomiting, diarrhoea, were significantly more frequent.

According to the UK National Initiative for the Care of the Elderly only specialists in the care of people with dementia (that is, psychiatrists including those specialising in learning disability, neurologists, and physicians specialising in the care of the elderly) should initiate treatment. Carers' views on the patient's condition at baseline should be sought.

Patients who continue on the drug should be reviewed every 6 months by MMSE score and global, functional and behavioural assessment. Carers's views on the patient's condition at follow-up should be sought.

IV.c.2. Memantine

A dysfunction of glutamatergic neurotransmission, manifested as neuronal excitotoxicity, is involved in the aetiology of Alzheimer's disease. Targeting the glutamatergic system, specifically NMDA receptors, offers a novel approach to treatment in view of the limited efficacy of existing drugs targeting the cholinergic system. Memantine is an N-methyl-D-aspartate (NMDA) receptor antagonist. Two RCTs met the inclusion criteria set by the Assessment Group for the systematic review of the clinical effectiveness of memantine. Both studies reported on participants with moderately severe to severe Alzheimer's disease, as measured by the MMSE, and treated with memantine 20 mg/day. One study compared memantine alone with placebo over a period of 28 weeks, and the other compared memantine plus donepezil with donepezil alone over 24 weeks. In the second study, participants were included on the basis that they had already been receiving donepezil for more than 6 months before entering the trial, and they had been at a stable dosage (5–10 mg/day) for at least 3 months. These participants were maintained on stable donepezil for the duration of the study.

In the RCT of memantine versus placebo, less deterioration of cognitive function was recorded following treatment with memantine compared with placebo, as measured by the Severe Impairment Battery (SIB). The adverse effects of memantine tend to be CNS-oriented, such as dizziness, headache and hallucination.

In the RCT in which participants received memantine and donepezil in combination, less deterioration in cognitive function was recorded in participants receiving combined treatment compared with donepezil alone, as measured by the SIB (mean change from baseline at end point for memantine plus donepezil and donepezil alone was 0.9 and −2.5, respectively, $p < 0.001$). Memantine also improves behavioural symptoms.

IV.d. Disease Modifying Treatment

For a neurodegenerative disorder, a disease modifying drug is usually considered as one able to reduce the progression rate. FDA, the US regulatory authority links disease modifying effects in a neurodegenerative disorder to an effect in the process of the disease. This must be related to the fact that recently there have been growing efforts to develop treatments directed not at neurotransmitters system but rather at the amyloid and tau cascades. Two of the more advanced disease-modifying agents that target buildup of amyloid plaques are Neurochem's Alzhemed and Myriad Genetics' Flurizan, both of which are being evaluated in Phase III clinical trials.

One of the most advanced is a glycosaminoglycan mimetic, to interfere with fibrillization of amyloid peptide. This anti-aggregation activity has been documented in vitro and in vivo using transgenic mice. Alzhemed is currently being evaluated in two Phase III clinical trials. The company's North American trial (in the United States and Canada) is a randomized, double-blind, placebo-controlled study in patients with mild to moderate AD. Patients are being treated for 18 months. Following completion of the study, patients are eligible to receive Alzhemed in an open-label extension study. Neurochem reports that this study is scheduled for completion in January 2007. A second Phase III trial of Alzhemed was initiated in Europe in September 2005.

Myriad Genetics reports that Flurizan is a selective amyloid-lowering agent (SALA) that reduces levels of the peptide amyloid beta 43 in cultured human cells and in animal models. Results of a completed Phase II follow-on study of Flurizan in patients with mild AD were presented in July 2006 at the International Conference on Alzheimer's Disease and Related Disorders. According to Myriad Genetics, results from this study reportedly

supported the hypothesis that Flurizan may have disease-modifying effects, and that the longer patients with mild AD are treated with Flurizan, the more slowly their disease will progress. Flurizan is currently being evaluated in two Phase III clinical trials.

Taking into account the rapid changes in this field the reader can upgrade the information in consulting the following web sites: www.alzheimers.org/clintrials/search.asp and www.nlm.nih.gov/medlineplus/alzheimersdisease.html.

IV.e. Medicosocial Care

Caring for a demented patient is a very heavy burden borne by the family. Medicosocial care should be designed to help lighten this burden providing psychological support to the main care giver and delaying institutionalization as long as possible. Likewise, all resources beyond drug therapy which can improve the patient's quality of life should be employed.

IV.e.1. Behavioural and Psychological Symptoms of Dementia (BPSD) Management

In degenerative dementias, BPSD have neurobiological basis which make the individual more vulnerable to environmental, physical and psychological factors. Standardised evaluation of behavioural symptoms is important. It must always be accompanied by individual clinical observation based on medical examination and multidisciplinary evaluation. Organisation of the management of BPSD is the concern of the overall plan of the institution. For a given patient, management involves the whole of the care team. The therapeutic strategy is under medical responsibility. For patients living at home, the family information on BPSD is of major importance.

Non-pharmacological management and support of the patient and their family are particularly important for the treatment of behavioural disturbances. They should be preferred and should be undertaken in usual practice. They are part of the personalised care plan. In this context, the following are particularly important:

- efforts to adapt the living environment in its spatial and temporal context
- the possibility of participation in structured recreational and social activities (walking groups, painting or cooking workshops) or physical activities
- training of care teams and assistance to caregivers.

Individual management interventions also exist which must be attempted and adapted, even in severe forms of dementia. The absence of scientific evidence or proof of efficacy of these methods should not prevent their application. It is essential to promote interventional studies in this field.

Pharmacological treatment should not be initiated if the symptom:

- is of physical origin (for example, pain),
- is of iatrogenic origin (hallucinations due to dopaminergic agonists, anticholinergic drugs, cholinesterase inhibitors, zolpidem, corticosteroids), or
- has responded to non-pharmacological environmental measures or behavioural therapies.

Treatment should be initiated in order to attenuate the symptoms which impair the patient's quality of life or which jeopardize them or those around. It should be ensured that the patient receives specific treatment for their disease (ChEIs and/or memantine).

IV.e.2. Advice for Patients and Families

Caring for a demented patient is a heavy burden for family and care givers. Therapeutic management must include all available medical, medicosocial and institutional means. Communication is the key to a successful environment of cooperative care. For drug therapy, it is important to recall the real therapeutic effectiveness of anticholinesterase agents which can be reinforced by adjunction of non-drug therapeutic support.

V. MIGRAINE

V.a. Background

The word migraine is derived from an old Greek word: hemicrania. The prevalence of migraine in adults is an estimated 10% in the general population with a three-fold predominance in women. Classically migraine is described as a unilateral recurrent headache of variable frequency associated with digestive tract disturbances and phono- and photophobia sometimes announced by inaugural and transitory neurological signs (aura). The International Headache Society (IHS) proposed diagnostic criteria in 1998 to reach a consensus on identifying migraine patients. They have been revised in 2004 and provide now criteria for seven subtypes of migraine.

V.b. Pathophysiology

The underlying pathophysiology remains to be fully explained, but is known to involve vasomotor phenomena (vasodilatation of the intracranial vessels, possible vasoconstriction in case of aura) and, according to the Moskowitz model, an axonal reflex in the trigemino-vascular system. It is generally accepted that the trigeminal nerve and the neurotransmitters serotonin, norepinephrine and dopamine are involved although new recently formulated theories suggest a meningeal cause or a causal relationship between migraine and microemboli via persistent permeability of the foramen ovale. In any case, migraine headache involves a cascade of complex neurovascular and biochemical events offering potential drug targets (explaining the broad spectrum of drugs proposed for treatment). Several substances or so-called proinflammatory mediators are implicated, including substance P, calcitonin gene related peptide (CGRP), prostaglandins, histamine, nitrogen oxide. The central role of serotonin has been suspected for many years and is supported by the effectiveness of certain agonists of specific serotonin receptors ($5HT_{1B/1D}$) including triptans which, for some authors, are also indicated for cluster headaches. A genetic component exists, as in the familial hemiplegic migraine. The gene has been mapped to chromosome 19p3. The concerned gene is the CACNA1A, which codes for the alpha 1 subunit of a voltage dependant P/Q calcium channel. A second gene has been mapped to chromosome 1q21-23, involved in the alpha 2 subunit of the sodium potassium pump.

V.c. Principles of Treatment

Several groups of compounds can be proposed for migraine headache. They can be divided into drugs indicated for acute episodes and those proposed for prevention.

V.c.1. Acute Treatment

The goal is to suppress or reduce the intensity of the clinical signs and stop their progression. The various mechanisms of action are related to the complexity of the pathophysiology of migraine headache. Schematically two mechanisms of action are proposed:

V.c.1.1. Cyclo-oxygenase inhibition. Inhibition of cyclo-oxygenase reduces the level of circulating prostaglandins and neurogenic inflammation. This is the mechanism of action of nonsteroidal antiinflammatory drugs (NSAID) and aspirin. The mode of action of paracetamol is less clear (inhibition of prostaglandins in the nociceptors of the posterior horn of the spinal cord and action on the supraspinal structures implicated in nociception).

V.c.1.2. Action on serotonergic and adrenergic receptors. Ligand–receptor interactions correct abnormal vascular activity occurring during headache. The induced vasoconstriction is mediated via $5HT_{1A}$, and $5HT_{1B}$, $alpha_1$ and $alpha_2$ receptors. The pharmacological class of triptan, act by stimulating $5HT_{1B/1D}$ receptors.

V.c.2. Preventive Treatment

The goal is to prevent future acute episodes or reduce their frequency. Generally given alone, these drugs may be prescribed if the patient experiences more than 1 or 2 episodes per month although social, occupational and familial consequences are in the forefront in the decision to initiate a preventive treatment. It is also important to control risk factors (fatigue, travel, stress, emotion, exposure to hot environments, smoking, alcohol, certain foods…) as best as possible on an individual basis. The mechanism of action of drugs used for preventive treatment varies greatly and, according to the principles of evidenced-based medicine, few have proven prophylactic efficacy. Schematically, amine antagonists, classic antagonists and NSAID are used.

V.d. Therapeutic Benefits

V.d.1. Preliminary Comments

All the drugs used for migraine headache are aimed at symptom relief and not against the yet unrecognized cause. Two observations are however most striking: first the impact on the concept of pain (for example see analgesics in the chapter on the treatment of pain) and secondly the fact that the pathophysiological principles are poorly defined.

V.d.2. Nonspecific Treatments

Nonsteroidal antiinflammatory drugs are used for their analgesic effect. Only a few, generally old, clinical trials are available. All studies demonstrate

that NSAIDs are at least as effective as the reference product. Ibuprofen and diclofenac are the most widely studied for this indication.

Aspirin: To facilitate digestive tract absorption, aspirin is usually combined with metoclopramide. Self-medication is widespread. Its efficacy *versus* placebo is well documented, generally at the dose of 1 g/d.

Paracetamol was often used as a comparative or backup treatment in recent clinical trials.

The real analgesic effect of paracetamol at the dose of 1 g/d was demonstrated empirically.

Opiate analgesics like codeine or dextropropoxyphene are generally given in combination with the drugs listed above. No specific study is available demonstrating their efficacy for acute episodes despite the beneficial effect observed in certain patients.

Many different formulations contain noramidopyrine. This drug is considered to be effective but can exceptionally provoke acute agranulocytosis.

V.d.3. Specific Treatments

Ergot derivatives and triptans are specific treatments for migraine. Both are $5HT_{1B/1D}$ serotonergic agonists.

The effectiveness of dihydroergotamine (DHE) and ergotamine tartrate was demonstrated in old clinical trials which probably would not meet currently accepted criteria for good methodology. For ergotamine tartrate, the dose usually recommended is 1–2 mg/d not to exceed 6 mg/d or 10 mg/week. DHE, which has a low bioavailability, is only effective after parenteral administration (subcutaneous, intramuscular, intravenous, or nasal-spray administration). The recommended dose is 1–2 mg/d.

Sumatriptan was the first compound in the pharmacological class of the triptans, followed by zolmitriptan, naratriptan, rizatriptan, almotriptan, frovatriptan and eletriptan. It can offer rapid relief. Theoretically, triptans should only be given at the moment of the aura (accentuation of the vasoconstriction and aggravation of the neurological signs).

Sumatriptan was specifically developed as an anti-migraine drug. Injectable sumatriptan has been shown to be more effective than injectable DHE at two hours but the rate of recurrence (30–40%) is higher than with DHE. Efficacy is better and delay to action is shorter with the injectable formulation. Both the nasal spray and the injectable formulation are particularly adapted for patients with nausea and vomiting.

Given at a dose of 2.5 mg, zolmitriptan can provide relief of headache in 2 hours in about 65% of patients. The rate of recurrence is similar to that for sumatriptan (31%).

Naratriptan is also dosed at 2.5 mg. Maximum dosage is 5 mg/d. Relief is achieved in 4 hours in 65% of the patients. The rate of recurrence, an estimated 27%, is similar to that for sumatriptan and zolmitriptan. Frovatriptan is also dosed at 2.5 mg. Relief is achieved in 2 hours in 42% of the patients. Eletriptan is dosed at 40 mg with a maximum dosage at 80 mg. Headache response is achieved in 2 hours in 60% of the patients. Recurence rate is estimated at about 20%. Rizatriptan is dosed at 5 mg with a maximum dosage at 10 mg. Headache response is achieved in 2 hours in 62% of the patients. Recurence rate is estimated at about 39%.

V.d.4. Adjuvant Drugs

Caffeine is often used in combination with ergotamine tartrate to improve digestive tract absorption. However caffeine has an antimigraine action itself.

Antiemetics are used to reduce nausea and vomiting concomitant with migraine. Metoclopramide increases the digestive absorption of ergotamine, paracetamol and aspirin by reducing the gastric paresis which occurs during acute episodes of migraine.

Anxiolytics can be used to reduce anxiety but are not per se part of the antimigraine armamentarium.

V.d.5. Preventive Treatment

Certain beta blockers have been shown to have an antimigraine effect, including propranolol, timolol, metroprolol, and atenolol. The beneficial effect appears to be comparable for the different drugs and independent of selective beta receptor blockage.

Methysergide is a lysergic acid derivative with an antiserotonin and antivasoconstrictor effect. Dosage is 5 mg/d, reserved for refractory migraine.

Primarily an alpha-adrenergic agonist, indoramine in a dose of 50 mg/d has also antihistamine and antidopamine properties.

Oxetorone has antiserotonin, antihistamine and alpha-adrenolytic properties. Dosage is 120–180 mg/d.

Clonidine, a central acting antihypertension agent (α_2 adrenergic agonist) is classically cited as an antimigraine drug although it is less effective than beta-blockers.

Flunarizine is the only calcium antagonist with a proven antimigraine effect. Classically used for vertigo syndromes, it can be given as a second intention preventive treatment.

Two NSAIDs have a proven, though modest, preventive effect: tolfenamic acid and naproxene.

V.e. Therapeutic Risks

V.e.1. Drug-Induced Headache

Certain drugs trigger headaches in specific clinical conditions. Drug-induced headache must be ruled out before establishing the diagnosis of migraine. Induced headache may result from hypertension (epinephrine, norepinephrine, amphetamines), vasodilatation (nitrate derivatives), biochemical effects (monoamine oxidase inhibitors, histamine, NSAID), intracranial hypertension (general anaesthetic, antibiotics). Induced headaches also include rebound phenomena and headache subsequent to overdosage of analgesics and antimigraine drugs themselves (transformed migraine).

V.e.2. Type A Effects

The adverse effects of these drugs are generally benign, subsequent to their pharmacological properties, but may lead to therapeutic adjustments. Taken once a day at recommended doses NSAIDs, like aspirin, are very well tolerated (2–10% digestive complaints) although chronic intoxication can occur with neurosensorial disorders. Paracetamol is well tolerated, with the exception of hepatic disorders related to toxic doses (10–15 g in one dose). The spectrum of adverse effects should be extended to concomitant drugs (constipation, nausea and somnolence for codeine, digestive disorders for dextropropoxyphene, tachycardia and anxiety for caffeine).

Ergotamine often causes nausea and vomiting. Acute ergotism is exceptional in case of overdosage and leads to acute peripheral ischaemia. Interactions with macrolides may affect the P450 cytochrome system and also lead to acute ergotism. Certain drugs (DHE) are habit forming, requiring strict compliance with dosage and treatment durations.

The adverse effects of the different members of the triptan class are quite similar, with the exception of chest oppression which is frequent with sumatriptan. Nausea, vomiting, fatigue, vertigo are frequently reported. Triptans are contraindicated (perhaps excessively) in aura migraine.

For preventive treatments, the adverse effects of the beta blockers are classical for this class: bradycardia, bronchospasm, hypotension, nightmares and depression. Indoramine induces neuropsychiatric effects (sedation, asthenia) and cardiovascular disorders (hypotension). Fluanarizine is strictly contraindicated in patients with Parkinsonism and depression.

V.e.3. Type B Effects

Type B effects are not related to the pharmacological properties of these drugs. Serious side effects may occur. Allergic skin and liver reactions to aspirin and paracetamol have been reported with risk of fibrosis, particularly in the retroperitoneal region for methysergide and hypersensitivity reactions with NSAID and pure analgesics.

V.e.4. Drug Interactions

Besides the classical ergotamine/macrolide interaction, attention has been focused on the DHE/triptan interaction with risk of acute vasoconstriction (this raises the difficult question of the acute treatment in patients taking a long term preventive regimen).

V.f. Advice for Patients and Families

As migraine is not socially accepted as a full fledged disease, patients tend to isolate themselves, creating a barrier to health care. Patients who are inclined to self-medication should be advised to carefully follow their treatment schemes (dose, duration), managing acute episodes with only one drug (shown to be effective by experience).

VI. STROKE

VI.a. Background

Stroke is a major public health challenge, not only for neuropharmacology, but for the society in general. Stroke causes physical and psychological suffering for patients and their family, increased hospitalization burden, and premature death. Every year, there are 500,000 new stroke victims in the United States, and as many in Europe. Stroke is the third leading cause of death and can occur in young subjects under 55 years of age (estimated incidence = 34/100,000), especially in men. In the United States

the estimated cost of stroke of 40 million US dollars, a cost which can be extrapolated to an equivalent sum in Euro's in Europe. For these reasons at least, we will limit our discussion to ischemic stroke, putting aside cerebral vascular disease (including chronic disease such as vascular dementia or acute cerebral hemorrhage), while emphasizing that the literature points to the enormous gap between acquired knowledge in neurosciences (epidemiology, pathophysiology) and the drug therapy armamentarium available today. With respect to vascular dementia and aspirin it should be noted that there is only one review in the Cochrane database and the reviewers conclude: "The most recent search for references to relevant research was carried out in July 2005, but no new trials were found. There is still no good evidence that aspirin is effective in treating patients with a diagnosis of vascular dementia".

Over the last twenty years, a large number of biological targets have been identified among the cascade of physiological events associated with hypoxia/ischaemia, warranting numerous clinical trials. The nearly constant failure of these trials has been a source of fatalism and nihilism (one can perceive the evolution of ideas on stroke in the selected articles mentioned in the references). Five new aspects have raised some hope: (1) epidemiological studies have identified risk factors susceptible of responding to treatment (hypertension, smoking, diabetes, hypercholesterolemia, oral contraception, alcoholism); (2) the development of stroke units which, for at least four reasons (rapid access to care, neurological expertise and diagnostic precision, simultaneous diagnosis and therapeutic care, clinical research), have enabled a 30% reduction in acute phase morbidity and mortality; (3) large multicentric international trials focus on secondary prevention; (4) progress in surgical treatment of tight symptomatic carotid stenosis which enabled, according to the NASCET study in 1991, the prevention of 17 ipsilateral infarctions (including 10 severe or mortal cases) at two years for 100 operated patients; (5) education of the public and physicians concerning the importance of emergency care for brain attacks to maintain ongoing antihypertensive therapy, avoid the danger of excessively rapid acting antihypertensives, maintain effective respiratory function, control fever and blood sugar, initiate physiotherapy early, and finally prevent thrombophlebitis.

VI.b. Pathophysiology

The biological mechanisms operating from acute ischaemia to cell death have been perfectly elucidated in animal models (occlusion of the four Pulsinelli vessels, occlusion of the middle cerebral artery, photothrombotic lesions), and more recently in humans using functional neuroimaging techniques. Cerebral hypoxia/ischaemia triggers a cascade of successive events. Time is therefore a crucial element. In humans, the therapeutic window lasts less than 6 hours after onset of the events. Schematically, ischaemia induces five fundamental events: (1) triggering of programmed apoptosis; (2) energy imbalance (membrane paralysis); (3) massive neurotransmitter release (glutamate); (4) inflammatory reaction with production of arachidonic acid (a source of free radicals); (5) endogenous thrombolysis with reperfusion phenomena. The time-course of each of these events is known, for example outflow of intracellular calcium or membrane or cytoskeleton lesions. The lesions extend progressively, which emphasizes the importance of intermediary zones where intact cells are 'paralysed' (and thus susceptible of recovering) and of selective vulnerability as certain anatomic structures of the brain die more rapidly than others (striatum, hippocampus) or finally of prognostic factors at the focus (pH, glucose, lactate, calpain, *cfos*, HIF-1, gelsolin). These reactions continue after the acute phase.

VI.c. Principles of Treatment

The pharmacology of the acute phase must be distinguished from the pharmacology of the post-stroke period. Therapeutic cocktails are to be envisaged. Brain infarction is not a homogeneous phenomenon, a fact illustrated by the proposed secondary prevention (anticoagulants in patients with emboligenic cardiopathies, antiplatelet agents in case of atherosclerosis). Aspirin (160 mg/d) is indicated in the acute phase. Cotherapies (anticonvulsivants) and drugs to be administered for conditions occurring late after the initial event (depression, dementia, epilepsy, spasticity) must be envisaged on a case-by-case basis. Secondary prevention is a separate topic.

VI.c.1. Thrombolysis

The first therapeutic strategy attempted for stroke victims was to disrupt the embolus and thus attack the cause of ischaemia/hypoxia. This approach appeared in 1996 with the advent of a tissue plasminogen activator, alteplase, to be administered

within three hours of the first clinical signs (theoretically during the transitional phase). A series of large-scale trials (using exemplary methodology) followed, largely dominated by the risk of increasing mortality by haemorrhage.

VI.c.2. Antithrombotics

Use of heparin and heparinoids is aimed at inhibiting thrombus propagation into large and small vessels and prevent arterial (and venous) re-embolisation. Very few clinicians use this approach, at least for the time being.

VI.c.3. Antiplatelet Agents

Although the experimental basis is rather limited, the goal with antiplatelet agents is to minimise the size of the infarction and limit the extension of the thrombus, thus avoiding early recurrence of stroke. Aspirin (160 mg/d) is widely studied.

VI.c.4. Neurocytoprotectors

The concept of neurocytoprotection remains in the domain of research. It is aimed at attenuating the intrinsic vulnerability of brain tissue by blocking the neurochemical steps leading to tissue damage and secondary cell death. The rationale is to administer an agent devoid of adverse effects (e.g. haemorrhage) and capable of blocking the chain of reactions leading to cell death. There is a long list of candidate drugs, most still in the research phase. Calcium and glutamate antagonists are the most widely studied. Therapeutic results have been more or less convincing. Older products, devoid of immediate adverse effects, formerly termed vasodilators or brain oxygenators, are still under study (e.g. piracetam and almitrine/raubasine).

VI.d. Therapeutic Benefits

A complete analysis of the clinical studies would require a catalogue just to list the trial anagrams; a complete bibliography would require a volume larger than this book. Schematically, these trials often referred to by their anagrams, have used mortality and disability scales (NIHSS, Barthel, Rankin, Glasgow) as outcome criteria to assess therapeutic success.

Aspirin in the acute phase. The meta-analysis of the IST + CAST + MAST studies has shown that aspirin (compared with placebo) reduces the rate of recurrent infarction by 7‰, that of stroke or death by 13‰, and that of death or disability by 13‰. These data favour the use of aspirin in the acute phase.

Antithrombotics in the acute phase. The classical indications for heparin at hypocoagulation dosage are maintained. Low-molecular-weight heparins can be used (reduced risk of haemorrhage).

Fibrinolytic agents. Intravenous fibrinolysis has been assessed in at least six major international studies. Streptokinase has been abandoned (haemorrhage) while rt-PA is given in the 3–6 hour therapeutic window (secondary analysis disclosed significant results on the RANKIN scale at 3 months (NINDS) and at 3 months (ECASS II)).

VI.d.1. Secondary Prevention

Aspirin and ticlopidine are used for their antiplatelet effect. They lower the risk of vascular recurrence by 27%. Asasantine™ (aspirin 50 mg + dipyridamole 400 mg) lowers the risk by 37% (ESPS2). Clopidrogel (75 mg) lowers the risk of recurrent vascular events after cerebral, cardiac or lower limb infarction by 8.7%.

Statins are a group of cholesterol lowering drugs that have been shown to be beneficial as published in 1997. In patients with ischaemic heart disease, the number of stroke events was reduced by 30% compared with placebo.

Antihypertension drugs reduce the risk of stroke by 42% and of death due to a vascular cause by 20%. The risk of a second stroke after a first stroke rises directly in proportion to usual diastolic pressures, likewise for late vascular dementia 'prevented' by nitredipine.

VI.d.2. Neurocytoprotectors

The subject of intense research, nitrocytoprotectors (piracetam, gingko biloba, almitrine/raubasine) are searching for their role in acute phase treatment. In certain countries, available drugs have been used in the functional rehabilitation phase (cognitive benefit). BN 80933 is an anti-free radical and anti-NO synthetase molecule which appears to have a powerful curative effect in animals.

VI.e. Therapeutic Risks

VI.e.1. Type A Effects

Both antiplatelet agents (including aspirin) and thrombolytics raise the major problem of haemorrhage with secondary transformation from infarction to cerebral haemorrhage. The clopidrogel study

showed a 9 (27% in the treatment group) to 9 (28% in the aspirin group) risk ratio (gastrointestinal bleeding was more frequent with clopidrogel). The same trial (ESPS 25) demonstrated induced haemorrhage in 74/1,649 patients in the placebo group *versus* 135/1,649 in the aspirin group (50 mg/d), 77/1,654 in the dipyridamole group, and 144/1,650 in the combination group. The cumulative risk of systemic haemorrhage with anticoagulant therapy varied from 1.3 to 5.7%. Intracranial haemorrhage varied from 0.7% (low-dose heparin) to 1.8% (curative dose). Whatever the causal drug, it is important to distinguish petichia, which occurs frequently, from intra-infarction haematoma in order to modulate accordingly (or stop) the antithrombotic agents.

VI.e.2. Type B Effects

Type B effects vary depending on the drug used, e.g. heparin and thrombocytopenia, ticlopidine and thrombocytopenia. Clopidrogel shows excellent acceptability. According to the results of phase I and phase II trials, the neurocytoprotectors currently under development have a very variable safety profile. Anti-NMDA agents can induce psychostimulation, psychotomimetic effects and increase blood pressure. For cardiac effects, QTc lengthening is still a problem with eliprodil and lubeluzole.

VI.e.3. Drug Interactions

It is clear that the perspective of attacking stroke with a cocktail of drugs will aggravate the risk of interactions. For example, combining antiplatelet agents with thrombolytics could favour the development of cerebral haemorrhage.

VI.f. Advice for Patients and Families

Stroke, like myocardial infarction, is a medical emergency. Rapid care by well trained teams in facilities allowing neuroimaging 24 hours a day is the key to better prognosis. Certain drugs have already proven to be beneficial, but much progress remains to be made in developing clinical research protocols.

VII. MULTIPLE SCLEROSIS

Multiple sclerosis is a frequently occurring CNS disease affecting approximately one million young adults, predominantly women, worldwide. Multiple sclerosis is characterised by episodic neurological symptoms followed by fixed neurological deficits. The resulting physical disability worsens progressively over 30–40 years. The therapeutic objective is to prevent relapse and progressive aggravation. The choice of drugs in a given individual is based on the pattern of progression and the probability of severe disability in accordance with the international nomenclature: relapsing–remitting, secondary progressive, primary progressive, or progressive relapsing multiple sclerosis. In addition patients who have multiple lesions on magnetic resonance imaging (MRI) at symptom onset are much more likely to have major disabilities later on. Numerous clinical trials have been conducted using assessment criteria based on MRI findings, the Expanded Disability Status Scale (EDSS), or the course of clinical features over time. The pathophysiological anomaly in MS is a multifocal inflammation with demyelinisation. Symptoms are often associated with a rupture of the blood–brain barrier, visualised on MRI, inflammation mediated nerve conduction block at the nodes of Ranvier, and myelin destruction via soluble and cellular mechanisms. Axonal transection is often correlated with irreversible neurological damage. Many arguments favour an autoimmune process in genetically susceptible persons subsequent to environmental exposure. Drug therapy in MS could target proinflammatory cytokines, activated T-cells, and mononuclear phagocytes.

Cytokines, including tumour necrosis factor (TNF) and interferon-γ, favour the secretion of numerous chemokines and the expression of adhesion molecules by endothelial cells. The mechanisms of action of the principle drugs used in MS, and in priority beta interferons, are the following: (1) inhibition of the expression of major histocompatibility complex class II molecules, (2) inhibition of metalloproteases, (3) induction of immunosuppressor cytokines.

Quite schematically, drugs generally used for relapsing MS are corticosteroids (methylprednisolone 1000 mg/d for 5 days, then 60 mg oral prednisone for 8 days), azathioprine (2–3 mg/kg/d), intravenous immunoglobulins (150–200 mg/kg/month), glatiramer acetate (20 mg s.c., a mixture of synthetic polypeptides composed of four aminoacids, is licensed for the treatment of relapsing–remitting multiple sclerosis in the USA and in Europe), and most importantly interferon-β (which has been studied in many recent clinical trials). In progressive

MS, the following immunosuppressors are classically prescribed: methotrexate (7.5 mg/week), cyclophosphamide, and mitoxantrone. Excepting mitoxantrone recently approved by the FDA for use in secondary progressive MS, none of these drugs has approval for specific forms of MS. The most recent and methodologically acceptable trials have been conducted with beta interferons (IFN-β). Three IFN-β are available: betaferon (IFN-β-1b), avonex, and rebif (IFN-β-1a). All three are used in relapsing-remitting MS. Only betaferon has supplementary approval for progressive MS. These drugs are administered parenterally (intramuscular injections once a week for avonex, subcutaneous injections every two days for betaferon and three times a week for rebif). These IFN-β are generally well tolerated and do not appear to be subject to drug interactions. The most frequent adverse effects are: flu-like syndrome, myalgia, fever, shivers, transpiration, skin lesions at the site of injection. Neutralising antibodies may develop, creating the problem of their antagonistic effect on membrane receptors of IFN-β and thus their possible role in long-term escape.

VIII. OTHER DISEASES

Many diseases or symptom-defined neurological entities other than those discussed in the preceding sections may respond to drug therapy. A detailed description would be beyond the scope of this chapter. In addition, many are very rare conditions with very complex diagnoses or limited to paediatric patients who require highly specialised care. Basically, the specialised therapeutic approach uses drugs targeted to the specific anatomic structures involved: muscle, peripheral nerve, neurosensorial organs, spinal cord, brain.

Because of the fact that these ailments are so rare very little evidence concerning their treatment is available. From a systematic review in the Cochrane database of six trials with 587 participants it is concluded that there is limited evidence that oral corticosteroids significantly slow recovery from Guillain–Barré syndrome. Substantial evidence shows that intravenous methylprednisolone alone does not produce significant benefit or harm. In combination with intravenous immunoglobulin, intravenous methylprednisolone may hasten recovery but does not significantly affect the long-term outcome (see Hughes et al., 2006).

VIII.a. Orphan Diseases

In the past, the absence of prolonged treatment was characteristic of health care in neurology. Although exceptional advances in neurosciences and neuropharmacology have greatly changed the situation, most neurological diseases are still orphans with no pharmaceutical agent for the neurological indication. In certain cases, the lack of marketing approval might appear to be a less serious problem. This situation calls for some serious thinking on the different aspects of the problem. Questions on bioethics, medical economics (limited market, insolvency of certain developing countries), industrial policies, and the lack of research motivation in these difficult domains as well as the absence of sufficient dialogue between the neurosciences and applied pharmacology, insufficient scientific financing for serendipitous discoveries, and the quasi-impossibility of obtaining valid assessments of efficacy using methodologies abiding by the guidelines required by administrative authorities (e.g. low recruitment levels) all require reasonable responses.

Freidreich's ataxia, Strümpell–Lorrain disease, Lewy body dementia, myopathies, certain neuropathies, sleeping sickness (tsetse) are just a few of these orphan diseases which certainly merit more aggressive research.

VIII.b. Other Diseases Responding to Drug Therapy

Drug therapy has been proposed, generally for symptom relief, in a number of other neurological diseases. In general, there is an international consensus on the therapeutic management of these diseases although the choice of drugs is quite limited (often to one drug) or restricted to specialist care. We can cite a few symptom/drug pairs that have been found effective: narcolepsia/modafinil; amyotrophic lateral sclerosis (ALS)/rilusole; dystonia and blepharospasm/botulinic toxin, essential tremor/propanolol; spasticity/spasticity drugs like baclofen, etc. and dopa-induced dyskinesia/amantadine; insomnia/benzodiazepines, zopiclone, zolpidem; myasthenia/antimyastenia drugs like peripheral anticholinesterase agents.

IX. PERSPECTIVES

The discussion in this chapter has been guided by the principles of evidence-based medicine, the

conclusions of the Cochrane Foundation, and the opinions of marketing approval authorities. Globally, evidence-based pharmacotherapeutics in neurology results from an application of our knowledge of what we may call synaptology. The perspective of advances in neuropharmacology will undoubtedly bridge the gap mentioned earlier between the neurosciences and therapeutics and lead to a more mechanistic approach, intervening upstream from the synapse.

In terms of clinical targets, the pharmacology of cognition is faced with the major challenge of improving the 'superior' functions performed by the human brain. These functions (memory, judgement, decision making), which go far beyond reflex response, are directly related to human thought and constitute the very foundation of human dignity. With the recently established dialogue between drug therapy and other neurotherapeutic tools such as deep brain stimulation, the perspective of seeing computer science intrude into the realm of neurotherapy to replace defective neurone networks and thus fulfil the tautological dream of an artificial brain (artilects) must be accepted as a real possibility. Finally the dissemination of information in such a fast moving field is in itself a new domain of research.

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Chapter 40

Drug Use for Malignancies

David J. Perez

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I. INTRODUCTION

The treatment of malignant diseases with drugs has expanded considerably in the past decade with the development of new cytotoxic and hormonal agents and also targeted therapies such as monoclonal antibodies and tyrosine kinase inhibitors. Since cancer frequently gives rise to local problems but at the same time metastases to distant sites, quality care demands a multidisciplinary approach. Drug treatment is used either as a single modality or as an adjunct to loco-regional forms of treatment such as surgery and radiotherapy. Drug treatment can be used either with curative, life extending or palliative intent. With all of these approaches and particularly for palliative intent, it is important to balance the intended outcome against the toxicity of treatment. In this respect the evolution of targeted therapies, which generally have lesser toxic effects, represents welcome progress in the field of cancer therapy.

I.a. Adjuvant Treatment

Adjuvant drug treatment is given after local therapy to patients who do not show evidence of macroscopic residual disease, but who are judged to be at high risk of having microscopic metastases and therefore risk of relapse, as indicated by adverse tumor characteristics. Experimental evidence based on cell kinetics and the potential for evolution of resistance indicates that tumors are most sensitive to chemotherapy at the earliest stages of growth. In addition the probability of intrinsic tumor cell resistance is a function of the total number of cells present. For these reasons subclinical tumors are more likely to be more sensitive to chemotherapy, with greater potential for cure, than metastatic tumors.

I.b. Neo-adjuvant Treatment

Neo-adjuvant drug treatment is similar in concept to induction therapy. It means that drug therapy is used as the initial primary treatment, preceding local therapy. Neo-adjuvant drug therapy is used to reduce tumor size in order to facilitate local tumor eradication with radiotherapy or surgery. It also avoids compromised vascularity from preceding surgery or radiation treatment that might result in poor drug distribution.

I.c. Treatment of Metastatic Disease

Most of the knowledge obtained in the treatment of cancer with drugs has been obtained in the treatment of metastatic disease. Once the disease has metastasized it is occasionally still possible to achieve cure, but in the majority of settings treatment at this

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stage is given with palliative or life extending intent. However, it should be stressed that good palliation is highly desirable for a highly morbid disease such as cancer. Most commonly, treatment is given with a combination of drugs to provide optimal efficacy for the following reasons. Drugs from different classes have different mechanisms of action and also of resistance, different drugs have different side effect profiles, and by combining chemotherapy one can sometimes benefit from specific pharmacological interactions.

The costs of cancer treatment vary considerably between countries. These costs are not only generated by the price of the chemotherapeutic agents, which can be very high for new agents, but also by the infrastructure necessary to optimize the delivery of the drugs to the patient and the treatment of adverse effects. Whether the costs of a certain treatment equal the benefits depends on many factors which are country specific and this analysis needs to be determined in the context of differing health systems.

It is impossible to review all aspects of drug treatment in oncology in this chapter. For detailed overviews the reader is referred to specific textbooks. In the following sections we will focus on the more frequent types of cancer, as well as on those types (even if infrequent) where drug treatment is given with the intention to cure.

II. HEAD AND NECK CANCERS

II.a. Squamous Cell Cancer of the Head and Neck

Head and neck squamous cell cancer (HNSCC) represents the vast majority of head and neck tumors, approximately 80%. Most of these cancers are related to smoking and high alcohol intake. The only curative treatments for HNSCC are surgery and radiotherapy, alone or in combination depending on the stage. Radiotherapy is used primarily in the treatment of early stages (I and II) with long-term cancer control in 60–80% of the patients. Surgery is usually employed in resectable stages III and IV disease followed by postoperative radiotherapy in case of stage IV, nodal disease or in patients with positive surgical margins. The prognosis of these patients is poor; more than 60% will develop loco-regional recurrence and 20% distant metastases (see Al-Sarraf and Hussein, 1995). The remainder of the patients with unresectable disease have traditionally been treated with radiotherapy alone.

The integration of chemotherapy has been pursued with the goal of increasing survival rates and organ preservation. Despite 30 years of research into the role of chemotherapy in the curative management of head and neck cancer, this role remains controversial. Induction (neoadjuvant) chemotherapy consisting of a combination of cisplatin and 5-fluorouracil results in significant tumor regression in 60–90% of patients with a complete response in 31–66% and a reduction in the occurrence of distant metastases (see El-Sayed and Nelson, 1996). Induction chemotherapy in combination with radiotherapy can enable the preservation of the ability to speak and swallow without compromising the chance for cure in patients with operable stage III and IV laryngeal and hypopharyngeal cancers, thereby improving their quality of life. Neo-adjuvant chemotherapy, however, has no impact on the ultimate loco-regional control of the disease nor does it improve survival compared with surgery or radiotherapy alone. Therefore the routine use of up-front chemotherapy cannot be recommended as standard treatment. Patients achieving a complete response on chemotherapy seem to have better overall survival than patients with a partial response or no response, however, this difference may be due to patient selection bias.

In patients with loco-regionally advanced inoperable disease chemoradiation now offers an improved outlook. The combination of radiosensitizing multi-agent chemotherapy, for example cisplatin and 5-fluorouracil, with standard or hyperfractionated radiation schedules produces enhanced survival and improved loco-regional disease control. A meta-analysis has revealed a small, but significant increase in overall survival with the use of concomitant chemoradiation (see Pignon et al., 2000). However, it must be borne in mind that this approach produces more toxicity, particularly mucositis and hematological toxicity. A promising new agent in the chemoradiation setting is the anti-EGFR (epidermal growth factor receptor) monoclonal antibody, cetuximab. Cetuximab is a radiosensitizer and a recent study revealed a 10% survival benefit at 4 years for patients receiving concomitant cetuximab and radiation compared to radiation alone (see Bonner et al., 2006).

Chemotherapy as a single modality still has a role as palliative treatment in recurrent or metastatic disease. However, the median survival for patients with

locally recurrent or disseminated HNSCC is only 6 months and survival has not been prolonged with the use of chemotherapy. Methotrexate, cisplatin, carboplatin, paclitaxel and docetaxel are the most active drugs with response rates of 15% or greater. Single agent therapy with one of these agents is worth consideration, particularly the taxanes as these have modestly superior tumor response rates. Cisplatin-based combination therapy results in higher response rates but at the cost of higher toxicity and median survival is not significantly prolonged. The advantage of choosing combination chemotherapy is limited to patients with excellent performance status, no prior chemotherapy and minimal tumor burden. These results underscore the need for new therapies and approaches. Several newer agents such as cetuximab and the tyrosine kinase inhibitors gefitinib and erlotinib are under active investigation.

II.b. Undifferentiated Nasopharyngeal Cancers

Undifferentiated nasopharyngeal cancer (NPC) is a relatively uncommon disease in North America and Western countries, but constitutes one of the most common malignancies in China and Southeast Asia, North Africa and the Mediterranean region. The etiological factors for endemic NPC include the Epstein–Barr virus, environmental risk factors, and genetic susceptibility. At presentation lymphnode involvement is frequently bilateral and bulky. Systemic dissemination occurs more frequently compared to HNSCC and constitutes a major cause of death. For early stage disease (T1-2, N0-1) radiotherapy is the primary treatment modality (see Vokes et al., 1997). Patients with large primary tumors (T3–T4) or nodal involvement (N2–N3) derive substantial survival benefit from chemoradiation utilising concomitant cisplatin-based chemotherapy as shown in the US Intergroup study (see Al-Sarraf et al., 1998) and this approach is now the gold-standard for locally advanced disease. In contrast to the benefits of concurrent chemoradiation the use of sequential radiotherapy and chemotherapy (before or after radiation) has not shown consistent disease-free or overall survival benefit. Administration of adjuvant chemotherapy following chemoradiation can be difficult because of poor tolerability.

In metastatic or loco-regional recurrent disease palliative chemotherapy can be effective but usually for relatively short periods. Occasionally prolonged remissions are seen in patients with limited extent distant metastatic disease. The most effective combinations are cisplatin-based regimens such as cisplatin/5-fluorouracil/bleomycin, cisplatin/epirubicin/bleomycin or cisplatin/gemcitabine. Taxanes appear active but more studies are required for confirmation. Nasopharyngeal carcinoma is a very chemosensitive tumor and response rates ranging from 60–90% with, complete remission in approximately 20%, have been achieved. These regimens consistently result in a small proportion of long-term disease-free survivors.

III. LUNG CANCER

III.a. Non-small Cell Lung Cancer

Lung cancer continues to be a major international health problem, it is the leading cause of cancer related death in many countries and its incidence is increasing in many nations. Unfortunately, approximately 70% of patients with non-small cell lung cancer (NSCLC) present with advanced, poor prognosis stage III and IV disease. Fewer than 20% of patients with locally advanced disease are amenable to surgical resection at presentation. For patients with unresectable NSCLC best supportive care, radiation therapy and chemotherapy are the currently available options. The use of chemotherapy in patients with NSCLC has been investigated for many decades. At present chemotherapy alone can be considered standard therapy for selected patients with stage IV disease or stage IIIB disease with a malignant pleural effusion or positive scalene lymph nodes (see Pfister et al., ASCO guidelines, 2004). In these stages prolongation of survival and enhanced quality of life can be achieved by treatment with chemotherapy compared to that achieved with best supportive care. For patients with loco-regionally advanced disease chemotherapy is now used as a component of multimodality therapy combined with radiotherapy or surgery.

Over fifty single agents have been tested in phase II studies in advanced non-small cell lung cancer. Of these, only a limited number of drugs have single agent activity inducing responses in 15% or more of previously untreated patients (Table 1). Since complete responses from single agent therapy are rare and the response duration is short (on average 2–3 months), combination regimens are the norm. Cisplatin-based combination regimens yield higher response rates compared to single agents and several regimens result in improved survival over single

Table 1. Active cytotoxic agents used in the treatment of non-small cell lung cancer

Cisplatin	Carboplatin
Vinorelbine	Vinblastine
Vindesine	Ifosfamide
Paclitaxel	Docetaxel
Etoposide	Gemcitabine
Mitomycin C	Pemetrexed
Irinotecan	

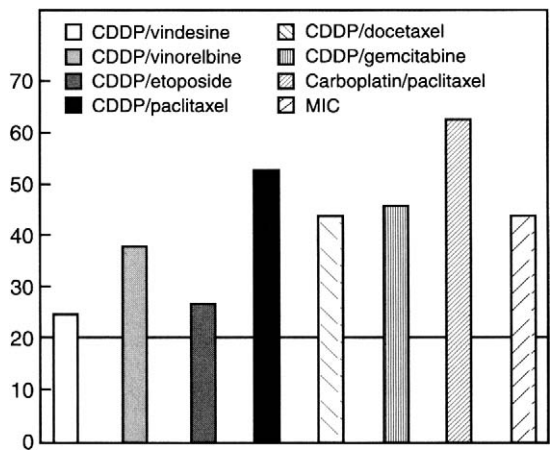


Fig. 1. Response rates of combination chemotherapy regimens used in the treatment of non-small cell lung cancer.

agents or treatment other than chemotherapy. On average, the median survival of the cisplatintreated patients improves by 10 weeks, and the 1-year survival rate improves by 15% (from 15 to 30%). Direct comparisons of cisplatin and carboplatin combinations in NSCLC have reported a modest improvement in tumor response rates with cisplatin but no clear survival advantage has emerged. The 'best' platin-based regimen is not well defined. The results of prospective, randomized trials indicate that relatively new drugs such as vinorelbine, gemcitabine, paclitaxel and docetaxel in combination with cisplatin can improve tumor response rates beyond that achieved with more established regimens (Fig. 1).

Modest advances have been seen with the application of chemotherapy to stage 3 (lymph node positive) NSCLC. A few patients with unresectable stage 3A disease can be rendered resectable by chemoradiation using concurrent radiation and cisplatin based therapy. Those who remain unresectable and those with stage 3B disease achieve an approximate 3 month prolongation of overall survival and enhanced quality of life with concurrent chemoradiation. A more encouraging recent development has been the demonstration of a significant survival benefit with adjuvant cisplatin based chemotherapy for resected NSCLC. This benefit is more evident for the higher risk stage 2 and 3 patients but also offers some benefits to those with stage 1B. A meta-analysis of the more mature phase III studies has reported a 4.2% survival advantage at 5.1 years median follow-up. Some of the studies in the meta-analysis were heterogeneous in design and the mature results of the more recent, homogeneous studies are awaited with interest.

The future of NSCLC management will undoubtedly include targeted therapies with monoclonal antibodies and tyrosine kinase inhibitors. The anti-vascular endothelial growth factor monoclonal antibody, bevacizumab, has enhanced response rates and modestly improved survival in combination with paclitaxel and carboplatin. Further studies with this agent are required to establish its definitive role. The small molecule tyrosine kinase inhibitors erlotinib and gefitinib have shown single agent activity in NSCLC however, only erlotinib has shown a survival benefit (see Shepherd et al., 2005). Features which predict for response with EGFR-tyrosine kinase inhibitors include female gender, non-smokers, Asian ethnicity, adenocarcinoma histology and the presence of EGFR mutations.

III.b. Small Cell Lung Cancer

Small cell lung cancer (SCLC) includes approximately 20–25% of all cases of lung cancer seen worldwide. SCLC differs from other types of lung cancer in its more aggressive course and its superior responsiveness to chemotherapy and radiotherapy. The main modality of treatment for SCLC is combination chemotherapy. For patients with limited disease achieving a major response on chemotherapy, this is usually combined with concurrent thoracic irradiation. Prophylactic whole brain irradiation is often administered to complete responders because of the high probability of CNS relapse with associated morbidity.

There are many active cytotoxic agents for SCLC. These drugs are listed in Table 2. Combination chemotherapy regimens yield the best response rates and the highest percentage of long term survivors in SCLC. Although many combination regimens for SCLC appear to possess similar activity, the most commonly used regimens include cisplatin with

Table 2. Active cytotoxic agents in the treatment of small cell lung cancer

Active single agent	Response rate (%)
Ifosfamide	50
Teniposide (VM-26)	50
Doxorubicin	50
Epirubicin	50
Irinotecan	50
Etoposide (VP-16)	40
Cyclophosphamide	40
Cisplatin	40
Carboplatin	40
Topotecan	35
Methotrexate	35
Vincristine	35
Vindesine	35
Paclitaxel	35
Vinorelbine	30
Docetaxel	30
Gemcitabine	25

etoposide and carboplatin with etoposide. Cisplatin may have a slight margin of efficacy over carboplatin so is preferred for those who have limited disease and good performance status. These regimens yield 65–70% overall response rates, a median survival of 12–20 months for patients with limited disease and a 10–12% 5-year survival rate. For patients with extensive disease a median survival of 7–11 months is achieved with few long term survivors. Chemotherapy regimens with more drugs or higher dose intensity have failed to deliver better outcomes. Administration of chemotherapy for 4–6 cycles is currently recommended as more protracted courses have failed to prolong survival.

IV. BREAST CANCER

IV.a. Treatment of Metastatic Disease

Patients with metastatic breast cancer are incurable using conventional therapy such as hormonal manipulation or chemotherapy. However, as in most other neoplastic diseases the bulk of knowledge on drug treatment has been obtained in this stage of the disease. The median survival from the manifestation of metastasis is approximately 18–24 months. It is, however, important to realize that metastatic breast cancer is a heterogeneous disease and for some patients the disease can be controlled for many years with relatively good quality of life.

The first consideration in the treatment of metastatic disease is whether the disease might be sensitive to hormonal manipulation. Patients with estrogen receptors in their primary tumors are likely to be sensitive to such hormonal treatment, while those with truly receptor-negative cancers rarely benefit. An increasing number of hormonal therapies are now available as shown in Table 3. Responses to hormonal therapies tend to be slow, so it is important to observe patients for 12 weeks or more before making a judgment about stabilization of the disease or tumor regression. The choice of hormonal therapy depends on the patient's menopausal status, as well as on the toxicity profile of the various agents available. The response rate is approximately the same for all of the various manipulations. There is no clear advantage combining the various hormonal agents. The median duration of response is between 6–9 months and depends on factors such as the site of metastases and the level of hormone receptor positivity. The difference in treatment approach between pre-menopausal and post-menopausal patients lies mainly in the choice of first line hormonal treatment. In pre-menopausal patients the first choice hormonal treatment is tamoxifen or ovarian ablation, presently most commonly achieved by LHRH agonists. There may be a modest advantage for the combination of tamoxifen and LHRH agonists. Failure of these two therapies usually demands the use of chemotherapy. For post-menopausal women the recent introduction of the 3rd generation selective aromatase inhibitors has led to a worthwhile advance in terms of drug tolerability and perhaps efficacy. Aromatase inhibitors are not associated with thromboembolism or enhanced risk of endometrial cancer but they can contribute to accelerated osteopenia and risk of fracture. Recent phase III studies comparing anastrozole or letrozole to tamoxifen as first line metastatic therapies have shown at least equivalent efficacy and, in the case of letrozole, a longer time to progression. Aromatase inhibitors are now considered the first line therapy of choice but tamoxifen still remains a useful agent, particularly for those women with pre-existing osteoporosis and as second line therapy. For those post-menopausal women who have enjoyed stable remissions on previous hormone therapies third line agents such as fulvestrant and megestrol acetate can be employed.

Patient with tumors predicted to be insensitive or proven insensitive to hormonal manipulation, or those patients with metastatic disease in vital

Table 3. Hormonal therapies for breast cancer

Selective estrogen receptor modulators	Tamoxifen
	Toremifine
Selective estrogen receptor down-regulators	Fulvestrant
Selective aromatase inhibitors	Anastrozole
	Letrozole
	Exemestane
	Formestane
Gonadotrophin releasing hormone agonists	Goserilin
	Leuprolide
Sex steroid therapies	Estrogens – e.g. diethylstilbestrol
	Progestins – e.g. megestrol acetate
	Androgens – e.g. fluoxymesterone

Table 4. Adjuvant therapy for breast cancer according to receptor and risk status

Hormone receptor status	Risk status (definitions below)		
	*Low risk	*Intermediate risk	*High risk
Positive			
Pre-menopausal and post-menopausal	Hormone or nil	Hormone +/− chemotherapy	Hormone + chemotherapy
Negative			
Pre-menopausal and post-menopausal	Nil *node − ve & < 2 cm & grade 1 & vasc invas^{n} − ve & HER-2 − ve & >35 yrs	Chemotherapy *node − ve & >2 cm or grade 2 or 3 or vasc invas^{n} + ve or HER-2 + ve or <35 yrs or 1–3 nodes + ve & HER-2 − ve	Chemotherapy *1–3 nodes + ve & HER-2 + ve or >3 nodes + ve

organs causing symptoms and requiring a rapid anti-tumor response are most commonly treated with combination chemotherapy. There is a wide variety of agents that have shown good or moderate activity as single agents but contemporary first line therapy is predominantly of combination type. The most frequently combined drugs include doxorubicin (A) or its analog epidoxorubicin (E), mitoxantrone, cyclophosphamide (C), methotrexate (M), 5-fluorouracil (F), capecitabine, the taxanes including paclitaxel and docetaxel, the vinca-alkaloid vinorelbine and more recently gemcitabine. Nowadays first line treatment decisions hinge on whether or not the tumor is HER-2 positive (see below). In women with HER-2 negative tumors the most frequently used first-line regimen consists of an anthracycline containing combination such as 5-fluorouracil-doxorubicin-cyclophosphamide (FAC) or FEC. In Europe epidoxorubicin is often used in place of doxorubicin, being less cardiotoxic. These anthracycline containing combinations have been shown to be more effective than the older combination of CMF, albeit at the price of greater toxicity. In recent years the taxanes paclitaxel and docetaxel have been used increasingly. Although a direct comparison has not yet been published it seems as if docetaxel is slightly more active than paclitaxel but also slightly more toxic. Taxanes have been combined with anthracyclines with associated high response rates but at the expense of considerable toxicity, particularly hematological. Less toxic taxane combinations can include capecitabine or gemcitabine.

HER-2 positive tumors have an aggressive natural history and are frequently treated with chemotherapy. Approximately 20% of breast cancers over-

express the oncogene HER-2 and these can be usefully treated with the humanized monoclonal antibody trastuzumab. Trastuzumab used as a first line single agent can achieve response rates up to 35%. However, its main contribution lies in combination with chemotherapy where synergistic interactions can occur. Chemotherapy–trastuzumab combinations with demonstrated efficacy include anthracyclines, taxanes, platinum analogs, vinorelbine and cyclophosphamide. Caution is recommended with the combination of trastuzumab and anthracyclines because of the potential for excessive cardiotoxicity. The current preferred combinations are with taxanes or vinorelbine and these result in higher response rates and longer times to progression.

IV.b. Adjuvant therapy

Occult metastases are commonly present at the time of first presentation of patients with breast cancer. This knowledge is based on the fact that even following effective local treatment many patients over time will present with metastatic involvement. For these patients improvements in cure rates can only be obtained by adding systemic therapy to local surgery and radiotherapy at the time of primary treatment. Evidence of benefit from adjuvant systemic therapy can only be obtained from appropriately designed large randomized trials. Currently most of our knowledge and understanding about the ultimate benefits of adjuvant therapies are obtained from the meta-analysis performed on over a hundred individual prospective randomized clinical trials (see Early Breast Cancer Trialists' Collaborative Group, 2005).

For subsets of patients adjuvant hormonal therapy is a standard recommendation (Table 4). Presently this treatment is given to most patients with hormone receptor positive tumors whose likelihood of breast cancer recurrence is greater than 10–15%. In effect, this only excludes those patients with small, node-negative infiltrating ductal or lobular cancers. Previously tamoxifen, used at a dose of 20 mg/day for 5 years, was the standard adjuvant hormonal agent. This still applies to receptor-positive premenopausal women where tamoxifen can be used alone or with ovarian suppression, however, the advent of aromatase inhibitors has resulted in these agents becoming the standard of care in the postmenopausal setting. The very large ATAC study (see Howell et al., 2005) compared anastrozole to tamoxifen for 5 years, and has reported a significantly reduced risk of relapse at 5 years which approximates a 3–4% disease-free survival difference. In addition the incidence of contralateral tumours is reduced. So far an overall survival benefit has not emerged. Similar results have been reported for letrozole. Extending hormone therapy to 10 years with the sequential use of tamoxifen for 5 years followed by letrozole for 5 years appears to add further benefits for disease free survival (see Goss et al., 2003). Unfortunately this study was terminated early on the basis of a positive interim analysis results so mature overall survival data will be lacking.

Adjuvant chemotherapy is now widely used, especially in women under 70 years of age (Table 4). The regimens that are used largely resemble those that are used in the treatment of metastatic disease (i.e. CMF, FAC/FEC, AC, taxane combinations). The Early Breast Cancer Trialists' Collaborative Group 2005 review reported a 7–8% mortality advantage for women aged less than 60 with an anthracycline combination given for at least 6 cycles compared to CMF. Anthracycline-based regimens have therefore become the standard of care for those women who can tolerate the associated toxicity. Further advances have been made for women with node-positive disease with the addition of taxanes to anthracycline regimens. The results of the addition of taxanes have been variable but there is increasing evidence that taxanes do contribute to improved overall survival. Both paclitaxel and docetaxel have shown benefit but the optimal taxane regimen remains to be defined. Another approach to achieving improved outcomes involves dose-dense chemotherapy with hemopoietic growth factor support. Further data are required before this approach is considered standard.

Neoadjuvant treatment of breast cancer has traditionally been used in inflammatory breast cancer, mainly in those patients not amenable to radical surgery and radiotherapy. The aim of the treatment is a downstaging of the disease. However, this approach can also be applied to tumors that are not initially suitable for conservative surgery but may become so post-chemotherapy. The overall survival outcomes are similar for the pre- and post-surgery approaches.

Finally, a major advance for women with HER-2 positive tumors is unfolding. The use of trastuzumab for one year concurrently (see Romond et al., 2005) or sequentially (see Piccart-Gebhart et al., 2005) with chemotherapy has shown very promising initial 1–2 year results showing an approximate 50%

reduction in the risk of relapse which translates into a 9% disease-free survival advantage at 3 years. Clearly longer follow-up is required to determine whether these early results are maintained and therefore translate into an overall survival advantage. Other outstanding questions include the use of anthracyclines with adjuvant trastuzumab and the optimal length of trastuzumab administration.

V. GYNAECOLOGICAL CANCERS

V.a. Cancer of the Cervix

Human papillomavirus (HPV) infection is a necessary factor in the development of nearly all cases of cervical cancer. A recently approved HPV vaccine, Gardasil, that blocks initial infection with several of the most common sexually transmitted HPV types may lead to significant decreases in the incidence of HPV-induced cancer (see Lowy et al., 2006).

Cytotoxic drugs have been used in the initial treatment of cervical cancer in various ways. Although several randomized trials have failed to show benefit from neo-adjuvant chemotherapy preceding local treatment, concurrent chemoradiation therapy has been more successful. The primary goal of chemoradiation has been to use chemotherapeutic agents to sensitize tumor cells to the effects of radiotherapy. For women with bulky stage IB–IIA disease chemoradiation with or without prior surgery is recommended. For stages IIB to IVA disease chemoradiation alone is appropriate. The most commonly used chemotherapy drug is cisplatin. A Cochrane meta-analysis (see Green et al., 2005) reported a 31% overall reduction in mortality for stages IB to IVA treated with chemoradiation compared to radiation alone.

In metastatic disease many drugs have been tested and at least 19 have been reported to yield response rates of more than 15% and are thus considered 'active' although the duration of response has been modest, in the range of 3–4 months. This information derives from non-randomized studies with the most convincing data being found for cisplatin and ifosfamide. More recently innovative drugs such as vinorelbine and topotecan have also shown activity. The question of whether combination chemotherapy is superior to single agent treatment has been addressed in a limited number of randomized trials. These have generally demonstrated improved response rates and progression free survival, however, the only study to demonstrate a survival benefit for combination chemotherapy was performed by the Gynecology Oncology Group (GOG) comparing cisplatin alone to cisplatin plus topotecan (see Long et al., 2005). The response rate for the combination was higher (27% vs 13%) and median survival was extended by almost 3 months.

V.b. Endometrial Cancer

Since endometrial cancers tend to be more frequent in elderly women, there has been considerable interest in treatment with hormones, which are relatively non-toxic. However, it is important to emphasize that responses to hormonal agents such as progestins and tamoxifen occur in less than 20% of patients and these tend to be of relatively short duration. In general treatment with progestins seems to yield superior results to tamoxifen. Of note, a study from the GOG has shown that there was no dose–response effect for medroxyprogesterone acetate (MPA); doses of 200 mg/day were equal to 1000 mg/day as far as anti-tumor efficacy was concerned (see Thigpen et al., 1991). While megestrol acetate seems to be even more potent than MPA, high doses of this drug do not appear to be more effective. Endometrial cancer appears to have limited responsiveness to aromatase inhibitors and LHRH agonists. Responses to hormonal treatment are generally limited to the minority of patients with a long disease-free interval from diagnosis, well-differentiated or receptor-positive cancers.

With regard to hormone use in the adjuvant setting a systematic review in the Cochrane database of six trials involving 4351 women concluded: "Current evidence does not support the use of adjuvant progestogen therapy in the primary treatment of endometrial cancer" (see Martin-Hirsch et al., 1999).

All other patients with locally recurrent or metastatic disease should be considered for treatment with cytotoxic chemotherapy. As for cervical cancer, various drugs have yielded activity. Among these are the anthracyclines, doxorubicin and epirubicin, cisplatin and its analog carboplatin and more recently paclitaxel and topotecan. Up to now conclusive evidence that combination chemotherapy is superior to single agent treatment is still lacking. There is accumulating evidence that paclitaxel containing regimens may improve response rates to 40–50% as well as improving survival but at the expense of greater toxicity. Several relatively small studies have

suggested that combination chemo-hormonal therapy may improve response rates and possibly survival.

V.c. Ovarian Cancer

The treatment of epithelial ovarian cancer is a clear example of the benefits of the multidisciplinary approach. While it is commonly accepted that patients with borderline carcinomas and those with stages IA and IB, well or moderately differentiated carcinomas do not require chemotherapy after surgery, for all other patients the usual approach is cytoreductive surgery when feasible, followed by chemotherapy. Cytotoxic agents from different classes have been shown to produce significant responses in patients with ovarian cancer (Table 5). Platinum compounds are considered the backbone of treatment. Cisplatin and carboplatin are considered to have similar efficacy but subjective toxicity for cisplatin is greater and associated quality of life can be diminished. For these reasons carboplatin is now the preferred platinum agent for epithelial ovarian cancer. Carboplatin dosing is based on the area under the concentration-time curve (AUC) formula (see Calvert et al., 1989). Following the demonstration of the pivotal role of platinum agents the taxanes have also become established as integral agents for ovarian cancer. Two large studies have shown the importance of paclitaxel in combination chemotherapy of ovarian cancer (see McGuire et al., 1996 and Piccart et al., 2000). The two studies differed mainly in the duration of administration of paclitaxel. The American study used a 24-hour infusion, while the European study used a 3-hour infusion. The latter tends to be less neurotoxic but more myelotoxic. The results of both studies were comparable showing that the combination of cisplatin plus paclitaxel was superior to cisplatin plus cyclophosphamide. Therefore the combination of cisplatin plus paclitaxel can be considered as a standard treatment. Long term results of large studies commenced in the early 1980s using the multimodality approach of optimal debulking surgery and combination chemotherapy suggest an approximate 15–20% 10-year survival which represents cure for the majority of these survivors.

Table 5. Antineoplastic agents for advanced ovarian carcinoma

Agents with response rates $\geqslant 20\%$	
Paclitaxel	Docetaxel
Cisplatin	Carboplatin
Melphalan	Cyclophosphamide
Ifosfamide	Doxorubicin
Hexamethylmelamine	Gemcitabine
Topotecan	Vinorelbine

A systematic review in the Cochrane database of forty-nine trials of chemotherapy for advanced ovarian cancer involving 8763 women concluded: "The available evidence, although not conclusive, suggests that platinum-based chemotherapy is better than non-platinum therapy. There is some evidence that combination therapy improves survival compared with platinum alone. No difference in effect has been shown between cisplatin and carboplatin" (see Advanced Ovarian Cancer Trialists Group, 1999).

As indicated above, appropriate cytoreductive surgery plus chemotherapy adds to the likelihood of achieving cure or prolonged survival in patients with ovarian cancer. Initially it was much less clear how patients should be approached when optimal debulking surgery was not feasible. In a study from the European Organization for Research and Treatment of Cancer, this question was investigated. Patients received three cycles of induction chemotherapy and were then randomized to undergo secondary cytoreductive surgery or no surgery. Both groups received additional chemotherapy. The progression-free and overall survival were both significantly longer in the group that underwent interval surgery. The difference in survival was 6 months. At 2 years following initial diagnosis 56% of the group who underwent surgery were alive compared to 46% of the group who did not (see van der Burg et al., 1995). Clearly, interval surgery should be considered after 3 cycles of induction chemotherapy for those patients where up-front cytoreductive surgery is not feasible.

Intraperitoneal chemotherapy has been under investigation for many years and accumulating positive indicators were recently reinforced by the phase III Gynecology Oncology Group study [GOG 172] (see Armstrong et al., 2006). This study randomized optimally debulked patients to either intravenous paclitaxel and cisplatin or to intravenous paclitaxel plus intraperitoneal paclitaxel and cisplatin. After a median follow-up of four years an overall survival advantage for the IP arm of 65.6 versus 49.7 months was seen.

With regard to hormone use for epithelial ovarian cancer a Cochrane review concluded that "there

is some evidence from observational studies that tamoxifen may produce a response in a modest proportion of women with relapsed ovarian cancer. However, there are no reliable data from randomised controlled trials". Eleven non-randomised studies, one non-randomised phase two study and one randomised trial were included in this review (see Williams et al., 1999).

VI. GASTROINTESTINAL CANCERS

Gastrointestinal cancers are a major problem in oncology. Together they are amongst the most frequently occurring cancers worldwide and because of the difficulties related to early diagnosis and treatment, they are among the major causes of cancer-related death.

VI.a. Gastric Cancer

As far as mortality is concerned, gastric cancer is the most lethal tumor type world-wide. Patients usually present late in the disease with non-specific symptoms and the tumor stage at diagnosis is frequently advanced. As a consequence the potential for effective local therapies is extremely limited. Unfortunately the efficacy of chemotherapy is also limited. There are only a limited number of drugs that have activity in gastric cancer including 5-FU, mitomycin C, doxorubicin, cisplatin, taxanes and irinotecan. These drugs have been reported to have single agent activity of approximately 20% in patients with metastatic disease, and although combinations of drugs have yielded improved response rates, there has not been an associated improvement in survival. A commonly used regimen is epirubicin, cisplatin and infusional 5-FU (ECF) (see Webb et al., 1997).

For many years adjuvant chemotherapy for gastric cancer has been considered to be of marginal benefit. Two recent studies have challenged this stance. The Intergroup 0116 post-operative chemoradiation study of completely resected gastric cancer (see Macdonald et al., 2001) and the ECF neo-adjuvant study (see Cunningham et al., 2006) both demonstrated an overall survival advantage of approximately 10% at median follow-up of 3–4 years. There are no data at present to suggest which approach is preferred and the choice usually depends on whether the patient is seen by the medical oncologist before or after surgery.

VI.b. Hepatoma

Hepatoma is a rare disease in the western world, but is a very common tumor type in the orient. Unfortunately for those stages of disease beyond resectability which is unfortunately the majority of patients, no drug treatment with proven benefit exists.

A systematic review in the Cochrane database of neo-adjuvant and adjuvant therapy for operable hepatocellular carcinoma conclued that "there is no evidence for efficacy of any of the adjuvant protocols reviewed. In order to detect a realistic treatment advantage, larger trials will have to be conducted" (see Chan et al., 1999).

VI.c. Pancreatic Cancer

Similarly for pancreatic cancer a major issue is that patients usually present late in the course of their disease with non-specific symptoms. As a consequence chemotherapy for pancreatic cancer has not been very rewarding. Recent data have suggested that gemcitabine, although inactive as far as response induction is concerned, has improved the quality of life of patients with pancreatic cancer and slightly prolonged survival (see Burris et al., 1997). Because of this study the drug is registered for the treatment of pancreatic cancer in many countries. However, since the method evaluating the patient benefit has not been validated yet, many investigators and physicians are still doubtful about the actual utility of gemcitabine. Despite numerous studies of combination chemotherapy none has shown a significant survival advantage compared to single agent gemcitabine.

With regard to adjuvant and neo-adjuvant approaches there is little consensus. A report from the German CONKO Group (see Oettle et al., 2007) reports a disease free survival advantage with adjuvant gemcitabine but confirmation from other studies is required. The results of the ongoing European ESPAC 3 study are awaited with keen interest. The contribution of adjuvant radiotherapy to chemotherapy is controversial and unresolved.

VI.d. Colorectal Cancer

VI.d.1. Treatment of Metastatic Disease

Following the synthesis of 5-FU in 1957 this drug remained the gold standard therapy, albeit with limited benefits, for metastatic colorectal cancer for the next 4 decades. Variations on the 5-FU theme such

as modulation by leucovorin and infusional schedules produced modest improvements but these were insufficient to improve overall survival. The introduction of the newer chemotherapy agents oxaliplatin and irinotecan in combination therapy has extended the frontiers of colorectal cancer treatment and, for the first time, extended overall survival to a current median of 22 months. Irinotecan has activity as a single agent and can be usefully used following 5-FU failure (see Cunningham et al., 1998), however, oxaliplatin has little effect as a single agent but has much improved activity when combined with 5-FU due to synergism between these two agents. At present the recommended first line regimens for metastatic disease include oxaliplatin and infusional 5-FU plus leucovorin (FOLFOX), oxaliplatin and capecitabine (CAPOX or XELOX) or irinotecan and infusional 5-FU plus leucovorin (FOLFIRI). These regimens achieve response rates of 40–45% and have extended median survivals by 3–4 months compared to 5-FU based therapy. The sequence in which these regimens are used is immaterial but both oxaliplatin and irinotecan regimens should be used to give the individual patient the best advantage. However, the toxicity of these regimens needs to be acknowledged in terms of greater myelotoxicity, gastrointestinal toxicity and, with oxaliplatin, neurotoxicity. Regimens with capecitabine have greater cutaneous toxicity and possibly gastrointestinal toxicity.

For patients who cannot tolerate the intensity of the oxaliplatin and irinotecan regimens the standard Mayo (see Poon et al., 1989), Roswell and de Gramont Park 5-FU regimens (see de Gramont et al., 1997) remain appropriate. In addition the oral fluoropyrimidine pro-drug, capecitabine, is equally beneficial.

The momentum for improvement in colorectal cancer therapy continues with the application of the targeted therapies bevacizumab and cetuximab. Bevacizumab is an anti-vascular endothelial growth factor antibody which demonstrates its best activity in combination with 5-FU based therapy plus or minus irinotecan or oxaliplatin. Preliminary data suggest that the addition of bevacizumab to oxaliplatin containing regimens can improve response rates by 10–15% and overall survival by up to 6 months. Such advances usually come with toxicity-related costs and in the case of bevacizumab this includes risk of bleeding, hypertension, bowel perforation, delayed wound healing and thromboembolism. Cetuximab is an anti-epidermal growth factor receptor (EGFR) blocking monoclonal antibody. Cetuximab has modest activity in relapsed colorectal cancer as a single agent but is more effective with irinotecan and possibly oxaliplatin based regimens where a doubling of the response rate has been observed. There is some evidence that cetuximab may reverse irinotecan resistance. Toxic effects of cetuximab include hypersensitivity reactions, malaise, nausea, headache and an acneiform rash.

VI.d.2. Adjuvant Therapy

The major impact of chemotherapy in colorectal cancer has been achieved in adjuvant application. After the initial report on the application of 5-FU based chemotherapy regimens following surgery, similar therapies have been extensively studied and have proven to increase absolute survival rates by up to 15% in poorer risk, stage 3 patients. The incorporation of new generation chemotherapy agents such as oxaliplatin has produced more encouraging results. The phase III MOSAIC and NSABP C-07 studies incorporated oxaliplatin into infusional and bolus 5-FU/leucovorin therapies respectively and at median follow-up periods of approximately 3 years disease-free survival was enhanced by 5% but subgroup analysis showed a greater benefit for stage 3 disease.

This benefit comes at a cost of significant toxicity, particularly neuropathic, and more mature data are necessary to demonstrate the ultimate benefit of adjuvant therapies on improved overall survival. So far irinotecan plus 5-FU based therapy has produced disappointing results in adjuvant treatment. Despite the present lack of data addressing overall survival benefit, oxaliplatin plus 5-FU/leucovorin is widely recommended as the gold standard adjuvant therapy for stage 3 disease. For those whose medical fitness or other contra-indications preclude oxaliplatin based therapy 5-FU/leucovorin on a weekly or monthly schedule is recommended. Oral capecitabine for 6 months has recently been reported to be at least equivalent to 5-FU/leucovorin.

The role of adjuvant chemotherapy in node negative, stage 2, disease is less clear. The majority of studies have not shown an overall survival benefit from 5-FU/leucovorin. However, some studies such as the large QUASAR study have reported a small disease-free survival advantage and this has been confirmed by some multi-study analyses and meta-analyses. Because the benefits of 5-FU/leucovorin are debatable for standard-risk stage 2 patients the

current approach is to offer such therapy to those with high-risk stage 2 disease – T4 tumors, presentation with perforation or obstruction or high tumor grade. Future reports from studies using oxaliplatin based therapy for stage 2 disease will be of considerable interest.

VII. GENITO-URINARY CANCERS

VII.a. Renal Cancer

Renal cancer, also referred to as Grawitz's tumor or hypernephroma, is a tumor derived from the proximal tubules of the kidney and accounts for approximately 3% of adult malignancies.

Surgery remains the mainstay of treatment for localized disease. Approximately 30% of patients present with metastatic disease. Although nephrectomy has traditionally not been recommended in the context of metastatic disease, except in cases of pain or hemorrhage due to local tumor burden, two recent phase III studies have reported modest improvement in durations of survival when carefully selected patients undergo nephrectomy followed by interferon therapy. The larger of the two studies reported a median survival advantage of 3 months.

Clear cell renal cell cancer is a chemotherapy-resistant tumor partly due to overexpression of the multidrug resistance-associated P-glycoprotein, with no single agent or combination regimen showing good activity. All commonly used agents reveal a response rate of $<6\%$ and show no survival benefit. Immunomodulation with interferon-α (IFN-α) yields response rates of 15–20% in patients with metastatic renal cell cancer with a median response duration in the range of 6–10 months. However, no survival benefit has been clearly established. In most studies, response is correlated with a good performance status, low tumor burden (prior nephrectomy) or lung-predominant disease. Although the optimal dose and schedule of administration of IFN-α has yet to be determined, intermediate dose regimens ($(5–10) \times 10^6$ IU/M^2, 3–5 times a week i.m. or s.c.) have been used most often. Interleukin-2 (IL-2) has also been used in different doses and schedules. High dose regimens are associated with greater toxicity but are more effective than low dose therapy and can elicit durable responses in 15–20% of patients. Combination cytokine therapy has failed to improve the clinical efficacy of IL-2 alone. A number of targeted therapies such as the tyrosine kinase inhibitors sunitinib and sorafenib and the anti-VEGF monoclonal antibody bevacizumab are showing promise for renal cancer but their roles are still being defined.

VII.b. Cancer of the Bladder

Bladder cancer is the fifth most common malignancy in men. Approximately 70% of cases present with superficial disease and 30% have muscle-invasive tumors or metastatic disease. Radical surgery remains the standard treatment for invasive disease. Following cystectomy for muscle invasive bladder cancer, up to 50% of the patients will develop distant metastases (see Sternberg, 1995).

For metastatic disease antitumor activity has been demonstrated for a number of single agents, including methotrexate, vinblastine, adriamycin, cisplatin, taxanes, ifosfamide and gemcitabine resulting in response rates of 15–30%. Single agent chemotherapy is usually associated with relatively short response durations, typically less than 6 months. Combination therapy with M-VAC (methotrexate, vinblastine, adriamycin, cisplatin), CMV (cisplatin, methotrexate, vinblastine), CM (cisplatin, methotrexate) and CG (cisplatin, gemcitabine) are considered among the most active regimens for metastatic bladder cancer resulting in a doubling of survival durations to 12–14 months. MVAC has been considered the most active regimen and has demonstrated a survival advantage compared to single agent therapy but this is achieved at the expense of considerable toxicity. Gemcitabine plus cisplatin is a more tolerable regimen and is showing promising anti-tumor effect which may be equivalent to that achieved with MVAC.

Neo-adjuvant chemotherapy for muscle invasive and locally advanced bladder cancer has been assessed in a number of randomized studies. Most studies have been relatively small and therefore underpowered. More recently the larger INT 0080 trial from the United States and the MRC/EORTC study from Europe reported survival advantages for neo-adjuvant MVAC and CMV but these differences did not quite reach statistical significance. A Cochrane Review (see Advanced Bladder Cancer Overview, 2004) concluded that cisplatin based neo-adjuvant chemotherapy provided a 5% 5-year survival benefit.

VII.c. Prostate Cancer

Adenocarcinoma of the prostate is one of the most common malignant tumors in adult males. For advanced disease palliative hormonal therapy has been

the mainstay of treatment. Androgen deprivation therapy (ADT) is achieved by bilateral orchidectomy or chemically with gonadotropin-releasing hormone (LHRH) analogs, estrogens, anti-androgens or aromatase inhibitors which achieve an 80% subjective response rate. There are no conclusive data to show superiority of one form of ADT over others although some suggestive results in favor of testicular androgen ablation exist. Combined androgen blockade with the addition of flutamide to testicular androgen ablation has shown variable results and any survival benefit is minor. This small advantage needs to be balanced against increased drug-induced morbidity and increased medication costs. Controversies remain concerning the optimal timing of ADT. A Cochrane review of four timing studies suggested benefits from early treatment in terms of progression free survival and, to a lesser degree, survival (see Nair et al., 2002). Chemotherapy may be used in hormone refractory disseminated disease. Several agents including docetaxel, doxorubicin, mitoxantrone, and estramustine show some activity but the newer regimens including docetaxel have a clear advantage in terms of PSA response, pain control and objective tumor response.

Androgen deprivation therapy (ADT) is being used increasingly as neo-adjuvant and adjuvant therapy. Neo-adjuvant ADT for 4–6 months before external beam radiation can enhance survival and reduce the prostate volume to be irradiated. Similar benefits have not been seen prior to radical prostatectomy. The benefits of neo-adjuvant therapy are most evident for high risk localized prostate cancer. Adjuvant ADT for up to 2 years following external beam radiation increases disease-free survival and overall survival for locally advanced (T3) tumors.

VII.d. Testicular Germ Cell Cancer

The vast majority of malignant tumors of the testes are of germ cell origin. Traditionally, germ cell tumors are classified as seminomas or non-seminomas based on morphological examination of the tumor. In clinical stage I seminoma, conventional therapy has consisted of orchidectomy with adjuvant radiotherapy to the para-aortic lymph nodes. Recently active surveillance or a single dose of adjuvant carboplatin, AUC 7, have become acceptable alternatives, all achieving overall survival approaching 100%. In clinical stage I non-seminoma testis a 'wait and see' active surveillance policy with chemotherapy used at relapse has been advocated. Alternative approaches include 1 or 2 cycles of adjuvant bleomycin, etoposide and cisplatin (BEP) for those with higher risk disease or adjuvant retroperitoneal lymph node dissection. All of these approaches achieve approximately 95% disease free survival rates.

Since the chemotherapy era began metastatic testicular germ cell tumors have been amongst the most curable metastatic tumors. Based on several independent prognostic factors, patients with metastatic germ cell tumors treated can be allocated to three prognostic categories: good prognosis (5 year survival 90%), intermediate prognosis (5 year survival 75–80%) and poor prognosis (5 year survival 48%). The treatment of patients with metastatic disease is dictated by the prognostic rating. Good-prognosis patients are treated with three courses of BEP (Bleomycin 30 mg day 1, 8 and 15, etoposide 120 mg/m^2 days 1, 3, 5 or 100 mg/m^2 days 1–5, cisplatin 20 mg/m^2 days 1–5) chemotherapy. The main goal of future trials in this group of patients is to reduce toxicity, while maintaining efficacy. In intermediate and poor risk patients four cycles of BEP is standard.

VIII. SARCOMAS

Sarcomas are tumors of mesenchymal origin, arising in skeletal tissues and extra-skeletal connective tissues including the nerves. They are very rare and mainly effect a younger population. Sarcomas of soft tissues are relatively insensitive to drug treatment and are therefore not discussed in detail in this chapter. A systematic review of fourteen trials of doxorubicin-based adjuvant chemotherapy for the treatment of soft tissue sarcomas involving 1568 patients concluded: "Doxorubicin-based adjuvant chemotherapy appears to significantly improve time to local and distant recurrence and overall recurrence-free survival in adults with localised resectable soft tissue sarcoma. There is some evidence of a trend towards improved overall survival" (see Sarcoma Meta-analysis Collaboration, 1999).

Skeletal sarcomas can be largely divided into osteosarcomas on one hand and the Ewings family of sarcomas, including peripheral neuro-ectodermal tumors or PNETs, on the other hand. Both groups share a sensitivity to chemotherapy and need to be managed by multidisciplinary teams to optimize potential curability.

VIII.a. Osteosarcoma

Before the advent of effective adjuvant chemotherapy, the outlook for patients with osteosarcomas was dismal. Since the late 1970s and early 1980s chemotherapy has become a standard for the treatment of osteosarcomas and is the backbone of treatment in this disease. The most common approach for patients with non-metastatic disease is treatment with neo-adjuvant chemotherapy. Initially American investigators had reported the efficacy of a very complex combination chemotherapy regimen including high dose methotrexate but more recently a study of the European Osteosarcoma Intergroup has shown that a more simple regimen of cisplatin plus doxorubicin is as effective, particularly in adults, while being less toxic (see Souhami et al., 1997). In view of this the present recommendation is to treat children and adolescents with the multi-agent/high dose methotrexate neo-adjuvant regimen when conservative surgery is feasible and adult patients with the simpler cisplatin/doxorubicin regimen. Surgery should be planned before chemotherapy is initiated. In the case of a good clinical response to treatment evident at surgery after 3 cycles of chemotherapy, and also on pathologic examination (necrosis of more than 90% of tumor cells), treatment with the same chemotherapy regimen should be continued post-operatively. Post-operative adjuvant chemotherapy is essential.

Metastatic osteosarcoma has a poor prognosis unless the disease is confined to the lungs and is resectable. Palliative chemotherapy can be employed with a number of drugs including doxorubicin, cisplatin, carboplatin, methotrexate, ifosfamide and etoposide.

VIII.b. Peripheral Neuro-Ectodermal Tumors (PNET) or Ewings Family of Sarcomas

The approach to PNET is similar to that described for osteosarcomas, although the chosen cytotoxic agents are different and radiotherapy plays a more important role. Treatment should be started with chemotherapy, usually comprising a combination of agents such as doxorubicin, VP-16, ifosfamide or cyclophosphamide, actinomycin-D and vincristine. After an optimal local response has been obtained, either surgery or local radiotherapy is applied depending on the site of the disease and the applicability of the technique. Sometimes a combination of both is applied. After optimal local treatment, chemotherapy is continued, usually for 6–12 cycles. The value of such continued treatment has been documented for children but in adults it is still at doubt. One of the approaches for studies in the near future is whether high dose consolidation chemotherapy with peripheral stem cell transplantation rescue could substitute for the long lasting consolidation treatment presently applied. Cure rates of 60% are not uncommon in patients with localized disease. Once the disease has metastasized or in patients with bulky disease up-front, the prognosis is much more dismal.

VIII.c. Gastrointestinal Stromal Tumors

Gastrointestinal stromal tumors (GIST) are a rare but fascinating group of stromal tumors. Approximately 80% of GIST express mutations in the KIT tyrosine kinase gene and this has a central role in oncogenesis and therapy. Imatinib inhibits the dysregulated KIT kinase activity and has extended the median survival of patients with metastatic disease to 4–5 years compared to 1–2 years in the pre-imatinib era (see Demetri et al., 2002). This is an impressive result for a tumor which characteristically is relatively chemotherapy resistant. Current studies are exploring the application of imatinib in the adjuvant setting since 50% of malignant GIST relapse following complete surgical resection.

IX. LEUKEMIAS

Relative to the treatment of many solid tumors, the care of the patient with leukemia, especially acute leukemia, depends on the highest level of supportive care to sustain the individual through the complications of therapy. Infection and hemorrhage have been the primary causes of death in leukemia patients, and most of the improvements seen in the care of leukemia patients over the last decades can be directly attributed to advances in supportive care. For more information on drug therapy for such supportive care the reader is referred to focused textbooks.

IX.a. Acute Myeloid Leukemia

The general approach to the treatment of acute myeloid leukemia has consisted of an anthracycline, usually daunorubicin, and cytarabine induction regimen followed by an intensive post-remission therapy phase most frequently comprising high dose

chemotherapy with bone marrow transplant rescue. Standard induction regimens based on combinations of cytarabine and an anthracycline yield complete remission rates for younger adults ranging from 65–75%. Over the past two decades there has been a major focus on dose intensification. The general consensus has been that dose intensification yields higher response rates and superior disease-free survival, however, long term outcomes have not been improved. The best predictor of outcome for AML is the cytogenetic and molecular genetic status of the blasts (see Mrozek et al., 2001). Patients classified as adverse prognosis on karyotypic grounds fare poorly with standard induction chemotherapy and new approaches, including non-cytotoxic therapies, may be preferable. The 5-year survivals for good, standard and poor risk patients are approximately 70, 50 and 15%, respectively.

After induction chemotherapy a post-remission therapy must follow. Although there is some controversy on the form of post-remission therapy, the need for such therapy is not debated. The options include intensified therapy with high dose cytarabine or high dose chemotherapy with autologous or allogeneic stem cell transplantation. Patients with favorable disease require high dose cytarabine only and studies over the past decade have suggested that transplantation does not offer any advantage for the intermediate prognosis group either. These results have caused many centers to re-evaluate the approach to treatment of AML patients in first remission. While some still recommend high dose therapy with transplantation, others reserve the allogeneic marrow transplant approach for relapsed disease.

The treatment of AML in patients older than 60 is problematic due to intrinsic adverse AML features plus diminished performance status potentially leading to poorer outcomes compared to younger patients. The options include standard induction therapy for those who are fit, low dose cytarabine, investigational therapies or supportive care only. It is vital that good information and open discussion are made available to older patients before a management strategy is defined.

IX.b. Acute Lymphoblastic Leukemia

The treatment of adult acute lymphoblastic leukemia (ALL) is typically divided into 4 broad categories: induction therapy, intensification or consolidation therapy, maintenance therapy and central nervous system (CNS) prophylaxis.

Since at presentation many patients can be quite ill with active infection and hemorrhage, the induction regimens have typically emphasized relatively myeloid-sparing cytotoxic agents. The mainstay of such therapy has been the combination of vincristine and prednisone plus asparaginase or an anthracycline, or both. These regimens achieve complete remission in 98% of children and 85% of adults.

Intensification or consolidation therapy is administered at relatively high dose intensity to patients already in complete remission. Because of their improved clinical condition, they are better able to tolerate myelosuppressive treatment. For children consolidation therapy commonly involves high dose methotrexate with mercaptopurine and high dose asparaginase. For adults the drug most frequently used is cytarabine (Ara-C). This is commonly combined with agents such as the anthracyclines, epipodophylotoxins, anti-metabolites and, for T-cell ALL, cyclophosphamide. In addition reinduction therapy has become an integral part of consolidation therapy. High dose therapy with transplantation is infrequently used in ALL but allogeneic grafting should be considered in those with high risk disease. Maintenance or continuation therapy is administered to patients in remission following the more intensive consolidation therapy. It is administered at a low dose intensity but for a protracted period of time and the current opinion is that two years of maintenance therapy is required for optimal results. The support for such treatment is not derived from randomized trials but mainly from reports of studies that failed to utilize maintenance therapy and reported low disease free survival rates. The two most important drugs in maintenance chemotherapy are oral methotrexate and mercaptopurine.

A unique feature of the treatment of ALL is CNS prophylaxis. The CNS can be considered as a ‘sanctuary’ site. This is an area were penetration of systemically administered cytotoxic agents is compromised, leading to the potential of localized relapse. CNS prophylaxis is achieved by intrathecal administration of cytotoxic drugs. Methotrexate is commonly used for this purpose and is administered concurrently with consolidation systemic therapy. Cranial irradiation can cause significant long-term morbidity so it is reserved for those with a high risk ALL or those who relapse. Using these therapeutic strategies the long-term disease free survival for children is currently 80% and for adults 30–40%.

IX.c. Chronic Myeloid Leukemia

The treatment options for chronic myeloid leukemia (CML) are numerous and decision making is complex. The options for chronic phase disease include chemotherapy, interferon, tyrosine kinase inhibitor therapy (e.g. imatinib, dasatinib) and allogeneic hemopoietic cell transplantation. Conventional chemotherapy for chronic phase CML involves mainly hydroxyurea and busulfan but this is only palliative in intent, as is the case with interferon. The advent of tyrosine kinase inhibitors has revolutionized the management of CML with cytogentic remissions now attainable (see Peggs et al., 2003). However, the durability of these remissions is still uncertain and it is unclear whether this approach is as productive long term as allogeneic transplantation when a matching sibling donor is available. Allogeneic transplantation has curative potential and can be recommended for younger patients with a matching sibling although there is an increasing trend towards early imatinib in this patient group with transplantation reserved for those who do not achieve a durable cytogenetic remission. It is still unclear whether early imatinib compromises the efficacy of subsequent allogeneic transplantation (see Deininger et al., 2006). In the accelerated phase of CML high dose chemotherapy with bone marrow transplant rescue has been shown to be effective but long term survival is rare.

IX.d. Chronic Lymphocytic Leukemia

Chronic Lymphocytic Leukemia (CLL) is the most commonly occurring leukemia and is typically a disease of elderly patients. This has major consequences for the approach to treatment. In the early, less extensive stages of disease involving predominantly lymphocytosis with or without lymphadenopathy, no treatment is administered. In the advanced stages of disease including hepatomegaly and/or splenomegaly, anemia and/or thrombocytopenia the prognosis is much more unfavorable and therefore early treatment is instituted. Purine analogs such as fludarabine and cladribine have now been shown to have superior response rates to the traditional alkylating agents although overall survival has not been prolonged. Unfortunately combination chemotherapy has not been shown to be more effective and presently there is no prospect for cure with standard therapies. Newer therapies which are still investigational include autologous or allogeneic transplantation and the monoclonal antibodies rituximab and alemtuzumab.

X. LYMPHOMAS

X.a. Hodgkin's Disease

Hodgkin's disease accounts for 1% of all new cancers diagnosed in Western countries and for 15% of all malignant lymphomas. In patients with early stage IA–IIA disease without B-symptoms or bulky adenopathy, therapy consists of either extended field radiotherapy or limited duration chemotherapy, e.g. ABVD (anthracycline, bleomycin, vinblastine, dacarbazine) for 3–4 cycles followed by involved field radiotherapy. Radiation alone results in a 10-year relapse free survival of 70–75% and, because of the efficacy of salvage chemotherapy for those who relapse, an overall survival of 80–85%. The combined modality approach results in fewer relapses but overall survival is similar. In order to reduce the long term morbidity of radiation current trials are exploring combined modality treatment with lower radiation doses versus chemotherapy alone.

All other stages of Hodgkin's disease are treated with chemotherapy followed, in selected cases, by radiotherapy. In 1964 the MOPP (Mechlorethamine, Oncovin, Procarbazine, Prednisone) regimen was developed and remained the chemotherapy benchmark for two decades until ABVD was developed – doxorubicin 25 mg/m^2 day 1 and 15, bleomycin 10 U/m^2 day 1 and 15, vinblastine 6 mg/m^2 day 1 and 15, dacarbazine 375 mg/m^2 day 1 and 15, repeated every 28 days. The ABVD regimen was formulated to reduce the risks of myelotoxicity, infertility and carcinogenicity. When adjusted for dosing differences, there appear to be no significant differences in longterm outcome when one of the following regimens is administered: MOPP, ABVD, MOPP alternated with ABVD or hybrid MOPP/ABV(D). More recently regimens of shorter duration but greater dose intensity have been developed. These regimens include the German BEACOPP (see Diehl et al., 2003) and the American Stanford V (see Horning et al., 2000) regimens. Initial results from these regimens look promising, particularly for high risk patients, but their ultimate role has still to be defined. The role of radiotherapy following chemotherapy is controversial except in the case of bulky mediastinal disease when it is routinely administered. Generally, when a complete response to chemotherapy is seen there is little justification for radiotherapy. When a partial response is achieved involved field radiation is usually advised.

Applying these strategies the overall survival for advanced stage Hodgkin's disease ranges from 70–80%. In patients relapsing more than one year from achieving a complete remission with chemotherapy, re-treatment with the same or similar regimen remains the standard approach. Patients progressing during primary chemotherapy or relapsing within 1 year are treated with high dose chemotherapy and autologous marrow or stem cell transplantation.

X.b. Non-Hodgkin's Lymphoma

The non-Hodgkin's lymphomas are a heterogeneous collection of neoplasms. There is a substantial variation in incidence worldwide ranging from about 3% of newly diagnosed neoplasms in most Western countries to 10–15% in certain areas of the Middle East. Treatment of lymphomas is based on the histological subtype (follicular or diffuse and small or large cell), stage of the disease, age, physiological status of the patient and special patterns of spread of the disease.

X.c. Low-Grade Lymphoma

Treatment of early stage low-grade lymphoma (follicular, small cell) consists of radiotherapy. There is no clear advantage for the use of combined chemotherapy and radiotherapy. The optimal treatment for patients with advanced stage low-grade lymphoma remains to be determined. A conservative approach, consisting of no initial treatment in the asymptomatic patient, followed by involved field radiotherapy or palliative single agent chemotherapy comprising chlorambucil or combination chemotherapy when required has been widely applied. The complete response rates to single alkylating agents in previously untreated patients range from 30–60%, with a median response duration of 18–24 months. In a randomized trial comparing single agent chlorambucil with CVP (cyclophosphamide, vincristine, prednisone) no significant difference in relapse free or overall survival was observed. Fludarabine alone or as part of a combination offers another option when a rapid response to therapy is required. More aggressive chemotherapy combinations have not shown any further advantage. The role of high dose chemotherapy with stem cell or bone marrow rescue has still to be defined for low grade lymphomas. However, pending the results of mature data from randomized trials, increasing numbers of patients with relapsed or refractory disease are being treated with autologous or allogeneic transplants and are achieving prolonged remissions.

Monoclonal antibody therapy is showing considerable promise for low grade lymphomas. The humanized anti-CD 20 antibody rituximab has shown good results as first line therapy but more substantial benefits, including prolongation of survival, are now being reported from phase III studies of rituximab–chemotherapy combinations compared to chemotherapy alone. In addition interval maintenance rituximab therapy has been reported to extend survival even further (see van Oers et al., 2006). Other promising novel therapies include radioimmunocongugates (Zevalin and Bexxar, anti-CD20 antibodies with radiation attached) and anti-sense therapies.

X.d. Aggressive Lymphoma

Patients with localized (stage I and II) aggressive (diffuse, large cell) non-Hodgkin's lymphomas are treated with a short course (3 cycles) of CHOP or rituximab–CHOP chemotherapy (cyclophosphamide 750 mg/m^2 day 1, [hydroxyl]doxorubicin 50 mg/m^2 day 1, vincristine 1.4 mg/m^2 day 1, prednisone 100 mg/m^2 orally day 1–5, repeated every 21 days) followed by involved field radiotherapy. With this treatment schedule an overall long-term survival of 80% can be achieved. Patients with bulky disease (mass greater than 10 cm) or other poor prognostic parameters should be treated similarly to patients with advanced-stage disease. For patients with advanced-stage aggressive lymphoma, combination therapy with rituximab-CHOP (R-CHOP) is the treatment of choice. The addition of rituximab to CHOP has produced enhanced progression-free and overall survivals in all age categories. Five year follow-up in the GELA R-CHOP study involving patients older than 60 revealed an overall survival advantage of 13%.

More complicated regimens combining six or more cytotoxic drugs have not improved the outcome in unselected patients with aggressive lymphoma, indicating that CHOP chemotherapy is still standard therapy. Other approaches currently under investigation include the scheduling of R-CHOP on a 14 day cycle with granulocyte growth factor support. It is too early yet to say whether this approach will offer a significant advantage. Another experimental approach is to consolidate primary chemotherapy with an autologous transplant in

those with unfavorable risk factors. At present the available data do not allow a clear conclusion.

The improvements in aggressive lymphoma management in the past decade have been encouraging, however, because approximately 50% of patients with standard risk aggressive lymphoma relapse following R-CHOP therapy, salvage therapy remains a key consideration. At present the standard approach is autologous transplantation for patients who still have chemo-sensitive disease. This achieves long term disease-free survival in 40% of such patients.

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Chapter 41

Haematological Disorders

Peter Jacobs, Lucille Wood

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I. BACKGROUND

Although the entire volume is intended for the developing countries this chapter is based on the principle that local management should not differ from international standards of practice. The recommendations are therefore designed to meet the needs of a wider readership including, particularly, medical undergraduates, nurses and other paramedical professionals as well as practising clinicians. Additionally consideration has been given to a worldwide concern about almost uncontrollable escalation in the cost of prescribing medications which, in many instances, have little or no advantages over their well-tried and generally less expensive generic counterparts.

Accordingly, the focus is to recommend treatment using products that are readily available and have a record of efficacy as well as safety with a brief commentary provided on newer formulations. Given increasing financial constraints many of the latter are in limited supply and these are exemplified by growth factors that range from erythropoietin through interleukins to granulocyte or monocyte stimulatory peptides. Our approach will be uniform and outline pathophysiology of the most commonly encountered entities as a basis for therapy. Thus useful investigations are noted where relevant but emphasis remains the provision of guidelines for the primary care practitioners whilst, at the same time, identifying those conditions that require referral to an experienced clinical haematologist for consultation.

II. RED CELL SERIES – ANAEMIA

Physiologically, oxygen transport to metabolising tissues is provided by haemoglobin contained within erythrocytes. This pathway starts in the bone marrow with immunohaematopoietic stem cells that differentiate to progenitors which proliferate to yield the recognisable normoblasts. The latter mature to reticulocytes, which are then released into the circulation. Overall regulation is primarily mediated by the renal hormone called erythropoietin.

Pathophysiologically, the normal red cell mass, reflected in haemoglobin level or packed cell volume, decreases in anaemia. The mandatory first step is to identify the cause for this change and correct it, wherever possible, prior to initiating treatment. It makes little sense only to replace iron in a patient who continues to rapidly loose blood from the gastrointestinal tract due to a heavy hookworm infestation or a resectable carcinoma of the caecum. Accordingly, it will be assumed throughout that a

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history has been carefully taken, examination has been meticulous and the use of appropriate laboratory tests employed as confirmation.

Classification is traditionally by examination of a well prepared and Romanowsky stained blood film although, increasingly, red cell indices are routinely provided by automated counters. These observations are given clinical relevance by their association with the most common causes in what is called the etiologic approach. In addition it is also possible to relate cytomorphology to disturbances in the functional capacity of the erythron so that anaemia is seen to result from impaired production of red cells or their shortened survival (Table 1).

II.a. Iron Deficiency

Physiologically, body stores are maintained by extracting approximately 10% of the iron provided in a balanced diet and this corresponds to 1.5 mg each day for males and slightly more for females to compensate for pregnancy and menses. The trace element is derived from food by peptic digestion and after reduction the ferrous form crosses the enterocyte to be released at the serosal pole via the ferroportin–hepcidin mechanism to be transported, by plasma transferrin, to developing red cells in the marrow for haemoglobin synthesis. At the end of their life span effete erythrocytes are removed by the reticuloendothelial system in the spleen, bone marrow and the liver.

Pathohysiologically, a sub-optimal diet remains a public health issue and centres on education or, increasingly, some form of supplementation. However, it is also possible to diminish bioavailabilty by concurrent ingestion of disproportionate amounts of other staples such as phytates, phosphates or large volumes of tea. Yet another cause of reducing intake is damage to the upper gastrointestinal tract that may result from surgery, tuberculosis, celiac disease or even lymphoma. Conversely, previously normal stores may be depleted by chronic bleeding that creates a negative balance and this is recognized by reduction in serum iron, percentage saturation of transferrin as well as ferritin levels where examples are hiatal hernia and diverticulae. If this unfavourable gradient is present long enough red cells become hypochromic and microcytic with the development of symptomatic anaemia.

Management necessitates correction of the underlying cause. In unusually severe cases, with haemoglobin levels as low as 20 or 30 g/l and particularly in elderly patients where heart failure is present, a single unit of packed red cells can be given over 6 hours with a loop-acting diuretic such as 10 mg of oral or intravenous furosemide. Haemoglobin levels will correct at the rate of 20 g/l every 3 weeks provided replacement is adequate. It should be noted that for stores to be reconstituted 3 and sometimes 6 months of oral treatment are needed.

Table 1. Morphology as the basis for classifying anaemia

Aetiology	Functional defect
Hypochromic and microcytic cells	
Iron deficiency	Impaired production
Sideroblastic anaemia	Impaired production
Thalassaemia and haemoglobinopathy	Shortened red cell survival
Normochromic and normocytic cells	
Bone marrow failure	Impaired production
Chronic inflammation	Impaired production
Antibody production	Shortened red cell survival
Macrocytic and hyperchromic cells	
Folate deficiency	Impaired production
Pernicious anaemia	Impaired production
Myelodysplasia	Impaired production

This outline is not exhaustive. For example there is an increasing awareness of the role played by infection with the human immunodeficiency virus while infiltration of the marrow with fibrous tissue or tumour cells will decrease production. In much the same way massive splenomegaly, so common in tropical Africa, sequesters significant volumes of red cells while malarial infection results in their accelerated breakdown. In some cases defects are multifactorial as in chronic lymphocytic leukaemia where infiltration decreases production, splenomegaly traps large amounts of blood while immune mechanisms lead to shortened survival or haemolysis.

Therapy is perfectly adequate with simple iron salts (Table 2). In adults ferrous gluconate, fumarate or sulphate are all of proven equal efficiency. Approximately 50 mg of iron is present in each tablet with the remaining 300 mg made up with an inert filler. These are given on an empty stomach at least twice a day but should nausea prevail they can be taken with food. Absorption of slow release preparations is not recommended since iron is detached from the carrier beyond the main areas of absorption in the duodenum or jejunum. Stools turn black in all cases and this is a useful index of patient compliance. In 25% of individuals gastrointestinal tract side effects are encountered in the form of diarrhoea or constipation and patients will often spontaneously discontinue medication. It is therefore essential that a tablet-count be carried out on a regular basis with a substitute being provided when this first-line medication is intolerable. In children the same preparations are favoured as syrups: these are given twice daily at a dose of approximately 1 mg/kg of iron calculated on a lean body mass. Additionally, it is essential to appreciate that acute toxicity may be found with overdose. Such accidental excess ingestion can lead to haematemesis, refractory hypotension and even death. In these circumstances emergency treatment is mandatory and takes the form of immediate transfer to a toxicology centre for gastric lavage, admission to hospital for cardiovascular monitoring and infusion of intravenous iron chelates.

Efficacy is appreciated clinically and has two distinct components. Initially there is reversal in the impaired effort tolerance that parallels regeneration of the haemoglobin levels. This is followed by a longer period when cognitive function gradually improves after stores are reconstituted. Oral iron typically needs to be given between 3 and 6 months and certainly until both percentage saturation of transferrin and serum, or preferably red cell, ferritin are normal. It is furthermore prudent that treated indi-

Table 2. Iron preparations and routes of administration

Formulation	Dose	Iron content (mg)	Comment*
Oral[1]			
Tablet			
Ferrous sulphate	300 mg	60	Relative cost = 1
Ferrous fumarate	200 mg	65	1.5
Carbonyl iron	–	–	–
Ferric polymaltose	–	100	3.4
Capsule			
Ferric polymaltose	–	50	4
Syrup			
Ferrous gluconate	10 ml	58	2.1
Ferrous lactate	1 ml	25	4.6
Intramuscular injection[2]			
Ferric polymaltose	2 ml	100	24
Intravenous infusion[3]			
Ferric sucrose	5 ml	100	24
Ferric polymaltose	2 ml	100	24

*Relative cost assigns a ratio, irrespective of local currency, to enable comparison to be made between a standard product and approximately equivalent amounts of iron in other formulations.

[1] Administration needs to be continued until haemoglobin levels are normal and body iron stores reconstituted. Tablets or syrup are given once or twice daily and typically for at least 3 months.

[2] This route is generally not favoured because of variable release from injection sites. It is nevertheless common practice in patients who cannot be depended upon to take their medication and where intravenous infusion is, for one or other reason, not acceptable.

[3] Highly effective as a sucrose complex is routinely used in the anaemia of chronic disease in conjunction with erythropoietin. In the case of the iron polymaltose, not currently a licensed recommendation in some parts of the world, dose is roughly determined by computing haemoglobin level and weight. However, a practical and universally effective technique is to dissolve 50 ml of the product in 1000 ml of physiological saline and infuse over 6 hours in a clinic with non-invasive cardiovascular monitoring.

– Data not available.

viduals be monitored over longer periods of time to recognize recurrence.

Alternative options are increasingly favoured in the form of oral iron polymaltose complexes. These are more expensive but attractive in that complications are less frequently encountered and the lethal toxicity that follows release of large amounts or ionic iron into the circulation does not occur. Carbonyl iron is not often used but available in some countries. In contrast combinations with vitamins and cobalt, still popular in certain areas, have no documented advantage and add quite unnecessary cost. Other routes are intramuscular injections and, except where oral administration is precluded, have disadvantages in that mobilization is unpredictable. Conversely, it is feasible to replace iron as a single total dose infusion but such procedures need to be given under supervised conditions. It is reiterated that the rate of rise in haemoglobin that follows adequate oral replacement is comparable to that achieved parenterally.

Prescribing perspective is therefore to identify and treat the cause of the lesion and reverse this if possible, then to correct the haemoglobin and replenish body iron stores with simple oral ferrous salts or syrup with iron polymaltose complexes as a reasonable alternative. Intramuscular or intravenous routes are reserved for special circumstances.

II.b. Sideroblastic Anaemia

Physiologically iron entering the developing erythrocyte is transferred to the mitochondrion where it is incorporated into a tetrapyrole synthesized from amino acids to form haem. This complex then returns to the cytoplasm where it is inserted into the globin molecule to make the red iron-transporting pigment called haemoglobin.

Pathohysiologically, this orderly sequence of events can be disrupted due to an inherited deficiency of the enzyme called chelatase or, more importantly, acquired from a wide variety of toxins such as lead or drugs frequently used in treating tuberculosis. An increasing awareness is that preleukaemia or the myelodysplastic syndrome may result in a refractory anaemia with ringed sideroblasts.

Management of the congenital lesions is with intravenous chelate, such as the regular infusion of desferrioxamine. These are expensive programmes and efforts are currently focused on developing oral equivalents such as deferiprone. Although occasional responses are seen with high doses of oral or preferably intravenous pyridoxal phosphate this occurs in a specific sub-category and is not recommended as a routine intervention. Once a cause has been identified discontinuation of the offending medication will lead to reversal of the anaemia and eventually correction of the iron overload. In myelodysplasia eradication of the malignant clone is achieved using high-dose chemotherapy followed by haematopoietic stem cell transplantation. Other alternatives, having variable outcome are erythropoietin, often with combined with GCSF and hypomethylating agents such as 5′ azacytine or decitabine.

II.c. Thalassaemia and Haemoglobinopathies

Physiologically, there is an orderly sequence observed from birth to adulthood in the genetically regulated production of the different globins that make up the haemoglobin molecule. Furthermore, the assembly of the α and β chains is precisely balanced.

Pathophysiologically, two broad categories are possible. Firstly, a point mutation can lead to synthesis of abnormal haemoglobin with clinical syndromes ranging from hereditary persistence of haemoglobin F to more distinctive entities with disproportionate levels of Hb S whereas raised levels of Hb C or E result in the formation of hypochromic and microcytic erythropoiesis. Contrastingly, in thalassaemia, there is an imbalance between the rates at which the component chains are generated so that one or other is present in excess. This causes intramedullary red cell breakdown called ineffective haematopoiesis as well as concurrent shortening of red cell survival in the circulation. The heterozygotes have little clinical problem but require that screening and genetic counselling be provided for family members. Homozygosity, in contrast, produces severe disease that significantly reduces lifespan. Treatment, particularly in areas of high gene frequency, requires accurate characterization of the population at risk and folate supplementation. In the homozygotes morbidity and mortality are substantial so that specialized management necessitates referral, wherever possible, to academic centres for haematopoietic stem cell allografting. It can reasonably be anticipated that with the increasing understanding and use of gene therapy much more selective intervention will become available with an even higher potential for cure.

Prescribing perspective is crucial since hypochromic and microcytic cells may be misinterpreted as iron deficiency and in patients with adequate or expanded stores as occurs typically in these entities, replacement therapy is given when such medication use is contraindicated.

II.d. Bone Marrow Failure

Pathophysiologically, this may arise on a congenital basis, as in Fanconi anaemia. Of the acquired lesions transient erythroblastaemia is found in childhood and is usually self-limited with spontaneous resolution. In the adults, occurrence of an autoimmune process may also selectively delete erythropoiesis in association with underlying thyroma or due to infection with the parvo B19 virus. More ominously is the pancytopenia that is a manifestation of severe degrees of haematopoietic hypocellularity and is known as aplasia or previously – and incorrectly – severe acute aplastic anaemia. In some instances this may be reversible as after cytotoxic chemotherapy but can be permanent following excessive exposure to ionising radiation. Other risk factors are occupational exposure to Benzene. Most cases are idiopathic and here disturbed cell and humoral immunity is believed to play a central role. Diagnoses rests on the bone marrow aspiration and particularly trephine biopsy that shows increase in fat cells, relative prominence of lymphocytes and plasma cells and absence of haematopoietic tissue. More sophisticated investigation with magnetic nuclear resonance imaging of the medullary cavity is diagnostic as are radionuclide studies but these are seldom necessary outside a research setting.

Management in patients with an irreversibly damaged marrow is sophisticated and depends upon whether a sibling or a matched unrelated volunteer donor is available for an allogeneic transplant. Where possible this is the treatment of choice. In the remainder, approximately 65% of cases will have varying degrees of response following intensive immunosuppressive therapy. These interventions are expensive and best administered in academic centres by experience clinical haematologists.

Therapy, when replacement of the marrow by allogeneic haematopoietic stem cell transplantation is not possible, comprises 500 mg of methylprednisolone by 8 hour intravenous infusion repeated for five consecutive days. Concurrently 15 mg/kg of antilymphocyte or antithymocyte globulin is given with prior premedication to block frequent occurrence of hypersensitivity reactions. Although a wide variety of products are available, with some of equine and others of rabbit source, it is likely that the optimum dose rather than the individual product is the significant issue. Additionally, differences also exist in the immunoglobulins as to whether they are directed at lymphocytes or thymocytes and here again, this distinction is probably less important than giving an adequate quantity of the protein. After completing the injection oral prednisolone is started at a dose of 0.5 mg/kg per day and cyclosporin at approximately 3 mg/kg, with this then titrated to maintain whole blood levels within the therapeutic range: note that this varies between centres since different assays are employed. The current method is the C_2 technique. Furthermore, the latter agent is nephrotoxic and monitoring serum creatinine, or preferably the clearance, is important while attention to the development of hyperglycaemia is sensible during the period of corticosteroid administration. In responding patients an arbitrary 3–6-month period is allowed with normal blood count values before the two maintenance drugs are gradually reduced over at least three months. Recognizing that early and accurate diagnosis is the cornerstone for successful outcome provides prescribing perspective. Persistence with well intentioned red blood cell or platelet transfusions, sometimes even misguided iron therapy, are not in the patient's best interest since they compromise success of subsequent haematopoietic stem cell transplantation.

II.e. Chronic Inflammation

Physiologically, the sequence of cellular events that govern the orderly production of normal numbers of functioning red cells continues to undergo investigation. Thus the influence of a large number of molecules, generated by lymphocytes or monocytes and loosely called cytokines, are now known to influence the differentiation of stem cells to yield committed progenitors that will proliferate and mature to culminate in the release of reticulocytes into the circulation. In clinical context the best known of these is erythropoietin, but the influence of interleukins and a variety of other stimulatory and inhibitory peptides from cells of the haematopoietic inductive microenvironment are offering new options for more selective intervention. As at the membrane of cell in the intestine so the regulation of flux in and out of

macrophages is seen to be modulated by ferroportin and the hepatic protein hepcidin.

Pathophysiologically normochromic and normocytic anaemia, as occurs in many clinical syndromes exemplified by renal failure, a number of cancers, rheumatoid arthritis and systemic lupus erythematosus, is typical. Initially erythrocytes are of normal size and degree of haemoglobinization. However, persistent impairment of iron supply, especially from mitochondria to globin in the cytoplasm, leads to them becoming hypochromic and microcytic.

Management is to recognize the cause and repair the defect, after which a reticulocyte response is noted with haemoglobin and red cell indices returning to normal. It is essential that iron not be given to these patients unless there is concurrent proven depletion of stores. Where reversibility is not possible, particularly in the face of uraemia, there may be excellent outcome to erythropoietin administration. Considerable judgement is necessary to select those cases where such high-cost intervention is appropriate given that response and survival have a rough inverse correlation with plasma creatinine or its renal clearance.

Therapy is always to reverse the underlying inflammatory state, after which the abnormalities in erythropoiesis spontaneously correct themselves. In those situations where hormone replacement is employed it would be usual to start at 50 IU/kg given subcutaneously three or four times a week and then titrated to correct symptoms and maintain a arbitrary haemoglobin level between 100–110 g/l. Newer data support a place 30,000–40,000 units of these products weekly and here a number of different formulations exist. It is important not to increase the dose exclusively to get normal blood values since rise in viscosity may predispose patients to thrombosis particularly where foreign substances such as venous catheters are in place. In the specific instance of cases undergoing dialysis there can exist a relative deficiency of iron. Here, the intravenous sucrose or polymaltose complex is given at a dose of 100 mg once or twice a week to keep the serum ferritin and percentage saturation of transferring at the upper limit of the normal range.

Efficacy is gauged by the appearance of a reticulocytosis that precedes increase in haematocrit or packed cell volume with this being an alternative measurement to red cell count or haemoglobin level.

Prescribing perspectives are again important and need to take into account the fact that many of these inflammatory states are reversible or respond to immunosuppressive therapy. Iron therapy should be avoided since stores are generally adequate and correction of the anaemia is a useful clinical reflection of successful treatment. In other patients, exemplified by those with untreatable cancer or end-stage renal disease, resulting from decreased synthesis by damage or loss of parenchyma, reversibility of the causative lesion is not possible. Alternatively, there seems to be a blunted response to the hormone and it is helpful to measure plasma levels in seeking to predict outcome. The pharmacologic doses advocated above work best where pretreated creatinine levels are less than three times the upper limit of the normal value for the particular laboratory used. In these circumstances erythropoietin is a valuable adjunct to improving quality of life but is expensive. Accordingly, judgement is necessary to select those where such intervention is appropriate. It is often useful to refer patients to an experienced clinical haematologist for evaluation, initiation of treatment and then the maintenance to be continued in association with a primary care provider accordingly judgement is necessary.

II.f. Antibody Production

Physiologically red cells are removed from circulation at the end of their lifespan by the reticuloendothelial system. This is thought to occur as the genetic machinery required to maintain intracellular mechanisms for defence from oxidative stress ceases to function and membrane integrity is lost.

Pathophysiologically antibodies are demonstrated in plasma, by a positive Coombs' or direct antiglobulin test, reflecting the presence of immunoglobulins or complement that is bound to the membrane and so accelerates their extravascular removal. There are marked increases in lactic dehydrogenase and a variable degree of conjugated hyperbilirubinaemia with urobilinogen demonstrable in the urine. Compensation is seen in erythroid hyperplasia in the bone marrow and a striking reticulocytosis evident provided that conditioned folate deficiency is not allowed to occur. In severe cases, exemplified by incompatible blood transfusions, the rate of breakdown may be so rapid that this becomes intravascular, with obstruction to glomerular blood flow and development of oliguric acute renal failure.

Management depends on recognising the causative mechanism and two broad categories exist. In

one the antibody, directed against erythrocytes, is associated with other pathology as in chronic lymphocytic leukaemia, systemic lupus erythematosus or rheumatoid arthritis. In contrast many of the patients have no underlying disease and such cases are designated as primary, idiopathic or autoimmune. Not unusually other haematopoietic lineages are involved so that there can be thrombocytopenia in Evans' syndrome or neutropenia particularly in the collagen-vascular diseases. It follows that if there is a precipitating factor this should be corrected after which the haemolytic anaemia will improve. Conversely, in those of unknown aetiology immunosuppression or even plasma exchange and emergency splenectomy can be life-saving.

Therapy requires adequate doses of prednisone and this should start at 1 mg/kg per day with vigilance for the development of systemic hypertension due to sodium and water retention, hyperglycaemia or hypokalaemia. Because of side-effects, associated with prolonged and often high-doses, steroid-sparing is undertaken with concurrent administration of cyclophosphamide or azathioprine and both start at a dose of 2 mg/kg per day. These agents are gradually escalated to the point when neutrophil counts drop to between (3–3.5) $\times$ 10^9/l. At this time they are slowly reduced until peripheral blood count values are stable although compensated cytolytic states, reflecting accelerated turnover of red cells, may persist and this is seen in the raised reticulocyte production index. Alternative options are very expensive and include high-dose gammaglobulin where 400 mg/kg are given for five consecutive days in association with 500 mg of intravenous methlyprednisolone. Occasionally dramatic benefit may result from apheresis when 1.5 times the patient's calculated plasma volume is exchanged against an electrolyte solution containing 5% albumin. Additionally, cyclosporin may be commenced at a dose of 2 mg/kg twice a day but it is mandatory that whole blood levels be monitored and the dose adjusted on a regular basis to maintain adequate levels without a rise in serum creatinine. In refractory cases emergency splenectomy may be unavoidable and the anti-CD20 monoclonal antibody rituximab has a place.

Prescribing perspective is the mandatory exclusion of underlying disorders or treatment of these on merit. The immunological component, whether this extends to involve the platelets or the granulocytes, is different between patients despite a relatively standardized treatment programme. In those where only low doses of steroid, in combination with cytotoxic drugs, is needed long periods of control and even discontinuation of medication is possible. In contrast poor response must be immediately recognised since progression may be rapid with fatal outcome. Guidance from an experienced clinical haematologist is prudent in such circumstances.

II.g. Folate Deficiency

Physiologically, this vitamin, after absorption, which takes place throughout most of the small bowel, is inextricably linked to its co-enzyme vitamin B_{12} and they share a final common pathway culminating in the optimum synthesis of deoxyribonucleic acid.

Pathophysiologically widespread changes occur in haematopoiesis with ineffective blood formation evident in red and white cells as well as megakaryocytes. Lactic dehydrogenase is increased and, in addition to the low haemoglobin, leukopenia and thrombocytopenia are found. Hyperbilirubinaemia gives the patients a distinctive lemon-yellow tinge to skin and conjunctivae. Effects are also seen on other organs having a high cell turnover particularly the gastrointestinal tract and skin. Diagnosis depends upon demonstrating low serum folate reflecting balance between intakes and, more reliably, decreased red cell levels that correlate with body stores.

Management has three important caveats. Firstly, it is mandatory that the causative lesion be reliably identified and, if possible, corrected. Here it should be remembered that a suboptimal intake of this vitamin is frequently seen in those who have diets deficient in vegetables and particularly fresh leafy products found in salads. Secondly, once treatment is initiated, there may be precipitous falls in serum potassium as ineffective haematopoiesis suddenly corrects and so removes the substantial delivery of the intracellular cation to the circulation: renal compensation requires slightly longer to adapt and in that interval cardiac arrhythmia and death can occur. For this reason patients either need to have plasma electrolytes monitored initially or arbitrary oral potassium replacement supplied. Thirdly, there may be a transient increase in haemoglobin, which then reaches a plateau, and this is the consequence of exhausting available iron stores so that monitoring is necessary or supplementation with simple ferrous salts provided.

Therapy for folate deficiency is simple, and takes the form of 5 mg oral tablet given once a day.

Prescribing perspective is vital so that, if there is any doubt as to whether the macrocytic anaemia is due to shortage of folate acid or vitamin B_{12}, then 1000 mg of the latter must be given by intramuscular injection prior to starting the oral replacement. This will protect the patient from inadvertent precipitation of irreversible damage to the spinal cord known as subacute combined degeneration.

II.h. Pernicious Anaemia

Physiologically, distinction from folate deficiency is often clinically and haematologically difficult because vitamin B_{12}, also known as cobalamin, functions as an essential cofactor for folate metabolism in the eventual synthesis of deoxyribonucleic acid.

Pathophysiologically, deficiency results from genetic predisposition in which there is autoimmune destruction of the gastric parietal cells leading to loss of both hydrochloric acid and intrinsic factor. Absence of the latter precludes the binding and transfer of vitamin B_{12} to the terminal ileum where receptors exist for absorption and movement, by means of the transcobalamins, to hepatic stores or developing red cells. A similar situation can be acquired with extensive resection of the stomach or damage by tumours that include lymphoma or carcinoma. Additonally, effective absorption is precluded by extensive pancreatic disease or lesions of the terminal ileum. Both the latter are recognized by carefully taken history and physical examination.

Management is essentially the same as for folate deficiency but the site of the lesion, that may necessitate further investigation and treatment, needs accurate definition by means of the Schilling test. Additional useful determinations are homocysteine and methylmalonic acid levels.

Therapy is possible with large doses of oral vitamin B_{12} where passive diffusion provides the microgram quantities necessary for daily needs. However, particularly in the autoimmune disease where there is extensive damage to the stomach or in those situations where the function of the terminal ileum is destroyed due to lympoma or following surgery, it is safer to give 1000 mg as hydroxocobalamin every 6 weeks. The older cyanocobalamin has fallen into disrepute but, in those areas where it is still employed, the same dose is used although preferably once a month.

Prescribing perspective predicates that, as previously stated, the underlying cause must be reliably identified and corrected if possible. Thereafter milligram quantities of vitamin B_{12} given orally are sometimes an effective alternative to parenteral replacement but place the onus on the prescribing doctor to be certain of patient compliance. Given the potential hazards of neurological damage many would regard it as preferable to give the missing vitamin by regular intramuscular injection.

II.i. Myelodysplasia

Pathophysiologically, there is a macrocytic anaemia with megaloblastic haematopoiesis that occurs in the face of normal folate and vitamin B_{12} and is refractory to therapeutic trials of these two nutrients. Patients are characterized as having a preleukaemic syndrome, which is currently regarded by many as a neoplastic process arising in the haematopoietic stem cells that is analogous to early acute myeloblastic leukaemia.

Management is controversial, but in the young and suitable case, current preference for high-dose chemoradiotherapy followed by immunohaematopoietic stem cell transplantation. Nevertheless between 25% and 30% of cases, which are unsuitable for aggressive treatment, will improve their quality of life and haemoglobin levels following erythropoietin administration. There is limited evidence that additional stimulatory peptides such as granulocyte colony-stimulating factor (G-CSF), sometimes in combination with corticosteroids, may be of benefit. These interventions do not alter the ultimately progressive nature of the neoplasm. Recent additions include the hypomethylating agents exemplified by 5′ azacytidine or decitabine and here variable response rates have been reported. Classification is now according to the World Health Organization.

Prescribing perspective necessitates an awareness of this diagnostic possibility and its reliable separation from simple folate or vitamin B_{12} deficiency. Here cytogenetic studies may be crucial. Once the diagnosis has been made a number of individuals are seen not to be suitable for aggressive intervention. In this situation the use of stimulatory peptides is of value but are expensive and should therefore be used only on the recommendation of an experienced clinical haematologist.

III. RED CELL SERIES – ERYTHROCYTOSIS

Physiologically the orderly progression of red cell formation proceeds from stem cells through progen-

itors to the recognisable precursors in the marrow. These normoblasts ultimately lose their nuclei to become reticulocytes and ultimately mature to red cells.

Pathophysiologically, overproduction can occur at a number of different levels (Table 3).

Management depends upon the underlying cause. The cardinal measurement, apart from the preliminary finding of a raised haemoglobin or haematocrit in the blood, is a separate determination of red cell mass and plasma volume using either flow cytometry or the traditional radonuclide methodology.

III.a. Spurious or Relative

Pathophysiologically, acute haemoconcentration results from loss of plasma to the exterior, as with extensive burns or severe diarrhoea, but a similar situation develops with shock, particularly that associated with bacterial infections, where fluid leaks into a number of tissues including the pulmonary parenchyma. Conversely, this may occur on a chronic basis as exemplified by stress erythrocytosis where the mechanism for the reduction of plasma volume is unknown. It is, however, noteworthy that this entity, previously known as the Gaisbock syndrome, is found in young male executives who are generally heavy smokers. The latter habit reduces plasma volume before deoxygenation has been present for a long enough time to lead to expansion of red cell mass, and it is possible that one or other of the products inhaled from cigarette smoke

Table 3. Classification of erythrocytosis

Spurious or relative
Haemoconcenration
Acute
Burns
Shock
Diarrhoea
Chronic
Smoking
Stress
Absolute – physiologically appropriate
Congenital
Due to haemoglobin with high affinity for oxygen
Physiological
Ascent to high altitude
Pathological
Carboxyhemoglobinaemia
Chronic obstructive airways disease
Pulmonary hypoventilation syndrome
Right-to-left cardiac shunt
Absolute – physiologically inappropriate
Ectopic erythropoietin production
Renal carcinoma and cysts
Hepatoma
Cerebellar haemangioblastoma
Massive uterine fibroids
Androgen-secreting tumours
Phaechromocytoma
Autonomous red cell proliferation
Primary proliferative polycythaemia

Patients are initially grouped by independent measurements of red cell mass and plasma volume. Where the latter is contracted the increase in packed red cell volume or haemoglobin in the peripheral blood is spurious or relative. In true erythrocytosis the red cell mass, and often the plasma volume, are both expanded. These individuals are further subdivided, depending upon whether tissue oxygenation is impaired, with consequent activation of normal physiological mechanisms. Conversely, this situation may reflect pathological production of erythropoietin or uncontrolled overgrowth of red cells in the chronic myeloproliferative syndrome.

brings about these changes. There is also limited evidence that endocrine change or alterations in vascular tone attributable to autonomic dysfunction have a similar effect but proof is lacking.

Management in the acute situation requires reversal of the underlying disease process followed by fluid replacement. In chronic haemoconcentration every endeavour must be made to exclude all possible underlying organic causes after which risk factors for stroke or myocardial infarction, such as smoking, hypercholesterolaemia, control of weight are corrected and a sensible exercise programme encouraged. Direct intervention by attempting to expand the plasma volume by infusion of fluid is pointless.

Therapy is directed at reducing whole blood viscosity where this is significantly raised. Small volume venesections, in which 250 ml as opposed to 500 ml of whole blood, are carried out at 2- or 3-week intervals. It should be noted that studies have demonstrated impairment of cerebral blood flow and a shortened survival in these individuals so that such intervention is appropriate in the severe cases.

III.b. Absolute – Physiologically Appropriate

Pathophysiologically, the congenital lesions occur with considerable rarity and reflect increased binding of oxygen to haemoglobin, a phenomenon known as a left shift in the dissociation curve. There is a consequential expansion of red cell mass. Of the acquired lesions the physiological response is exemplified by ascent to high altitude. Of greater importance are the pathological causes, all of which are characterized by varying degrees of change in blood flow or rheology. The basic problem is an increase in whole blood viscosity that develops as the haemoglobin level rises in response to impaired oxygenation of metabolically active tissue. It matters little whether this follows displacement of oxygen by carbon monoxide in smokers, severe degrees of respiratory dysfunction, alveolar hypoventilation from gross obesity or right-to-left cardiac shunts. As the blood gets thicker flow in the microcirculation is slowed and this cannot be adequately compensated for by the increased oxygen carrying capacity broughy about by the raised number of red cells. These effects may be evident in the extremities with plethora and cyanosis. Furthermore, this is a risk factor for development of coronary and cerebral vascular disease.

Management centres on phlebotomy since the hazards from stroke or myocardial infarction in patients with untreated erythrocytosis is substantial and survival rates of only 50% at 18 months are reported.

Therapy, since neither white cell nor platelet count are raised, is venesection at whatever interval necessary to maintain packed cell volume between 40% and 45%. If this continues long enough iron stores will be depleted and the time between consecutive blood collections is extended. This deficiency state should not be corrected except in the very rare circumstance of paradoxical hyperviscosity where symptoms are related to the poor deformability of the hyprchromic and microcytic red cells in the microcirculation. Where possible, underlying medical illnesses such as cardiopulmonary disease, should be corrected and the patient advised to stop smoking. In those individuals where respiratory function is normal during the day it is necessary to repeat this whilst asleep at which time the hypoxic stimulus may be revealed.

III.c. Absolute – Physiologically Inappropriate

Pathophysiologically, there are two broad mechanisms whereby red cell mass is expanded despite optimum oxygen delivery to tissues. Firstly ectopic sites of erythropoietin production or generation of closely related proteins that the capacity to stimulate differentiation and proliferation of the red cell series from the haematopoietic stem cells, need to be excluded because, if present, surgery offers a chance for cure. Secondly, there is the opposite where no increase in hormone level occurs and, indeed, may actually be reduced. In this situation erythropoiesis has become autonomous. Such patients are categorized as belonging to the chronic myeloproliferative syndrome and specifically designated primary proliferative polycythaemia: previously called polycythaemia rubra vera *vide infra*.

Management depends upon the underlying cause.

Therapy in those with ectopic erythropoietin production depends upon correcting the hormone level by removing whatever tissue is responsible for its production and examples include nephrectomy for renal carcinoma or the classical, albeit rare, cerebellar haemangioblastoma. Where metastases have occurred appropriate cytotoxic chemotherapy is needed and response in haematocrit becomes a rough indicator of the success with which the tumour is responding to therapy. In some individuals venesections are necessary to control the raised haemoglobin.

III.d. Autonomous Red Cell Proliferation

These are indolent neoplasms characterised by uncontrolled expansion in the erythron where additional hazards are added by the thrombocytosis and, to a lesser extent, leucocytosis. There is a specific point mutation in the Janus Kinase 2 or JAK 2 gene that better defines these cases.

Management depends upon phlebotomy to keep viscosity in the physiological range. However, myelosuppression is additionally necessary. Useful agents are busulphan starting at a dose of 2 mg daily and titrating this to achieve the desired peripheral blood values. A practical alternative is hydroxyurea commencing at 15 mg/kg per day. In both instances xanthine oxidase inhibitor, given as 300 mg allopurinol each 24 hours is needed to prevent the complications of hyperuricaemia. Alternatively, particularly in the elderly, although hardly used any longer, is radioactive phosphorus, which can be administered at a dose of 3.5 mCi/m^2 and repeated every 3–6 months. Pruritus is a frequent problem and long-acting antihistamins such as loratadine may need to be administered daily at a dose of 10 mg orally.

IV. WHITE CELL SERIES – LEUCOPENIA

Physiologically, protection from the effects of microorganisms gaining access to the body occurs at two levels. First, there is an intrinsic or innate system in which the phagocytes are predominantly active. The neutrophilic granulocytes remove invading bacteria while the monocyte–macrophage system eradicates intracellular organisms. Second, there is a supportive or reserve mechanism to deal more specifically with any microbes that either escape the first-line defence or reinfect the host. In this latter adaptive pathway a mononuclear population ingests the foreign antigen and, after processing it, activates T lymphocytes for direct removal of the antigen. Concurrently B cells, that include their terminally differentiated progeny or plasmacytes, produce antibodies that further protect the internal environment through what is known as the humoral arm of the immune system. All these activities are closely integrated with disturbances at different levels resulting in distinct clinical syndromes many of which are potentially lethal.

Pathophysiologically quantitative reduction, often with qualitative impairment in function, occurs in granulocytes, monocyte–macrophage series or plasma components and these are relatively common. Since they sometimes give rise to life-threatening clinical situations many require urgent treatment.

IV.a. Neutropenia

Pathophysiologically there is a confirmed reduction granulocyte count below 1.8×10^9/l, and once this is under 0.5×10^9/l there is an increased risk of infection that is greatest when neutrophils are absent and agranulocytosis is said to be present. It is important to appreciate that certain ethnic groups, including the black populations of Africa, have consistently low counts, and this is a normal racial variant with figures not unusually in the region of 1.5×10^9/l. Similarly, before embarking on treatment, the entity of cyclic haematopoiesis must be excluded since here the counts drop low but then oscillate upwards in a relatively constant manner.

Of more clinical relevance are the two broad categories of impaired production or accelerated peripheral removal of these cells from the circulation. In the first the lesion can be genetically determined as in Fanconi anaemia. Conversely, the abnormality may be acquired. Here causes include extensive infiltration of the marrow, ineffective and megaloblastic haematopoiesis due to folate or vitamin B_{12} deficieny and, of major clinical importance, reversible but severe myelosuppression as a result of drug therapy as seen with cytotoxic chemotherapy. Redistribution is often difficult to confirm although typically associated with splenomegaly and hypersplenism. Finally there may be rapid clearance from the circulation on an immune basis as part of the collagen-vascular diseases: however this is often of undetermined origin and therefore considered an autoimmune process.

Management rests on making an accurate diagnosis and promptly reversing the underlying disorder wherever this is possible. Nevertheless, if peripheral granulocyte count is less than 0.5×10^9/l, the patient should be isolated and, when pyrexial, appropriate antibiotics commenced.

Therapy, to provide the missing cells is possible in three ways. Leukocyte transfusions were, for a long time, employed but fell into disfavour. However, with the availability of stimulatory peptides it is quite practical to harvest large numbers from donors by apheresis technology so that this approach is re-emerging, particularly, in children. Lithium carbonate is of value in some patients although generally of doubtful benefit. In recent years the molecules

that regulate normal white cell production have been identified, isolated and, after cloning, commercially produced in purified form.

These growth factors are named by the way they influence bone marrow growth in the laboratory as granulocyte or monocyte active factors and include molgramostim or filgrastim.

Prescribing perspective is important to distinguish between legitimate and frivolous use of these expensive products since persistence with the latter *laissez-faire* administration will tarnish their justifiably good reputation. In patients who have reversible and severe granulocytopenia, as with agranulocytosis due to idiosyncratic response to drugs, they may be life-saving. Conversely, the arbitrary administration to individuals who are well and whose granulocyte and monocyte counts are either only slightly reduced or already regenerating have not been shown in properly controlled clinical trials to have significant benefit from such intervention. It is emphasized that failure to observe the existing guidelines for their use is cost-ineffective. A preferred approach is to refer potential candidates to an experienced clinical haematologist for consultation.

IV.b. Lymphocytopenia

Pathophysiologically, the important immunohaematological problem is the decrease in the CD4 or T-helper population that characterizes the acquired immunodeficiency syndrome.

Management of these patients has undergone dramatic changes in recent years. Thus, intervention takes into account both the number of viral particles or virons in the plasma and the state of lymphocytes. Furthermore, there are an ever-increasing number of antiretroviral agents available that fall into the two broad categories of reverse transcriptase and protease inhibitors. Additionally, in specific circumstances, the former may be combined with cytotoxics such as hydroxyurea, but experience is needed since in some cases this may be counter-productive rather than beneficial. The previously nihilistic attitude to this infection is undergoing rapid revision at a time when the numbers of patients continue to relentlessly increase and drug resistance is now emerging as a major problem. It follows that all individuals with low lymphocyte counts justify careful evaluation to confirm or refute this possible diagnosis. There is now a large amount of literature that defines the many side effects of each class and prescribing physicians need at least a basic understanding of drugs with haematologic side effects.

Prescribing perspective is dealt with elsewhere in this monograph but it needs to be clearly recognised that effective therapy is available although expensive. Sadly the beneficiaries of modern technological and pharmacological advances will be limited to some 10% of infected people, on a worldwide basis. This is because the prevalence is highest in Third World or developing countries where limited budgets place the appropriate treatment beyond research of all but the most affluent.

IV.c. Hypogammaglobulinaemia

Physiologically, these plasma changes are included here since they reflect impaired numbers or function of B-lymphocytes. Two broad categories are recognizable. First, such immunodeficiency states may exist on congenital basis and often do so with concurrent defects in the T cells (Fig. 1). Alternatively, severe reductions in immunoglobulin levels often develop in the course of chronic lymphocytic leukaemia and myeloma. Not dissimilar impairment of immune competence is found with nephrotic syndrome, protein-losing enteropathy or even malnutrition, and in these instances is equally profound.

Therapy is relatively simple and requires only intravenous infusion of gammaglobulin. Unfortunately, the cost is high although it is essential to appreciate that such replacement therapy does not necessarily need to raise the amounts of protein in the plasma to be life-saving. The important clinical requirement is the decrease and preferable abolition of acute bacterial infections.

Prescribing perspective devolves upon precise characterization of the causative lesion and here reference to a specialized centre is prudent. However, the primary care physician can realistically carry out subsequent management. Local practices may vary and products such as stabilised human serum may be less expensive than some of the commercial equivalents whilst having equal efficacy (Table 4).

V. WHITE CELL SERIES – LEUKOCYTOSIS

Increased numbers, particularly of neutrophils, characterize many inflammatory states. This is a physiologically appropriate response and no treatment is necessary. Conversely, there may be elevations due to underlying haematological malignancies or seen in acute or chronic leukaemia. Once such a suspicion arises the patient should immediately be referred to a clinical haematologist. Specialist investigation and management falls outside the ambit of this chapter.

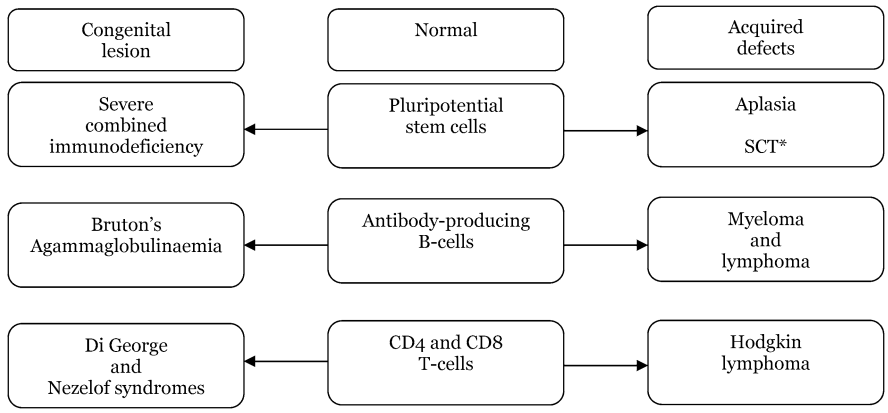


Fig. 1. The immunodeficiency states. The ways in which the various defects are related can be appreciated by considering the evolution of lymph-haematopoietic lineages in the bone marrow.
*SCT – Transiently following immunohaematopoietic stem cell transplantation.

Table 4. Replacement therapy for hypoglammaglobulinaemia

Product	Relative cost
Stabilized human serum contains 13 g/l	R480.00/500 ml
Polygam contains 6 g/200 ml	R957.36/200 ml
Intraglobin F contains 1 g/20ml	R1721.00/100 ml

Locally prepared products such as stabilized human serum are attractive because the donors from whom the plasma is harvested have an antibody spectrum that most closely matches the needs of patients drawn from the same population. This analysis shows that for an approximately equivalent dose of 6 g of immunoglobulins the local product is less expensive on a gram-for basis. Additionally, a comparison of the antibody titres (Jacobs and Wood, unpublished) showed a broader spectrum than some of the commercially available commodities. Exchange rate: € = R9.50; £ = R14.35.

VI. MEGAKARYOCYTE-PLATELET SERIES – THROMBOCYTOPENIA

Physiologically, immunohaematopoietic stem cells give rise to progenitors that mature to recognizable megakaryocytes in the marrow. The latter release platelets into the circulation where they have a mean life-span of 10 days after which they are removed by the reticuloendothelial cells of the spleen, liver and bone marrow. There are three broad categories giving reduced counts.

VI.a. Production Defects

Pathophysiologically, this arises in three ways. First, output may be ineffective as occurs with deficiencies of folate and vitamin B_{12}, or in the myelodysplastic syndromes. Second, extensive infiltration by malignant disease or fibrous is to blame. Third, the blood-forming tissue is deleted – usually reversible in cytotoxic chemotherapy but this damage is permanent in severe aplasia. In these examples pancytopenia rather than selective thrombocytopenia is seen in the blood count.

Management is similar to that outlined above for the red cell series but purpura or more severe haemorrhage requires replacement.

Therapy, to be effective, depends upon administration of an adequate number of platelets, generally 5×10^{11}, in a 70 kg man or a 60 kg woman given over 15 minutes – with suitable adjustment for body surface area in children. It is mandatory that the increment is calculated and the duration of response be documented at 24 hours. The optimum practice is to relate the number infused to changes achieved in the patient by means of the corrected count index. This step anticipates the emergence of resistance that limits the value of repeated transfusions. Occasional allergic reactions have to be blocked by premedication with an intravenous injection 100 mg of hydrocortisone, 12.5 mg of phenergan and 1 g of paracetamol

either as two tablets or 40 ml of the syrup with the recent preferred option of the same dose being infused intravenously.

Prescribing perspective requires that an arbitrary level such as 20×10^9/l not necessarily be retained but rather that this intervention be reserved for those who have significant bleeding that includes extending purpura and particularly retinal haemorrhages. Often surprisingly low counts are tolerated if adults are given between 500 and 1000 mg of cyclocapron orally every 8 hours.

VI.b. Splenic Sequestration

Pathophysiologically, splenomegaly brings about redistribution with falling numbers correlating with organ enlargement.

Management may on occasions have to be splenectomy but in these situations there are generally other factors. For example, in chronic lymphocytic leukaemia contributions to the thrombocytopenia that occurs from reduced production of the one hand and rapid clearance due to immune mechanisms on the other.

VI.c. Accelerated Peripheral Removal

Pathophysiologically, there is little difficulty in recognizing disseminated intravascular coagulation and then treating this on merit. Much more frequent are immunologically mediated mechanisms that may be secondary to underlying collagen-vascular diseases such as systemic lupus erythematosus or where the defect exists in isolation and the process is defined as primary, idiopathic or autoimmune.

Management is determined by precise diagnosis.

Therapy depends upon demonstrating that adequate numbers of megakaryocytes are present in the marrow. Thereafter, consumptive coagulopathy is corrected by reversing the causative pathology whether this is severe sepsis, intrauterine fetal death or the life-threatening thrombotic thrombocytopenic purpura. By way of contrast antibody-mediated thrombocytopenia employs regimens centred on immunosuppression and typically starting a daily dose of 1 mg/kg of prednisone with attention to side effects that include systematic hypertension, hyperglycaemia and hypokalaemia. Also epigastic discomfort may predicate the use – preferably proactively – of proton pump inhibition. Failure to respond within 1 or at most 2 weeks calls for splenectomy, after which corticosteroids are gradually withdrawn over a 3-month period. Relapse or failure to sustain normal counts can be reversed in about two thirds of patients by restarting the prednisone in combination 2 mg/kg of either cyclophosphamide or preferably azathioprine. The availability of anti-CD-20 monoclonal antibodies has been shown effective in the refractory case. Interestingly there exists a possibility to use this intervention *in lieu* of splenectomy but control data has not yet established the correct treatment algorithm between these two options. An alternative approach is with pulsed oral dexamethasone given 40 mg/kg for 4 consecutive days each month: generally six cycles will achieve a relapse-free remission.

Prescribing perspective is crucial. First, is recognition and reversal of any underlying cause. Second, that platelets *are not routinely* infused since the product is immediately subject to the same antibody coating that exist within the recipient, so there is prompt phagocytosis by the reticuloendothelial system of the allogeneic cells. Third, persistence with prednisone in the non-responding patient, beyond 3–4 weeks, adds only morbidity: vinca ackaloids are an alternative. Very costly immunoglobulins may be a little better than less-expensive steroids, and in male patients who are rhesus positive and carrying D antigen on their red cells, the corresponding antibody may be preferable particularly since it can be re-used. In emergencies, and particularly following apheresis, gammaglobulin allows sustained elevation accounts into the normal range, making surgical procedures possible. Finally in refractory cases plasma exchange can be life saving but effects are short term.

VII. MEGAKARYOCYTE-PLATELET SERIES – THROMBOCYTOSIS

Physiologically, this is often reactive due to iron deficiency, bleeding or ongoing inflammation. In contrast the idiopathic, primary of essential variant, preferably known as thrombocythaemia, is a member of the myeloproliferative syndrome where the autonomous production is a neoplastic process.

Management depends upon distinguishing benign from malignant causes.

Therapy is not needed in the first category. However, myelosuppression can be with radioactive phosphorous in the elderly when a dose of 3.5 mCi/m^2 is given and repeated as needed: this is a less favoured option with newer agents available. Alternatively, cytotoxic drugs are useful and safe: two

options exist. Hydroxyurea is started at 15 mg/kg per day and titrated to keep counts between (150–200) $\times 10^9$/l. There is an associated increase in mean red cell volume often over 120 fl with desired doses limited by fall in haemoglobin or white cell count. Troublesome disturbance in taste occurs and dry skin is unacceptable to some individuals: leukemogenicity is unproven to date. Alternatively, busulphan is given at 2 mg per day with adjustment every second week to achieve the desired effect. Increase in skin pigmentation pulmonary damage and an Addisonian-like wasting syndrome may be found. Newer treatment is anagrelide, which is more specific to this lineage and is commenced at 0.5 mg four times a day with escalation until the counts are at the target level.

Prescribing perspective is to recognize that the previously acceptable counts, on treatment, between (500–650) $\times 10^9$/l are hazardous since microvascular occlusion, including stroke, remain risks. The concurrent role of aspirin continues to be defined. Thus, while this has a sound theoretical benefit and is recommended to decrease platelet–endothelial cell interaction, occasional gastrointestinal tract bleeding may be found. Furthermore, associated hypercoagulability may be found and determinations of proteins C and S, mutations of factor V and II or elevated homocysteine, as well as the presence of anticardiolipin syndrome or lupus anticoagulant should not be overlooked.

VIII. PLASMA – HAEMORRHAGE

Physiologically, the maintenance of blood circulating freely in the vascular system reflects a meticulous balance between coagulation and fibrinolysis. After microvascular injury subendothelial structures are exposed to which platelets adhere. This is followed by their aggregation and activation of the coagulation cascade with the ultimate conversion of fibrinogen to fibrin.

Pathophysiologically, *primary* haemostatic defects, characteristically due to malfunction of vascular endothelial or platelets, are exemplified by von Willebrand disease and agents such as aspirin and non-steriodal anti-inflammatory drugs (NSAID) where there is a prolonged bleeding time or abnormality in closure using the laboratory equivalent of platelet function analyse the PFA-100. In contrast, *secondary* bleeding, follows a period of haemostasis then a delayed haemorrhage and is characteristically due to inadequate fibrin formation. This may be congenital, as in haemophilia, or acquired through vitamin K deficiency or liver disease.

Management depends upon accurate diagnosis. Often crucial in emergencies is that this information is immediately available and use of medic-alert bracelets, or some means of notification for those at risk is mandatory.

VIII.a. Von Willebrand's Disease

Therapy varies slightly with the sub-type but response is almost universal to infusion of material rich in von Willebrand protein and factor VIII. Type 1 and 3 are quantitative defects whereas type 2, of which there are a number of subgroups, are qualitative and this information underlies optimum management. Generally cryoprecipate will be effective at a dose of 1000 or 2000 units 12-hourly to control the bleeding. An alternative is fresh-frozen plasma but this needs to be blood group specific and doses between 10–15 ml/kg are given twice a day: volume overload may occur needing diuretics. In both these circumstances the adequacy of infusion is determined by correction of low levels factor VIII, the von Willebrand antigen or ristocetin co-factor in the plasma and this is proven by appropriate laboratory measurement. Desmopressin acetate (DDAVP) can be administered at doses of 0.3 g/kg diluted in 50 ml in saline and given over a 30-minute period particularly in geographical areas where there is a risk associated with potentially contaminated blood products. It is best in type 1, variable response in type 2 and contraindicated in type 3. This approach is not suitable where major bleeds are concerned.

VIII.b. Factor VIII Deficiency – Classic or Haemophilia A

Therapy is determined by the level of factor VIII deficiency. Severely affected patients have concentrations less than 1 %, in moderate disease this is present between 1 and 5 % whereas plasma levels between 5 and 30 % may be associated with bleeding only after trauma such as dental extraction. Additionally, the choice of replacement is modified by the site of bleeding and the presence or absence of inhibitors that interfere with the function of the factor. Cryoprecipitate or lyophilised concentrate is becom-

ing standard with the same approach used as outlined above. Recombinant antihaemophiliac globulin is preferred but these, of which a number are available, are expensive.

Therapeutic levels immediately after infusion, irrespective of which product is used, require factor VIII levels between 5 and 20 % for haemarthrosis and muscle bleeds. However, haematoma in dangerous areas, such as extensive dental extractions, should have levels between 20 and 40 %. For major surgery and serious accidents these need to be between 100 and 150 %; levels should not drop below 50 % at any point in the day and should continue until wound healing is complete; in major surgery this may be 7 or 10 days.

Dental extractions require special comment, and a prophylactic dose of 30 units of factor VIII/kg is given just prior to the procedure. Tranexamic acid or Cyclocapron, which inhibits the breakdown of fibrin clot, is started intravenously at a dose of 10 mg/kg and continued orally every 6 hours for up to 10 days. It is wise to use a 5-day course of oral penicillin V, at a dose of 500 mg every 6 hours. Hospitalisation may be unavoidable in the post-extraction period unless this is completely uneventful.

Of special note are a group of between 5 and 10 % of haemophiliacs who have developed inhibitors in the form of immunoglobulins that interfere with factor VIII function. These are expressed in Bethesda units and levels may rise slowly or extremely rapidly on re-exposure to antigen. This pattern determines choice of therapy. This is a haematological emergency when haemorrhage occurs and requires immediate referral to an experienced clinical haematologist. Sometimes very large doses can over-ride the blocking effect of the antibody but immunosupressive drugs that include pulsed cyclophosphamide with corticosteroids, plasma exchange or plasma products that activate the coagulation system distal to factor X are usually unavoidable. Currently recombinant activated factor VII is favoured.

Prescribing perspective requires access to a full range of nursing, physiotherapy and often orthopaedic specialists, coupled with avoidance of drugs that aggravate bleeding such as aspirin or the non-steroidal anti-inflammatory drugs. A medic-alert bracelet should be worn and, as far as possible, home therapy developed as the most practical and cost effective way of preventing frequent visits to hospitals.

VIII.c. Factor IX Deficiency – Christmas Disease or Haemophilia B

Management is the same as that outlined above but replacement is with fresh frozen plasma or freeze-dried factor IX concentrate. A wide range of commercial equivalents can be used but are costly.

VIII.d. Vitamin K Deficiency

Therapy of haemorrhagic disease occurring in the newborn requires correction of subnormal concentrations of the procoagulants factors II, VII, IX and X with the bleeding state typically developing between the second and third day of life. The defect is more severe in premature infants and following prolonged breast-feeding. Prophylaxis may be undertaken by giving 1 mg of synthetic phytomenadione by intramuscular injection although, there is some concern about this practice and familiarity with the local policy is appropriate. If bleeding is active, fresh frozen plasma provides immediate correction to cover the lag period between the injection and hepatic synthesis of the clotting proteins.

VIII.e. Oral Anticoagulant Overdose

Therapy in patients who have prolongation of the prothrombin time, correctly expressed as the international normalized ration (INR), is best controlled by giving 10 ml/kg of group-specific fresh frozen plasma as an intravenous infusion over 1 hour. Currently bioplasma or other equivalents are more convenient and this freeze-dried or lyophylised product is available in most pharmacies. Two units are typically given, each intravenously over 1 hour, and the INR titrated back into the therapeutic range. The regimen can be repeated, with loop-acting diuretic, every 2 or 3 hours until correction is adequate. Since the effect of warfarin may continue for 2 or 3 days monitoring is necessary. It is possible to reverse the haematostatic defect by oral, intramuscular or intravenous injection of vitamin K but these practices are unwise since normal levels are achieved and the patient again placed at risk from whatever cause necessitated anticoagulation in the first instance. Additonally, there is a lag period of anything from 6 to 18 hours before the newly synthesized procoagulants reach physiological levels. More safely and efficiently – is use of recombinant activated factor VII.

VIII.f. Liver Disease

Therapy in these individuals require attention to a number of components that include thrombocytopenia due to portal hypertension with associated splenomegaly and cholestasis that prevents bile salts from reaching the gastrointestinal tract so that absorption of fat soluble vitamins, including K, are defective. The liver cells also play an important role in synthesizing factors II, VII, IX and X so that a multifactorial and often profound haemorrhagic state exists. With deterioration in hepatic function there is superimposed consumption coagulopathy. Reversal of a potentially life-threatening situation depends upon infusion of fresh frozen plasma, cryoprecipitate and platelets, together with intravenous vitamin K and at least twice daily haemostasis monitoring.

VIII.g. Pathological Fibrinolysis

Pathophysiologically, accelerated breakdown of fibrin occurs secondarily to disseminated intravascular coagulation or primarily in prostatic surgery.

Therapy depends, where possible, on correcting the precipitating process. Thereafter, the consumption coagulopathy is reversed by intravenous injection of adequate amounts of cryoprecipitae, fresh frozen plasma and platelets at whatever interval is necessary to achieve measurable plasma levels in parallel with sustained clinical improvements.

Prescribing perspective is important in determining the extent to which cyclocapron is given by intravenous injection or orally.

IX. PLASMA – THROMBOSIS

Physiologically, haemostasis is a normal extravascular process, typically limited to a few initial cells, resulting in repair to blood vessel injury (Fig. 2).

Pathophysiologically, thrombosis is the same sequence of events but now occurring in abnormal anatomical sites with intravascular obstruction that results in distal tissue ischaemia. These are often systemic disorders affecting the whole circulation and are described as hypercoagulable syndromes. Defects may lie at the level of the endothelium, inappropriate activation of the coagulation cascade or impaired activity of the fibrinolytic system. Segments of thrombus can become detached and travel peripherally in arterial tree, giving rise to acute insufficiency. Conversely, on the venous side, these are trapped in the lungs resulting in signs and symptoms of major, minor or recurrent pulmonary emboli.

Management in all cases has the same three components. First, the obstruction must be removed or lysed. Second, risk factors such as cigarette smoking, hyperlipidaemia, diabetes mellitus or systemic hypertension recognized and corrected.

Third, there is a need to determine the underlying cause since this may be on an inherited basis described as thrombophilia where all family members need to be investigated. Experience and access to a superior haemostasis laboratory is needed. Defects may extend from hyperhomocysteinaemia through sticky platelet syndrome to mutations of factors V and II or reduced levels of the naturally occurring anticoagulants. Treatments differ and more than one abnormality in what is known as genetic coexpression may co-exist. Correspondence acquired lesions may reflect environmental influences.

IX.a. Arterial–Anti-platelet Drugs

Pathophysiologically, occlusion in these high-flow areas comprises primarily consecutive layers of adherent platelets – the white head thrombus.

Therapy, in the short term, is with intravenous unfractionated or subcutaneous low molecular weight heparin. Aspirin, given in low doses between 50 and 100 mg per day, is sufficient to diminish platelet–vessel interaction. Alternatives include 100–200 mg of sulphinpyrazone once or twice a day or dipyridamole where 100 mg four times a day can be used on its own or between 25 and 75 mg combined with aspirin three times a day. More recently thiopyridines, as a class, has been shown to have equivalence at 250 mg twice a day. In hyperhomocysteinaemia the risk is reduced by 5 mg of folate and 100 mg of vitamin B_6 daily, with addition of oral vitamin B_{12} of less clearly defined benefit. The effect of this intervention requires re-assay at 3-monthly intervals, following standard methionine challenge, to ensure that suitable suppression has been achieved in the plasma amino acid level (Table 5).

IX.b. Venous – Heparin, Coumarin and Fibrinolysis

Pathophysiologically, although vascular damage and platelet involvement occurs, the major component in the clot is fibrin.

Therapy with heparin is immediately effective. Two options are available. The first is unfractionated

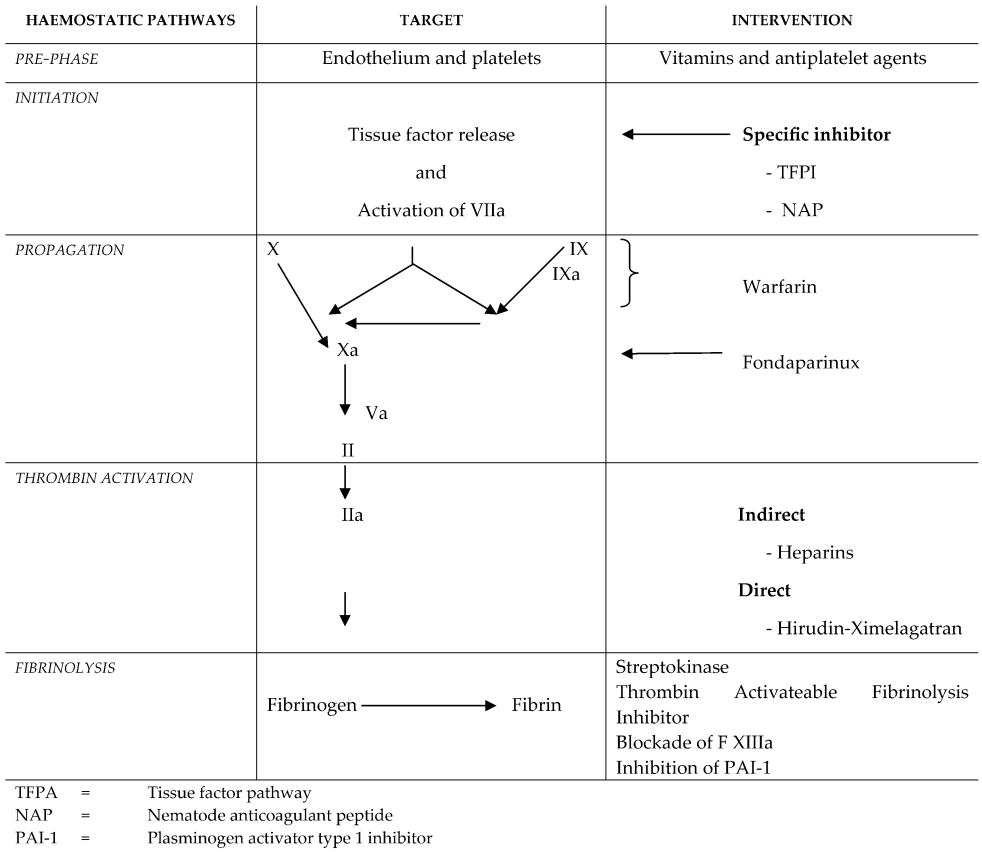


Fig. 2. Target-specific selection of antithrombic options. Based on current understanding of the exquisitely integrated steps in haemostasis it is conceptually useful, although clearly artificial, to recognise five consequential phases in this normal repair process. Extrapolation of these concepts to the more widespread changes in hypercoagulability facilitate investigation and treatment of the underlying defect whilst also providing a basis that includes increasing use of new agents. (From Jacobs et al., 2007. Reproduced with acknowledgement and permission: The Editor – Specialist Forum.)

product, which is cheaper but requires frequent measurement of partial thromboplastin time titrated to keep this measurement between 2–3 times normal. A loading dose of 75 mg/kg is given intravenously and followed by subcutaneous injections or a continuously running infusion with adjustments made every six to twelve hours. In contrast there is increasing recourse to low-molecular weight equivalents. These can be assayed by their anti-IIa and anti-Xa activity but, in practical terms, this is seldom carried out. Furthermore, while there are a number of products that are marketed as having minor differences they are generally comparable and monitoring is less critical. One example is Enoxaparin where 40 mg is given therapeutically every 12 or 18 hours and only marginal changes become evident in the laboratory. As a generalization 1 mg/kg can be given subcutaneously every 12 hours. These have a useful place in the high-risk pregnant female and are favoured throughout this time as well as during breastfeeding (Table 6).

Coumarin should be commenced within 3–5 days of the acute event and while the patient is still on the above therapy. Warfarin is a well-tried product and 5 mg is given orally and there are compelling argurments for its use concurrently with aspirin. After approximately 5 days and when the INR is maintained around three the heparin is discontinued but aspirin retained. Experience dictates that the more severe events require longer periods of treatment at higher levels of INR but bleeding complications then increase and it is mandatory that patients be fully informed about this risk. The decision about maintenance anticoagulation is incorporated in a number of guidelines and it is wise to consult these or consult with a clinical haematologist in all cases.

Table 5. Anti-platelet drugs

Long established is acetylsalicylate or aspirin where current evidence suggests that previous concept of differential sensitivity between pathways for metabolism of arachidonic acid in endothelium and platelets is not correct and additional benefits accrue from higher dose although the risk of bleeding rises. Adenosine diphosphate receptor blockade with the thienopyridines is an alternative and logic dictates that they can be and are often used together. The most effective option for paralyzing platelet adhesion to intimal cells is at the level of the glycoprotein IIb–IIIa monoclonal antibodies continue to undergo evaluation.

Acetylsalicylate

- Low-dose
  - Selectively inhibits cyclo-oxygenase activity
  - Differing effects on vessel walls largely theoretical
  - Global inhibition dominant effect
- High-dose
  - Increases fibrinolysis
  - Decreases prothrombin synthesis
  - Improves endothelial function
  - Blunts anti-inflammatory effects

Thienopyridines

- Adenosine diphosphate receptor blockade
  - May cause thrombotic thrombocytopenic purpura
- Ticlopidine
  - Decreased usage due to neutropenia
- Clopidogrel
  - Costly but approximately interchangeable with aspirin

Glycoprotein IIb/Iia – monoclonal antibody

- Inhibit aggregation and induce thrombasthenic-like syndrome
- Abciximab – irreversible with risk of bleeding
- Others
  - Eptifibatide – synthetic and Tirofiban – reversible
- Oral formulation – ineffective

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Table 6. Low molecular weight heparins

Drug name	Trade name(s)	Manufacturer	Method of preparation
Enoxaparin	Lovenox	Aventis	Benzylation followed by alkaline hydrolysis
Daleparin	Fragmin	Pharmacia & Upjohn	Controlled nitrous acid depolymerization
Tinzaparin	Innohep	Leo and Pharmion	Heparinase digestion

These products vary in effects on factor IIa and Xa. A common sense approach is to become thoroughly familiar with one of this class of anticoagulant and employ this consistently rather than switching between different preparations.

Fibrinolysis is extremely effective in clot lysis, particularly when the latter is under 3 days of age. Defibrination is available in three broad categories. Certain snake venoms, such as ancrod, are given at a dose of two to three units per kilogram in 200 ml saline over 6 hours and maintained at 2 units per kilogram every 12 hours. Second, streptokinase is infused at a loading dose of 600,000 units in the first 60 minutes and maintained at 100,000 units hourly for up to 62 hours if needed. The dose for the alternative product, urokinase, is an initial injection of 4400 units per kilogram over 10 minutes and then the same dose repeated hourly for 12 hours. The latter generally causes less allergic reactions but in both instances premedication with hydrocortisone, phenergan and paracetamol are wise precautions to obviate hypersensitivity reactions.

Currently, in both arterial and venous occlusion, newer products such as alteplase which is recombinant human tissue-type plasminogen activator where 10 mg is given as an intitial bolus and a further 90 mg infused over 2 hours are offering alternative regimens. Although costly they have apparent benefit in stroke and acute coronary syndromes.

In all these situations considerable experience is needed and the guidance of an experienced haematologist is prudent. Furthermore, venograms are carried out on a daily basis and therapy discontinued once complete resolution of the intravascular obstruction has been demonstrated. In our experience 3 days is the maximum period ever needed and during this interval meticulous monitoring to avoid overdose is necessary and includes partial thromboplastin time, INR and maintenance of thrombin time between two and three times basal or pre-treated levels. While fibrin degradation products are invariable present in high concentration, fibrinogen levels should be noted.

Prescribing perspective dictates that once the lytic regimen is completed full heparinization and use of coumarin anticoagulation is commenced with close attention to monitoring.

IX.c. Newer Anticoagulants

It is sensible that use of those products are at least reviewed with experienced clinical haematologists in each case to select the agent or combination most likely to have greatest benefit and least risk – including duration of treatment. Specific inhibition of factor VIIa is possible with a tissue factor pathway molecule and, interestingly, nematode anticoagulant peptide. The coagulation cascade factor Xa competitors are found in a synthetic pentasaccharide that inhibits the critical point in the sequence but upstream from thrombin and offers both potency and safety. Fondaparinux is the methoxy form of this natural sequence of these five sugars working by activation of aphysiological inhibitor known as antithrombin.

Of the indirect inhibitors of thrombin are the heparins and new delivery systems have been improved with a generation of molecules that can be absorbed by the gastrointestinal tract.

In contrast direct-acting preparations have the ability to inhibit fibrin-bound thrombin and include hirudin derived from medicinal leeches but now produced by recombinant technology. Particular interest centres on ximelagatran which may be a possible replacement for conventional vitamin K antagonist therapy.

In much the same way the number of interventions are possible at the level of fibrinolysis including thrombin-activateable fibrinolysis inhibitor, agents that block factor XIIIa or inhibit plasminogen activator inhibitor therapy.

X. SUMMARY AND CONCLUSION

These guidelines are based on pathophysiological principles since it is our firm belief that this is the most rational approach to pharmacological intervention in modern medicine. Only the more common clinical entities have been described and in each case recommendations limited to well established regimens. In this way efficacy and side effects have been documented and outcomes are therefore reasonably predictable. Wherever relevant, newer and alternative approaches are commented upon. In some areas rapid addition of new agents are entering clinical use often before fully evaluated where examples include anti-IIb:IIIba inhibitors to impairing platelet–vessel interaction in unstable angina. It is emphasized that, throughout the international world, financial constraints vary but there is a universal appreciation that cost-effective or evidence-based medicines are the cornerstones for preferred therapeutic practices. Finally, it needs to be restated that quality of life requires evaluation with all interventions and it is an obligation for the health-care professional to discuss potential complications in the context of anticipated benefits. Awareness needs to exist that individual variation or even idiosyncratic responses may occur and these need to be reported to local authorities without delay.

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Chapter 42

Endocrine Diseases

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I. INTRODUCTION

Endocrine diseases and their treatment have a major impact on health throughout the world, particularly in terms of diabetes, thyroid disease, steroid therapy, and control of fertility. Most endocrine therapy is simple and relatively cheap, but a clear understanding of their actions and uses is essential for safe and cost-effective treatment. In this chapter we will focus mainly on well established and validated endocrine therapies that are widely used throughout the world, with briefer mention of drugs that have recently been introduced. In the sections that follow we outline the major issues in the current clinical pharmacology of endocrine disease, covering each of the major endocrine systems in turn.

Endocrinology is widely covered in the Cochrane Library. At the time of writing no less than 34 systematic reviews with diabetes, 8 with thyroid, 3 with pituitary and 24 with contraception in the record title were available in the Cochrane database. Of course space does not permit to refer to all these particular reviews individually. However, the indications given and the treatments which are recommended rely as far as possible on evidence-based data as covered by the Cochrane Collaboration Reviews.

II. DIABETES MELLITUS

II.a. Introduction

Diabetes mellitus is characterized by hyperglycaemia and disturbances of carbohydrate, fat and protein metabolism that are associated with absolute or relative deficiencies in insulin action and/or insulin secretion. Although diabetes is an endocrine deficiency or resistance state its major manifestations are those of metabolic disease with wide ranging tissue effects. Insulin resistance does exist in type 2 diabetes, however it is also exists in many individuals without diabetes. It is difficult to accept insulin resistance is the sole determining pathogenic factor in type 2 diabetes. Therefore, it is more appropriate to describe type 2 diabetes as a condition of β-cell dysfunction in an insulin resistance background.

The characteristic symptoms of diabetes include excessive thirst, polyuria, pruritus, polydipsia with otherwise unexplained weight loss, and often symptoms from one or more of its related complications. Type 2 diabetes may be asymptomatic, so that the diagnosis is sometimes made as a result of abnormal screening tests on blood or urine. The onset of type 2 diabetes can occur up to 7 years before clinical diagnosis (see Harris et al., 1992).

Diabetes affects populations in both developed and developing countries. Due to its high prevalence

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and the high risk of developing vascular, renal, retinal and neuropathic complications leading to premature disability and death, diabetes mellitus constitutes a significant public health problem in most countries (see Pickup and Williams, 2002).

II.b. Diagnosis and Classification

Traditionally the diagnosis of diabetes was based on symptoms due to hyperglycemia, but during the last decade the need to identify diabetes and other forms of glucose abnormalities in asymptomatic individuals has been emphasized. Criteria established by the WHO and the American Diabetes Association (ADA) for the diagnosis of diabetes have been widely adopted by endocrinologists (Table 1).

The formal definition of diabetes is based on an oral glucose tolerance test (OGTT), using a 75 g glucose load. In the presence of symptoms together with a random plasma glucose of $\geqslant$11.0 mmol/l (200 mg/dl) confirmed the diagnosis of diabetes. For epidemiological studies and in the absence of overt hyperglycemia, estimates of diabetes prevalence should be based on both *fasting plasma glucose* $\geqslant$7.0 mmol/l (126 mg/dl) and two hour post-load glucose concentrations. Impaired glucose tolerance (IGT) is defined by a fasting plasma glucose of $\geqslant$6.1 mmol/l (110 mg/dl) and 2-hour plasma glucose of $\geqslant$140 mg/dl) and $<$11.0 mmol/l (200 mg/dl).

The cut-off points for diabetes on fasting and 2 h post-load values were primarily determined by the values where the prevalence of retinopathy, which is a specific complication of hyperglycemia, starts to increase. Evidence shows that diabetes mellitus is a group of disorders that are aetiologically and clinically heterogeneous but that share hyperglycaemia in common. In 1997, American Diabetes Association proposed a new 'etiologic' classification of diabetes. Basically, diabetes mellitus may now be classified as: Type 1 diabetes, characterized by β-cell destruction leading to absolute insulin deficiency, and type 2 diabetes characterized by both β-cell secretory defect and insulin resistance. Type 1 diabetes usually occurs in young individuals, but may occur at any age. Since the evidence that malnutrition can directly cause diabetes is not convincing, the class MRDM has not been included in this new classification. However, gestational diabetes and other specific types, including MODY (maturity onset diabetes of the young) and secondary diabetes has been retained. The terms IGT and IFG are also retained. In the absence of pregnancy, IGT and IFG are not clinical entities in their own right but rather an intermediate category between normal glucose homeostasis and diabetes and risk factors for future diabetes and cardiovascular disease.

II.c. Type 1 Diabetes Mellitus

This is immune-mediated pancreatic β-cell destruction characterized by absolute insulin deficiency,

Table 1. Criteria used for glucometabolic classification from WHO (see WHO Consultation, 2006) and ADA

Glucometabolic category	Source	Classification criteria (venous plasma glucose mmol/l (mg/dl)
Normal glucose regulation	WHO	FPG $<$ 6.1 (110) + 2 h PG $<$ 7.8 (140)
	ADA (1997)	FPG $<$ 6.1 (110)
	ADA (2003)	FPG $<$ 5.6 (100)
IFG	WHO	FPG $\geqslant$ 6.1 (110) and $<$7 (126) + 2 h PG $<$ 7.8 (140)
	ADA (1997)	FPG $\geqslant$ 6.1 (110) and $<$7 (126)
	ADA (2003)	FPG $\geqslant$ 5.6 (100) and $<$7 (126)
IGT	WHO	FPG $<$ 7.0 (126) + 2 h PG $\geqslant$ 7.8 and $<$11.1 (200)
IGH	WHO	IFG or IGT
Diabetes mellitus	WHO	FPG $\geqslant$ 7.0 (126) or 2 h PG $\geqslant$ 11.1 (200)
	ADA (1997)	FPG $\geqslant$ 7.0 (126)
	ADA (2003)	FPG $\geqslant$ 7.0 (126)

FPG = fasting plasma glucose; 2 h PG = 2-hour post load plasma glucose; IGH = impaired glucose homeostasis; IFG = impaired fasting glucose; IGT = impaired glucose tolerance. IGT can only be diagnosed by OGTT. OGTT is performed in the morning after 8–14 h fast, blood sample is taken before and 2-hours after intake of 75 g glucose dissolved in 250–300 ml water.

abrupt onset of severe symptoms, proneness to ketoacidosis and dependence on exogenous insulin to sustain life. It manifests mostly in young age although the disorder may occur at any age (slow-progressing type 1 diabetes or latent autoimmune diabetes in adult). Type 1 diabetes is not genetically predetermined but an increased susceptibility to the disease may be inherited. Since destruction of β-cells is attributable to an auto-immune process, it is characterized by the presence of islet cell auto-antibodies (ICAs), auto-antibodies to glutamic acid decarboxylase (GAD), autoantibodies to tyrosine phosphatases 1A-2, 1A-2 beta, or insulin (IAAs). Some forms of type 1 diabetes have no known evidence of autoimmunity and these cases are classified as type 1 idiopathic.

II.d. Type 2 Diabetes

This is the most common form of diabetes ($\sim$95% of all cases), and comprises a spectrum of predominant insulin resistance with relative insulin deficiency at one extreme, to a predominant insulin secretory defect with lesser degrees of insulin resistance at the other. At least initially these patients do not need insulin therapy for survival. Most are obese, seldom developing ketoacidosis (if it occurs it usually arises in association with the stress of intercurrent illness such as infection). It is often associated with stronger genetic predisposition than type 1 diabetes, but the genetics of this form are complex and not clearly defined yet. This form may go undiagnosed for many years because the hyperglycaemia develops gradually and the classic symptoms are unnoticed. Circulating plasma insulin levels may be normal, increased or even decreased; therefore, they may need insulin for better metabolic control. Nevertheless such patients are at increased risk of developing microvascular and macrovascular complications. The three basic pathophysiological abnormalities are: impaired insulin secretion, excessive hepatic glucose production and insulin resistance in skeletal muscle, liver and adipose tissue.

II.e. Diabetic Complications

Patients with both type 1 and type 2 diabetes are prone to complications. The specific *chronic* diabetic complications are due to microangiopathy and include neuropathy, retinopathy and nephropathy. Recent data stress the vital role of hyperglycaemia and oxidative stress in their pathophysiology. Premature atherosclerosis (which can be considered as macroangiopathy, and similar to atherosclerosis in general population), due to aggregation of many cardiovascular risk factors, also occurs in diabetic populations. The macroangiopathy may precede hyperglycemia. Prevention of these angiopathic complications should include smoking cessation, lipid and blood pressure control, as well as normalisation of blood glucose.

Acute complications of diabetes include diabetic ketoacidosis, hyperglycaemic non-ketotic hyperosmolar coma, lactic acidosis and hypoglycaemia.

II.f. Guidelines for Therapy

Individuals with diabetes should receive medical care from a team coordinated by a physician. Such a physician-coordinated team may include nurses, a dietician and a pharmacist preferably trained as diabetes educators. The management plan should be discussed with the patients and their family, and prescribed as individualized therapeutic plans.

The aims of diabetes therapy are to achieve well-being, i.e. to alleviate and prevent symptoms of hyperglycaemia and hypoglycaemia, to prevent acute and chronic complications of diabetes by achieving optimal metabolic control, and to reduce cardiovascular risk factors for each patient. This requires measures to control body weight, lipids, blood pressure, as well as blood glucose levels. Cessation of smoking is vital. Non-pharmacological and pharmacological measures are available.

The Diabetes Control and Complications Trial (DCCT), the Stockholm Diabetes Intervention Study (DIS), the United Kingdom Prospective Diabetes Study (UKPDS), and the Japanese Kumamoto study show unequivocally that vigorous treatment of diabetes can decrease both the morbidity and mortality of the disease by reducing chronic complications.

Every patient with diabetes requires some form of dietary assessment, and often therapy. This is important to allocate the relative amounts of energy derived from carbohydrate, protein and fat of total recommended daily calories in proportion to the patient's body weight and height and daily requirements, while avoiding atherogenic diets. Diets with 'high' carbohydrate content (50–60%), low fat (30–35%) and adequate protein (10–15%) is recommended. Fibre-rich foods are preferable. The use of non-nutritive sweeteners (saccharin, aspartame, acesulfame K and sucralose) are acceptable. Alcohol intake should be assessed since excess consumption

can potentiate the hypoglycaemic action of oral hypoglycaemic drugs and of insulin. Good glycaemic control is unlikely to be achieved with oral therapy or insulin if diet is ignored.

Exercise is an essential yet neglected aspect of treatment for type 2 diabetes especially in its early stages where insulin resistance may predominate. Accumulation of at least 30–40 minutes of moderate physical activity on most days of the week is recommended. For type 1 diabetes the emphasis must be on adjusting the therapeutic regimen to allow safe sports participation to prevent precipitation of ketoacidosis or hypoglycaemia. Extra care is required in cases with known complications like proliferative retinopathy, nephropathy, foot ulcers and cardiac or peripheral vascular disease.

Drug therapy for diabetes includes insulin and the oral hypoglycaemic agents, the sulphonylureas, the biguanide metformin, the thiazolidinedione (glitazone), the α-glucosidase inhibitors, the glinides, and the incretin derivatives. Insulin is indicated in nearly all cases of type 1 diabetes. Patients with type 2 diabetes can be treated with diet alone, oral agents, or combination of oral agents with insulin, or solely insulin, according to circumstances. To achieve the best metabolic control, combination of two oral agents with different mechanisms of action (e.g. sulphonylurea with metformin, sulphonylurea with glitazone, metformin with glitazone) is warranted. Insulin can be combined with oral agents.

In diabetic metabolic emergencies (ketoacidosis, non-ketotic hyperosmolar coma, sepsis or other severe cases) oral drugs or intermediate-acting as well as long-acting insulin should be stopped and soluble or rapid-acting insulin should be given. However, continuous intravenuous insulin infusion mimicking basal insulin profile is the method of choice.

II.f.1. Type 1 Diabetes Mellitus

Results of the DCCT in type 1 diabetes showed that improving glycaemia with intensive insulin treatment delayed the onset and slow the progression of microvascular complications, such as retinopathy, neuropathy and nephropathy.

Currently, in patients with type 1 diabetes, the gold standard is intensive insulin therapy based on appropriate medical nutrition therapy and ability of self-monitoring blood glucose, targeting HbA1c $<7\%$ is. Episodes of hypoglycemia should be titrated against this goal. Severe hypoglycaemic events should be few (below 15/100 patient-years) (see Ryden, 2007).

II.f.1.1. Insulins. Insulin is the most effective of diabetes medications. Insulin has profound effects on carbohydrate, protein, fat metabolism and electrolytes. It has anabolic and anticatabolic actions. In a state of insulin deficiency, glycogenesis, glucose transport, protein synthesis, triglyceride synthesis, LPL activity in adipose tissue, cellular potassium uptake all decrease; on the other hand, gluconeogenesis, glycogenolysis, protein degradation, ketogenesis, lipolysis increase.

The aim of insulin treatment is to mimic as closely as possible the normal profile of insulin secretion from non-diabetic pancreas, while minimizing discomfort and inconvenience to the patient. The closest regimen so far devised therefore consists of treatment designed to mimic continuous basal insulin secretion, with superimposed prandial peaks of plasma insulin associated with ingestion of food. Basal insulin levels, achieved by long-acting preparations (NPH and long-acting insulins), restrain hepatic glucose production, keeping it in equilibrium with basal glucose utilization. At mealtimes, prandial doses of short-acting insulins *or rapid-acting insulin analogs* stimulate glucose utilization and storage while inhibiting hepatic glucose output.

Insulin, potentially may decrease any level of elevated glucose to normal. There is no maximum dose of insulin beyond which a therapeutic effect will not occur. For type 2 diabetes, relatively large doses of insulin, compared with those required to treat type 1 diabetes, may be needed to overcome the insulin resistance of type 2 diabetes.

II.f.1.2. Insulin preparations. Insulins are characterized by three major aspects: time course of action, degree of purity and species of origin (see also Table 2 in Chapter 24). *Short-acting* or rapid onset insulins (e.g. regular or soluble insulin); *intermediate-acting* insulins, e.g. NPH (isophane) or lente (insulin zinc suspension) insulin; *long-acting* insulins, e.g. ultralente (extended insulin zinc suspension) or protamine zinc insulin (PZI). Insulins are defined as *purified* when they contain <10 ppm of proinsulin. Most if not all available insulin preparations for clinical use are now highly purified (monocomponent) insulins. Insulin was originally extracted from bovine or porcine pancreas, but recently insulin of the same amino acid sequence as native human insulin has been commercially produced both by recombinant DNA technology and by enzymatic conversion of pork insulin to the human sequence.

Insulin allergy occurs in as many as 3% of patients receiving pork or beef insulin but smaller proportion in those using human insulin. However, the immunogenicity of insulin is determined more by the purity of its preparations and since the use of monocomponent insulin, insulin allergy has become extremely rare.

The normal prandial incremental secretion of insulin can best be replicated in type 1 diabetes by giving preprandial injections of short-acting insulin, at least 20–30 minutes subcutaneously before the meal, or rapid-acting insulin analogs immediately before meals. Basal insulin levels are provided *either* by twice daily intermediate-acting (the larger dose at bedtime), *or* by giving one or two injections per day of long-acting insulin (ultralente), one or two injections of intermediate-acting insulin, or one injection of loan-acting insulin analogs. In the absence of infection, for patients with typical type 1 diabetes who are within ∼20% of ideal body weight, the total daily insulin dose required approximates 0.5–1.0 U/kg/day, of which 30–40% of the total dose fulfils the basal insulin requirement. Other possible schedules include (a) 'split-mixed insulin regimen' (twice daily mixture of short- and intermediate-acting insulin), (b) morning dosing with a mixture of short and intermediate insulin, pre-supper short-acting insulin alone, and a bedtime dose of intermediate-acting insulin to minimize nocturnal hypoglycemia. A variety of commercial insulin mixtures in different ratios are also available, for example 70/30 insulin mixtures comprise 70% intermediate-acting and 30% short-acting insulin.

Human insulin analogs are molecules that differ from human insulin in amino acid sequence but that bind to insulin receptors and act similar function as human insulin. In one example, the positions of the Proline residue at B^{28} and the Lysine residue at B^{29} are reversed, forming the Lys B^{28}, Pro B^{29} human insulin analogue (insulin lispro, Eli Lilly Co.). Insulin lispro does not self-associate to form aggregates of insulin monomer and is therefore easily absorbed when injected and act fast (rapid-acting insulin analogs). Two other rapid-acting insulin analogs approved for clinical use are insulin aspart (Novo Nordisk) and insulin glulisine (Sanovi Aventis). Glargine (Sanofi Aventis) and Levemir (Novo Nordisk) are two basal-insulin analogues available for clinical use. Compared to conventional NPH insulin and PZI, the use of basal-insulin analogs may decrease the risk of hypoglycemia.

II.f.1.3. Insulin delivery. Traditionally insulin was given intramuscularly and later subcutaneously. New technology has provided devices for insulin administrations including pen-devices, air powered injectors, external insulin infusion pumps (or continuous subcutaneous insulin infusion, CSII), and implantable insulin infusion pumps. Some novel forms of insulin delivery have been introduced, for example intranasal insulin gives peak insulin concentrations at 10–20 minutes after administration, but most insulin is still administered subcutaneously.

II.f.2. Type 2 Diabetes Mellitus

Type 2 diabetes is heterogeneous disease. The basic guidelines of treatment outlined above apply also to type 2 diabetes. Oral hypoglycaemic agents have a major role in its treatment. For obese patients, weight reduction by dietary measures, physical exercise or drugs is often critical for lowering the glucose level. Initially, insulin is usually not required except for special conditions like diabetic metabolic emergencies. However, during the course of the disease, insulin is usually required for better glucometabolic control. In all instances of insulin use, the insulin dosage must be individualized and balanced with medical nutrition therapy and exercise. The basic observation of DCCT in type 1 diabetes, that lowering blood glucose prevents complications, seems applicable also to type 2 diabetes.

II.f.2.1. Oral hypoglycaemic agents. There are now five groups of orally active drugs available to lower blood glucose in clinical practice (Table 2). These are sulphonylureas, biguanides, alpha-glucosidase inhibitors, thiazolidinediones, and the incretin derivatives.

II.f.2.2. Sulphonylureas. These drugs stimulate pancreatic β-cell insulin secretion, reduce serum glucagon levels, potentiate insulin action on target tissues, and improve β-cell function. The sulphonylureas differ in their potency, extent of hepatic metabolism, hypoglycaemic activity of their metabolites, renal excretion, peak and duration of action, side effects and costs.

However additional peculiarities are found in some preparations. Glimepiride results in lower insulin and C-peptide levels with similar glucose control, probably due its greater extrapancreatic effect on insulin target tissues. Gliclazide has a lower secondary failure rate than glyburide or glipizide,

Table 2. Orally active drugs effective in type 2 diabetes

Drug potency	Daily dose (mg)	Dose/day	Duration of action (h)	Metabolism and excretion
Sulphonylureas				
Tolbutamide weak	500–3000	2–3	6–10	Hepatic
Acetohexamide medium	250–1500	2	12–18	Renal
Tolazamide strong	100–1000	1–2	16–24	Hepatic
Chlorpropamide strong	100–500	1	24–72	Renal
Glyburide/glibenclamide strong	2.5–20	1–2	16–24	Hep+renal
Glipizide strong	5–15	1–2	12–16	Hepatic
Gliclazide medium	40–320	1–2	10–20	Hep+renal
Gliquidone strong	45–180	1–2	18–24	Hepatic
Glimepiride strong	1–8	1	24	Hep+renal
Biguanides				
Metformin weak	1000–2000	2–3	12–20	Unchanged In urine
Alpha-glucosidase inhibitors				
Acarbose weak	50–300	2–3	Small-intestinal passage time	Minimally absorbed from the gut
Thiazolidinedione derivatives				
Troglitazone	200–600	1	16–34	Hepatic

and an anti-platelet effect that may be beneficial in terms of vascular risk. Chlorpropamide can be associated with hyponatraemia because of its antidiuretic hormone-releasing effect. Although tolbutamide, glyburide, glipizide and gliclazide are better absorbed and more effective if given 30 minutes before meals, this may decrease compliance. The once daily preparations may improve compliance.

Long-acting sulphonylurea (e.g. chlorpropamide, glybenclamide, glypizide, glyclazide, glymiperide) mainly reduced fasting hyperglycemia, while short-acting sulphonylurea mainly reduced postprandial hyperglycemia. It gives a mean lowering of initial HbA1c 1.0–2.0%.

Adverse effects are rare and comprise allergic reactions or gastrointestinal intolerance. Severe effects like hepatotoxicity, severe dermatitis, haemolytic anemia, agranulocytosis have been reported infrequently. As might be expected hypoglycaemia is the most common adverse event encountered. The risk of severe hypoglycaemia is increased in elderly people and in patients with impaired renal function.

Other problems with the use of sulphonylureas are their interactions with other drugs that *increase* (salicylates, fibrates, serotoninergic agents, monoamine oxidase inhibitors, ACE-inhibitors and adrenergic blockers) or *decrease* their hypoglycaemic potency. It should be borne in mind that patients on sulphonylureas tend to gain weight. 'Secondary failures' of this oral therapy can arise with long-term administration, which may be improved by combination with metformin, thiazolidinediones or insulin. 'BIDS' therapy – bedtime insulin and daytime (or suppertime) sulphonylrea is popular now.

II.f.2.3. Biguanides. The two important drugs of this class are metformin and phenformin. Phenformin is now rarely used due to its high risk of lactic acidosis and in many countries it is even taken

off the market. Its mechanism of action includes suppression of endogenous hepatic glucose production, reduction of glucose transport across intestinal mucosa, and improvement in insulin sensitivity (by increasing activation and translocation of GLUT1 and GLUT4 in different tissues and possibly other mechanisms). Patients using metformin tend to lose weight, hence this drug is indicated in obese type 2 diabetes. Furthermore, the UKPDS study showed that metformin may reduced the risk of CVD.

Metformin mainly reduced fasting hyperglycemia and has a mean lowering of initial HbA1c 1.0–1.5%. The known side effects are gastrointestinal symptoms, metallic taste and rarely lactic acidosis. To avoid lactic acidosis metformin is not indicated in elderly people, in patients with cardiac failure, respiratory diseases with anoxic tendency, renal or hepatic impairment. A low dose (500 mg) should be started at meal times and may be increased gradually. Metformin may be used in combination with sulphonylurea, glitazones, incretin derivatives, or insulin. Its insulin-sparing effects are at least as strong as those of the sulphonylureas. Metformin is also regarded as insulin sensitizer.

II.f.2.4. Alpha-glucosidase inhibitors. Epidemiological studies show that both microvascular and macrovascular complications begin to develop during the phase when only postprandial hyperglycaemia is the predominant abnormality, that is, up to seven years before fasting hyperglycaemia becomes evident. Acarbose, voglibose and miglitol belong to this class. Their mechanism are similar although not identical. Acarbose is the most widely prescribed alpha-glucosidase inhibitors.

These drugs competitively bind to of alpha-glucosidase enzymes that convert non-absorbable dietary starch and sucrose into absorbable monosaccharides (e.g. glucose). The net effect is to slow the digestion of carbohydrate and allow undigested carbohydrates to pass into large bowel where they are fermented causing flatulence, bloating and diarrhoea. They are clinically indicated to reduce postprandial glycaemia.

Alpha glucosidase inhibitors mainly reduced postprandial blood glucose and has a mean lowering of initial HbA1c of 0.5–1.0%. The major side effects are abdominal discomfort. Hence it is advised to begin with a low dose (25–50 mg) at the start of meals and increase slowly up to a dose of 100 mg three times daily, as judged by the patient's response.

II.f.2.5. Thiazolidinedione derivatives. Thiazolidinedione derivatives act as agonists at the nuclear hormone receptor PPAR (peroxisome proliferator activator receptor)-γ. These drugs function as transcriptional regulators and act to reduce insulin resistance resulting in enhanced insulin action and reduced hyperinsulinaemia, and can thus be regarded as 'insulin-sensitizing' drugs. Clinical studies involving thiazolidinediones (pioglitazone and rosiglitazone) suggest that the direct effects of these glucose-lowering agents on adipose tissue can contribute to improvements in hepatic and peripheral insulin sensitivity in patients with type 2 diabetes (see Sharma and Staels, 2007).

In addition to the impact on adipose tissue and glucose homeosatsis, PPARγ activation is associated with potentially beneficially effects on the expression and secretion of a whole range of adipokines, including increased expression of adiponectin, and decreased expression of pro-inflammatory cytokines (e.g. resistin, leptin, IL6 and TNFα), as well as angiotensinogen. The increased expression of adiponectin appears to be an important mediator of PPARγ agonist-mediated improvement of insulin sensitivity, particularly with respect to improving hepatic insulin sensitivity. Thiazolidinedione derivatives mainly reduce fasting hyperglycemia and induce a mean lowering of initial HbA1c 1.0–2.0%. There have been concerns about unwanted potential problems including impaired liver function and coronary vascular disease (Ryden, 2007).

Its absorption can be reduced by co-administration with cholestyramine or terfenadine, and co-administration with oral contraceptives containing ethinyloestradiol and norethisterone reduces the plasma concentration of both by 30% and may lead to loss of contraceptive effect.

II.f.2.6. The incretins. In response to a meal, insulin secretion is stimulated and glucagon release is suppressed. Incretins, glucagon like peptide 1 (GLP-1) and glucose-dependent insulinotropic peptide) (GIP), are intestinal peptide hormones secreted in response to a meal. They are degraded by an enzyme called DPP-4 and inhibition of this enzyme enhances their effects. Incretin mimetics (exenatide and liraglutide) and dipeptidyl peptidase-4 (DPP-4) inhibitors are new classes of antidiabetic agents that enhance incretin action. In phase III trials, exenatide and liraglutide administered subcutaneously once or

twice daily to ongoing therapy in patients suboptimally controlled on oral antidiabetic agents may reduce HbA1c by 0.8–1.75%. Gastrointestinal upset was the most prominent adverse event but mild, transient, and generally tolerable.

Vildagliptin and sitagliptin are DPP-4 inhibitors that may reduce DPP-4 activity and thus increase and prolonge the action of GLP-1. Vildagliptin given at a daily dose of either 100 mg once as a single drug or 50 mg twice daily in combination with metformin may reduced HbA1c 0.8% compared to placebo. Similar effectiveness has also been reported with sitagliptin. Both incretin mimetics and DPP-4 inhibitors (incretin enhancers) are new classes of antidiabetic agents of great interest for the treatment of type 2 diabetes. However, long term clinical studies are still needed to compare these agents with existing oral hypoglycemic drugs or insulin for the treatment of type 2 diabetes.

III. THYROID DISEASE AND IODINE

III.a. Thyroid Physiology

Thyroid diseases rank second after diabetes mellitus in endocrinological practice, even more so in developing countries where iodine deficiency is common. The thyroid releases two different types of hormones; the thyroid hormones and calcitonin. The thyroid hormones tri-iodothyronine (T3) and thyroxine (T4), are produced by follicular cells lining thyroid follicles, and affect the function of virtually every organ system. Thyroid hormones are the only iodine-containing compounds with biological activity. Calcitonin, produced by thyroid C-cells, affects bone and mineral metabolism, and its use as a therapeutic agent will be discussed briefly in the section concerning bone and mineral metabolism.

The thyroid hormones T4 and T3 contain 65% and 59% of iodine respectively as an essential component for biological activity of the molecule. Iodine from dietary sources or medication enters the body via gastrointestinal tract. The recommended daily adult intake is 150–300 μg. Iodine is rapidly absorbed and enters the extracellular fluid pool. Iodide is removed from the blood largely by the thyroid and kidneys. The higher the intake the lower the fractional iodine uptake by the thyroid.

III.a.1. Thyroid Hormone Biosynthesis

The follicular cells trap iodide at the base of the cell and transport it across the cell. This active transport, *iodide trapping*, is inhibited by perchlorate and thiocyanate ions. Iodide is oxidized by thyroid peroxidase to form iodine at the luminal surface of the cell, and this is rapidly incorporated into tyrosyl residues of thyroglobulin (Tg) to form monoiodotyrosine (MIT) and diiodotyrosine (DIT) residues. This *iodide organification* process is blocked by propylthiouracil and transiently by high intrathyroidal iodide (known as the Wolff–Chaikoff effect). The thiocarbimide drugs, such as carbimazole, inhibit thyroid peroxidase thus resulting in decreased oxidation of iodide. Within Tg, iodinated tyrosine undergoes oxidative coupling which results mainly in the formation of T4 and lesser amounts of T3. This oxidative coupling may be catalyzed by the same peroxidase responsible for the conversion of iodide to active iodine. Thyroid hormones are released from Tg by exocytosis and proteolysis of Tg at the apical colloid border. Colloid droplets obtained through pinocytosis merge with lysosomes containing proteolytic enzymes which hydrolyze Tg and release T4, T3, MIT and DIT. MIT and DIT are deiodinated within the gland and the liberated iodine is reutilized. This proteolysis is blocked by high intrathyroidal iodide. The ratio of T4 to T3 within Tg is 5:1. This means that most of the hormone released is T4 while most of the circulating T3 is derived from peripheral deiodination of T4.

III.a.2. Transport and Peripheral Metabolism of Thyroid Hormones

Most of the T3 and T4 circulating in the peripheral blood are reversibly bound to protein (mostly to *thyroid-binding globulin*, TBG), and only 0.04% of total T4 and 0.4% of T3 exist in the free, biologically active, form. TBG concentrations are affected by a number of drugs, notably oral contraceptives and HRT preparations, which raise TBG and thus total immunoassayable T4 and T3. Some drugs also affect the binding of thyroid hormones to binding proteins (e.g.: phenytoin, salicylates, phenylbutazone, diazepam).

The biological activity of thyroid hormone depends on the location of the iodine atoms. Deiodination of the *outer ring* of T4 produces T3 which is 3–8 times more potent than T4, while deiodination of the *inner ring* of T4 produces reverse

T3 (rT3), that is metabolically inert. Thus outer-ring deiodination is the 'step-up' process to increase metabolic activity and the inner-ring deiodination is the 'step-down' inactivation process. Further deiodination of the molecule abolishes hormonal activity. Drugs such as ipodate, beta-blockers, and corticosteroids influence 5′-deiodinase, resulting in low T3 and high rT3 levels in serum.

III.b. Thyrotoxicosis, Hyperthyroidism and Anti-thyroid Drugs

The term *thyrotoxicosis* refers to any condition of excess circulating thyroid hormone, resulting in a clinical syndrome of nervousness, heat intolerance, weight loss despite good appetite, sweating, palpitations, insomnia, frequent stools, tachycardia, and tremor. The hormone excess may originate from extrathyroidal sources (excessive thyroid hormone treatment, struma ovarii) or from overactivity of the thyroid gland itself. The latter is termed *hyperthyroidism;* however in practice both terms are used interchangeably. The commonest causes of hyperthyroidism (95%) are Graves' disease and toxic thyroid adenoma.

Hyperthyroidism can be differentiated into overt and subclinical hyperthyroidism. Overt hyperthyroidism is diagnosed when the TSH level is suppressed, with free thyroxine (T4) and/or tri-iodothyronine (T3) levels above the normal reference range, in a person with symptoms of hyperthyroidism. Subclinical hyperthyroidism is diagnosed when the TSH level is suppressed, with free T4 and T3 levels within the normal reference range. The prevalence of overt hyperthyroidism is about 20 per 1000 women and 2 per 1000 men (including previously treated cases) with the annual incidence of overt hyperthyroidism is about 1 per 1000 women and is negligible for men. The prevalence of subclinical hyperthyroidism is 2% in adults, and 3% in those older than 80 years.

Three main modalities of therapy should be considered for patients with thyrotoxicosis, namely, medical therapy, surgical thyroidectomy, and radioiodine. The choice between these therapies should be dictated by the clinical nature of the disease, the patient's general health, her desire for pregnancy or need to care for young children, and overall patient preference. Treatment is initially monitored by free thyroxine (T4) values, as suppression of thyroid-stimulating hormone (TSH) may persist for months despite adequate management.

Graves' disease is a syndrome that consists of diffuse goitre, ophthalmopathy (and dermopathy), tachycardia apart from the clinical picture of thyrotoxicosis, due to stimulation of the thyroid by circulating antibodies (TSAb). Since immunomodulation in Graves' is not available yet the principle of treatment is to inhibit the hormonogenesis (with antithyroid drugs) or to decrease the amount of functional thyroid tissue (by thyroidectomy or radioactive iodine). *Toxic adenoma* is an autonomous benign neoplasia of the thyroid associated with excess secretion of thyroid hormone. The patient will show the clinical picture of thyrotoxicosis. Surgery is usually the preferred treatment here, although antithyroid drugs and radioiodine may also be useful.

III.b.1. Anti-thyroid Drugs

Agents to treat hyperthyroidism may be classified as follows: (1) drugs that impair trapping of iodide (anion inhibitors); (2) drugs that inhibit thyroid hormone synthesis (thioamides); (3) drugs impairing release and proteolysis (iodides); (4) drugs that interfere with conversion of T4 to T3 (iodinated contrast media); (5) drugs that alleviate the peripheral symptoms of thyrotoxicosis (beta blockers); and (6) agents that destroy the thyroid follicular cells (radioactive iodine).

III.b.1.1. Anion inhibitors. Perchlorate, periodate, pertechnetate and thiocyanate (a naturally occurring goitrogen) are classified as iodide pump inhibitors, antagonizing iodide transport through competitive inhibition. This effect can be overcome by large dose of iodides. Perchlorate is used to block reuptake of iodide in cases of amiodarone induced hyperthyroidism and for the 'perchlorate discharge test'.

III.b.1.2. Inhibitors of hormonogenesis: thioamides. The active antithyroid compound is thiocarbamide. Methimazole, carbimazole (which is converted to methimazole *in vivo*) and PTU (propylthiouracil) are mostly used to treat hyperthyroidism.

PTU possesses special benefit; it inhibits peripheral deiodination, thereby blocking the conversion of thyroxine to the active hormone tri-iodothyronine. PTU is rapidly absorbed from the gut, reaching peak blood levels within one hour, and is excreted in urine as the inactive glucuronide within 24 hours. In contrast methimazole which is absorbed at variable rates, is excreted slower (only 65–70% within 48 hours in urine). The short plasma half-life of

drugs has little influence on the dosing since both are accumulated by the thyroid gland and intrathyroidal concentration is most important. However for propylthiouracil six hourly administration is reasonable since a single 100 mg dose can inhibit 60% iodine organification for 7 hours, while a single daily dose for methimazole can be given in mild or moderate hyperthyroidism.

Both drugs cross the placenta and accumulate in the fetal thyroid, which should be considered when using these drugs in pregnancy. Propylthiouracil is often slightly preferred in pregnancy due to its stronger protein-binding and lower placental transfer. It is also not secreted in large amounts in breast milk (only 0.077% of the oral dose is excreted in the milk). However it is prudent to advise mothers wishing to breast feed their infants to take no more than 200 mg PTU daily, in divided doses and taking each dose after feeding.

The onset of effect of these drugs is slow; 2–4 weeks is required before stored hormons are depleted and clinical signs of improvement are observed. Short-term treatment is indicated to prepare patients for surgery or radioiodine therapy, while long-term treatment is indicated for cases inappropriate for surgery or radioactive modalities or where medical therapy alone is used. Usually the patient is advised to continue treatment for 1–2 years: spontaneous remission occurs in about 50% of cases treated in this way. There is no way to predict remission confidently, however hormone levels, TSAb titer, and goitre size are useful guides.

Adverse effects occur in 3–12% in the form of rash, fever, urticaria, vasculitis, arthralgia, a lupus-like reaction, cholestatic jaundice, hepatitis, lymphadenopathy and polyserositis; but the most dangerous adverse effect is agranulocytosis (it occurs only in 0.3–0.6%). The reaction is readily reversible when the drug is discontinued. Cross-sensitivity between propylthiouracil and methimazole is about 50%, therefore switching drugs in patients with severe reactions is not recommended.

The initial dose for carbimazole or methimazole is 20–60 mg/day until the patient is rendered euthyroid with maintenance therapy of 5–15 mg/day. For propylthiouracil the initial dose is 300–450 mg/day with maintenance doses of 50–150 mg/day. Higher doses are sometimes used in severe disease. Two different treatment regimens may be used: (1) titration regimen, to try to achieve a euthyroid state by dose tritation and (2) block-replacement regimen, with the use of concomitant thyroid replacement therapy which has the advantage of avoiding iatrogenic hypothyroidism and the need for frequent biochemical monitoring. This regimen is contraindicated during pregnancy.

Evidence from three randomized controlled trials suggests that the optimal duration of treatment for the titration regimen is 12–18 months, and for the block-replace regimen is 6–12 months. However, people frequently relapse when treatment is stopped. People most likely to achieve remission are those with mild disease and small goitres. This approach is sometimes more convenient for the patient, with greater stability of thyroid function, though it cannot be used in pregnancy.

III.b.1.3. Iodides. Iodides have several actions, inhibiting hormone release and organification, and decreasing the vascularity, fragility and size of the hyperplastic thyroid gland. In pharmacological doses (>6 mg daily) the main effect is to inhibit hormone release. Rapid clinical improvement can be expected within 2–7 days, hence its indication in severe cases and thyroid crisis. Iodine is useful to prepare the patient for thyroidectomy: potassium iodide in doses of 60 mg orally 8-hourly for 10–14 days or Lugol's iodine 0.1–0.3 ml 8-hourly will render surgery safer.

Iodides should not be used alone since the normal gland will *escape* from iodide blockade in 2–8 weeks. Chronic use in pregnancy is not recommended because it crosses placenta and cause fetal goitre. Iodide treatment results in high intrathyroidal iodide content that can delay the onset of thioamide therapy or delay the use for radioactive iodine therapy for weeks if not months. Adverse effects include '*iodism*' which is rare and reversible. The clinical symptoms are acneiform rash, sialadenitis, mucous membrane ulceration, conjuctivitis, rhinorrhoea, metallic taste and rarely anaphylactoid reaction.

III.b.1.4. Iodinated contrast media. When iodides or thioamides are contraindicated, the contrast media ipodate and iopanoic acid may be used to treat hyperthyroidism. These drugs rapidly inhibit conversion of T4 to T3 in the liver, kidney, brain and pituitary gland, and the effects are so rapid that they are sometimes helpful in the treatment of thyroid storm (see below). The drugs are non toxic and have prolonged effect. Precautions are similar to iodide,

and normally are given orally, using 0.5–1 g/day for 3 days. Other drugs such as propranolol, corticosteroids, lithium and PTU have similar effects on T4 → T3 conversion.

III.b.1.5. Beta-adrenergic blocking drugs. In hyperthyroidism many symptoms simulate beta-adrenergic hyperactivity, which is believed be due to increased tissue sensitivity to catecholamines. Beta-adrenergic blockade thus relieves the symptoms of hyperthyroidism but does not block the hormone metabolic effect nor modify the course of disease. It is often used while waiting for antithyroid drugs or radioactive iodine treatment to start working. It is advisable to use non-selective beta-adrenergic drugs, and propranolol is mostly used in clinical practice. Larger and more frequent doses may be required because people with hyperthyroidism may be relatively resistant to the effects of beta-blockers. Propranolol and metoprolol are widely used but, because hepatic metabolism is increased in the hyperthyroid state, they need to be given three to four times a day. Atenolol only needs to be taken once a day (as it is mainly excreted by the kidneys) but is not licensed for this use. In hyperthyroid people with heart failure, much lower starting doses should be used, and cardioselective beta-blockers (bisoprolol and carvedilol) are licensed for heart failure.

III.b.1.6. Radioactive iodine. Radioactive iodine (Iodine-131) is a radioactive isotope of iodine, usually taken in an oral solution formulation as sodium ^{131}I. Given orally as sodium ^{131}I, radioactive iodine is rapidly absorbed, concentrated and stored in the thyroid follicles. The therapeutic effect depends on beta-ray emission and destruction of thyroid parenchyma manifests some weeks after treatment. It is relatively safe, cheap, painless and avoids side effects associated with surgery. It is widely regarded as the treatment of choice in adults with toxic multinodular goiter, toxic nodule and people who relapse after a course of antithyroid medication.

Early worries about risk of cancer or leukaemia have proven unfounded in prolonged follow-up studies. However radioactive treatment is contraindicated in pregnant woman or nursing mothers. Other risks for the fetus are abortion, intrauterine death, congenital malformation and congenital hypothyroidism (if administered after 12 weeks gestation). It is customary to avoid pregnancy for the first 6 months post-treatment. Men are advised not to father children for at least four months following treatment.

Pretreatment with antithyroid drugs is necessary to avoid the risk of 'thyroid storm' (exacerbation of hyperthyroidism with fever and tachycardia) in the following groups: the elderly, people with cardiac disease, and people with severe hyperthyroidism. Antithyroid drugs should be stopped at least 4 days before radioactive iodine is given, and restarted no sooner than 3 days after, to permit uptake of the iodine into the thyroid gland. Antithyroid drugs can usually be stopped after 2–6 weeks as the radioactive iodine takes effect.

The expected long-term risk of radioiodine is progressive hypothyroidism. This occurs in 6–25% of cases, depending on dose, in the first year after treatment, and the cumulative rate increases by 2–3% annually. This implies that patient must be followed up *indefinitely*, until the onset of hypothyroidism. Once this occurs then thyroxine replacement should be given for life.

III.b.2. Surgery

Surgery is usually a near-total thyroidectomy, with main indications being: suspected coexistent thyroid carcinoma, solitary toxic nodule, large goiter, failed medical treatment, patient preference and occasionally in pregnancy if adverse effects from antithyroid drugs occur.

The complications following surgery include haemorrhage, wound infection, recurrent laryngeal nerve damage, and transient (up to 20% of cases) or permanent (2%) hypocalcaemia. After near-total thyroidectomy relapse of hyperthyroidism should be rare, and this operation has largely replaced the older approach of 'sub-total thyroidectomy' which had higher relapse rates.

III.b.2.1. Preparation for surgery. Euthyroidism is mandatory for safe surgery. This is achieved by using thioamide drugs plus beta-adrenoreceptor blocker (propanolol or atenolol) for comfort, adding iodide (potassium iodide or Lugol's iodine solution) 7–10 days before operation (not sooner) to reduce the vascularity and fragility of the gland. It usually takes 4–6 weeks to prepare the patient for surgery in this way. Some prefer to use only propranolol but this is probably hazardous, and the masking of symptoms may give a false sense of security.

III.b.3. Management of Hyperthyroidism During Pregnancy and Breastfeeding

Pregnancy may be adversely affected by poorly controlled hyperthyroidism, with an increased rate of fetal loss. The goal of treatment during pregnancy is to maintain euthyroidism, using the smallest doses of anti thyroid drugs possible.

For women planning pregnancy within the next 2–3 years, initial treatment with radioactive iodine or surgery may be best. Antithyroid drugs are the treatment of choice during pregnancy with little evidence of teratogenicity, although there is a possible association of carbimazole with fetal aplasia cutis (a very rare congenital scalp defect) and oesophageal atresia. Thyroid function should be monitored every 4–6 weeks during pregnancy to maintain optimum control, and also because both drugs cross the placenta and over-treatment can cause fetal goitre and hypothyroidism. If it is clinically possible, the dose may be reduced or discontinued 3–4 weeks before delivery, to reduce the risk of neonatal complications. There is a higher incidence of malformations and other forms of fetal toxicity if the maternal hyperthyroidism remains untreated.

Graves' disease often improves during pregnancy, and in some cases drug treatment can be withdrawn in the third trimester.

Antithyroid drugs may be used during breastfeeding as long as neonatal development is closely monitored and the lowest effective dose is used. Beta-blockers can be used for symptomatic relief until antithyroid drugs start working. Propranolol and metoprolol can be used during breastfeeding, but atenolol should be avoided. Block-replacement regimens must not be used, as the higher doses of antithyroid drugs used in block-replace regimens result in an increased risk of fetal goitre and hypothyroidism. Radioactive iodine is contraindicated in pregnancy and during breastfeeding.

III.b.4. Thyroid Crisis ('Thyroid Storm')

Occasionally patients develop a dramatically acute and severe form of thyrotoxicosis which may be life-threatening, termed thyroid crisis or thyroid storm. In this condition the patient is at risk of cardiac complications, notably arrhythmia and ventricular failure, and it requires very urgent treatment. It is essential to use high doses of anti-thyroid drugs, and PTU is often preferred for this, particularly because of its fast absorption. Iodides or ipodate are often used, and although there is no controlled trial evidence for this use, it seems reasonable to exploit their rapid effect on hormone release by the thyroid gland. Beta-adrenergic blocking drugs are important to protect the patient from arrhythmias, and are, in this instance, indicated in the presence of heart failure. Occasionally corticosteroids are used, though there is no convincing evidence that their use is beneficial.

III.c. Hypothyroidism and Thyroid Hormone Replacement

Hypothyroidism is the clinical and biochemical syndrome that results from decreased thyroid hormone production by the thyroid, usually due to primary thyroid failure, or more rarely from hypopituitarism. Hypothyroidism can be differentiated into overt and subclinical hypothyroidism. Overt hypothyroidism is diagnosed on the basis of characteristic clinical features, with a serum thyroid-stimulating hormone (TSH) concentration above the normal reference range and a serum free thyroxine (FT4) concentration below the reference range. Subclinical hypothyroidism is diagnosed when the TSH concentration is increased above the reference range but the FT4 concentration is within the normal range. Hypothyroidism is usually due to primary thyroid failure, or more rarely from hypopituitarism, either congenital or acquired. Whatever the cause, treatment with thyroid hormone should be instituted. Hypothyroidism may occur in utero, or in infancy, childhood or adulthood. Since thyroid hormones play a central role in growth and development, deficiency in fetal or infant life can have devastating consequences, particularly impairing brain development, such that permanent cretinism can result.

In the adult population, the prevalence of overt hypothyroidism is 19 per 1000 women and 1 per 1000 men with annual incidence of overt hypothyroidism is 4 per 1000 women and 0.6 per 1000 men. Subclinical hypothyroidism is also more common in women, the incidence increases with age, with up to 10% of women older than 60 years having an increased thyroid-stimulating hormone concentration. Subclinical hypothyroidism is more common in people who have been treated for hyperthyroidism with radioactive iodine or surgery, and in those with organ-specific autoimmune diseases, such as pernicious anaemia, type 1 diabetes mellitus, or Addison's disease.

Clinical manifestations of overt hypothyroidism are usually obvious; though minor deficiencies may be more easily missed they may have pronounced adverse effects on patients' well-being. The diagnosis nowadays should always be confirmed biochemically (with detection of low serum T4 and high TSH levels), and highly sensitive and specific immunoassays are now readily available in most countries.

Management of hypothyroidism consists of identifying the underlying cause and then providing thyroid hormone replacement to normalize thyroid status. The goal of treatment is to reduce serum TSH levels to normal, which for most assays is roughly between 0.5 and 3 mU/l. Oversuppression of TSH levels is probably not advisable, as overtreatment may predispose to cardiac arrhythmias (particularly atrial fibrillation), and may have subtle effects on bone mineral density.

Drugs available are L-thyroxine (T4), L-triiodothyronine (T3), or combinations of T4 and T3. Desiccated thyroid is now rarely used as there is no proven benefit over T4 treatment alone, and it may be of variable quality with unpredictable effects. T3 has a short effective plasma half-life, with short-lived peaks after oral dosing, so that oral T4 is generally the best treatment. Most healthy adults under 60 years of age can begin with complete replacement dose of 1.6–1.8 μg L-thyroxine/kg ideal bodyweight, giving typical doses of 100–125 μg per day. For patients over 60, with coronary artery disease, or with long-standing hypothyroidism, the dose should be initiated more slowly, starting with 25 μg daily, and increasing by increments of 25 μg every 4–8 weeks until an appropriate replacement dose is reached.

Adverse effects are usually due to excessive doses (which may occur if the initial increase in metabolism is too rapid) and correspond to symptoms of hyperthyroidism, but they usually disappear after dose reduction or withdrawal of treatment. The most common adverse effects affect the following system as: Heart: arrhythmias, anginal pain, Central nervous system: headache, hyperactivity, sweating, tremor, heat intolerance, Gastrointestinal tract: diarrhoea, excessive weight loss, vomiting, Musculoskeletal system: muscle cramps, muscle weakness.

Some evidence indicates that levothyroxine overtreatment (leading to a hyperthyroid state) could lead to long-term bone mass loss (especially in elderly women) or atrial fibrillation (especially in elderly people). Levothyroxine has a narrow therapeutic range, and small changes in absorption or metabolism can result in clinical or subclinical hypothyroidism or hyperthyroidism. Calcium, iron, sucralfate, aluminium hydroxide, lovastatin and anion-exchange resins reduce absorption of levothyroxine. Liver enzymes inducing drugs (e.g. carbamazepine, phenytoin, phenobarbitone, primidone, and rifampicin) accelerate metabolism of levothyroxine. Close monitoring and adjustment of the levothyroxine dose are needed when dose changes are made to these medicines. People taking concomitant warfarin need careful monitoring. Levothyroxine may increase the anticoagulant effect of warfarin (as well as other oral anticoagulants), and the warfarin dose may need to be reduced. Amiodarone may reduce the effects of levothyroxine. There are also a few conditions where the dose must be adjusted. It may need to be increased in malabsorption, liver cirrhosis, and also in the elderly.

T3 has been proposed for routine replacement therapy as an addition to T4, but this remains controversial, with little clear evidence supporting its use at present.

III.c.1. Women of Childbearing Age with Hypothyroidism

In case of a preconceptual woman with pre-existing overt hypothyroidism, it is advisable to perform thyroid function tests before conception if possible, to check adequacy of treatment and to make sure the woman is stable and understands the importance of compliance with levothyroxine. At diagnosis of pregnancy, some endocrinologists routinely increase the levothyroxine dose by adding 25–50 μg to the routine dose, but this should normally depend on the dose the woman is already taking and the current thyroid-stimulating hormone (TSH) and free thyroxine (FT4) concentrations. The target of treatment is to maintain circulating TSH concentrations in the low–normal range (0.4–2.0 mU/l) and a FT4 concentration in the upper part of the reference range. The thyroid function tests should be repeated at least each trimester. This is especially important in the first trimester. More frequent tests may be necessary if the dose is being titrated until the person is stabilized.

If the woman is planning a pregnancy or is confirmed as pregnant and overt hypothyroidism is newly diagnosed, the levothyroxine starting dose is usually 50–100 μg to be taken each morning, as there should be no delay in starting treatment. A pregnant woman with newly diagnosed overt hypothyroidism

should have her thyroid function tests rechecked in 4–6 weeks, and the levothyroxine dose should be titrated as necessary until stabilized.

Women with subclinical hypothyroidism who are pregnant or planning a pregnancy and are not receiving levothyroxine treatment should be started on levothyroxine therapy. The experts recommend different starting doses (varying from 25 to 100 to be taken each morning). The dose of levothyroxine should be increased and monitored as for women with known subclinical hypothyroidism who are already receiving levothyroxine treatment.

III.d. Iodine Deficiency Disorders

Iodine enters our body through food and water, and iodine deficiency is a global problem that affects large populations living in environments where the soil has been depleted of iodine. Glaciation in the past, heavy rainfall, and flooded rivers remove iodine from the soil. This leads to iodine deficiency in all plants and cereals grown in the soil. Populations living in this eco-system are therefore 'locked into' iodine deficiency unless they receive deliberate iodine supplementation. Iodine deficiency is also exacerbated by a high consumption of natural goitrogens that are present in some staple foods such as cassava. The antithyroid action of goitrogens is related to the presence of thiocyanate which inhibits thyroid iodide transport and, at higher doses, competes with iodide in the synthesis of thyroid hormones. Goitrogenicity is determined by the balance between the dietary supply of iodine and thiocyanate: goitre develops when the urinary iodine (μg) : thiocyanate (mg) ratio falls below 3. Recent calculations show that the total population at risk is in excess of 1.5 billion in Asia, Africa, Latin America and Europe.

Iodine deficiency disorders (IDD) comprise a cluster of clinical syndromes that affect growth and development, particularly that of the brain, that can be prevented by correction of iodine deficiency. Formerly the term *endemic goitre* was used to describe the effects of iodine deficiency, but the term IDD is to be preferred as it emphasizes the range of biological effects of the problem. Endemic goitre is therefore the most visible consequence of iodine deficiency, but the most damaging is on the developing brain. Populations with iodine deficiency show part or all of the clinical spectrum of IDD, which includes increased perinatal and infant mortality, increased early and late pregnancy loss, neonatal hypothyroidism (as judged by high TSH levels at birth), growth impairment and intellectual retardation, endemic goitre, and the most severe form, endemic cretinism. A meta-analysis of 19 studies conducted in regions of severe deficiency showed that iodine deficiency is responsible for a mean IQ loss of 13.5 points among affected populations.

Endemic cretinism is defined by three major features: its epidemiological association with severe iodine deficiency and endemic goitre, its prevention by iodine replacement, and its clinical features. Two clinical presentations are recognized, namely neurological and myxoedematous cretinism, of which the first is the commonest type and the second type is prevalent only in a few areas (Zaire, Nepal and Western China). Although the two types were thought to represent either distinct clinical entities or the two extremes of a continuum of abnormality, recent data indicate that endemic cretinism is the product of prenatal and postnatal hypothyroidism on neurological and somatic development. The neurological deficits points to an intrauterine insult to the developing fetal nervous system around midtrimester.

III.d.1. Assessment of the Iodine Status of a Population

Countries affected by iodine deficiency require to develop national programmes to assess the extent and severity of the problem. Once an IDD control programme is initiated monitoring and evaluation are required. There are three major components needed to meet this goal, namely determination of thyroid size and goitre prevalence, the determination of urinary iodine excretion, and the measurement of thyroid function, including serum TSH levels.

The definition of *goitre* and accepted criteria for estimation of goitre size and grading are available in WHO publications. Schoolchildren aged 6–12 years form a good population for sampling. Grade 0 denotes that the thyroid is neither palpable nor visible. All thyroid glands larger than this are considered goitrous. An enlarged thyroid gland that is palpable but not visible when the neck is in the normal position is classified as Grade 1. This includes nodular alteration(s) which can occur even when the thyroid is not visibly enlarged. A swelling in the neck that is visible when the neck is in a normal position, and is consistent with an enlarged thyroid when the neck is palpated, is classified as Grade 2. However, since

there is a problem of reproducibility with assessment by palpation, especially with smaller glands, it is advisable to use more objective measures if formal classification is necessary, e.g. ultrasonography. Using one of these methods of assessment, epidemiological criteria of endemia based on the total goitre rate (TGR) are as follows: TGR $< 5\%$ no endemia, 5–20% mild, 20–29% moderate and $>30\%$ severe endemia.

Urinary Iodine Excretion (UIE) provides the best single measurement of iodine intake of the population and Should be used for initial and follow up assessment. For epidemiological studies, population and not individual levels are is required. To achieve this 40 casual samples from a particular group can be collected (may be collected from schoolchildren at the same time as the goiter is assessed). The values are expressed as a median. Median UIE in the population below 100 µg/l indicate iodine deficiency. Thus median UIE $\geqslant$ 10 µg/l means no deficiency, 50–99 µg/l indicates mild, 20–49 µg/l moderate, and <20 µg/l severe IDD.

Thyroid status can be assessed using dried blood spot specimens for epidemiological surveys. Since TSH levels (as a marker of hypothyroidism) are stable in dried blood spot specimens for months this is the preferred assay for monitoring purposes. TSH monitoring is used in this way in India, China, Zaire, Thailand and Indonesia.

III.d.2. Assessing the Severity of IDD as a Significant Public Health Problem

Based on goitre prevalence (TGR), median UIE level, and the proportion of population with TSH $>$ 5 mU/l, populations can be classified as having *no iodine deficiency*, or *mild*, *moderate* or *severe iodine deficiency.* Severe iodine deficiency bears the risk of endemic cretinism and hypothyroidism, while moderate and mild endemia have lesser risk of growth and development impairment (Table 3).

III.d.3. Prevention

The therapeutic strategy should rely on preventative measures. Endemic goitre and endemic cretinism as well as more subtle deficits of neurological function associated with iodine deficiency have been shown to be prevented with adequate iodine prophylaxis. Adequate and continuous supply is the key to successful prevention programmes.

'Iodide' or 'iodate' are used to iodize salt. The level of salt iodization depends on per capita salt consumption, moisture, light, heat, and contaminants. The recommended daily iodine requirements are 50 µg for infants, 90 µg for children (2–6 yrs), 120 µg for schoolchildren (7–12 yrs), 150 µg for adults and 200 µg for pregnant and lactating women.

For special target populations the use oral or injectable *iodinated oil* may be suggested (WHO/UNICEF/ICCIDD, 1996). The most widely used preparation is Lipiodol (Laboratoire Guerbert, France), which is a poppyseed oil with 38% weight as iodine; 1 ml contains 480 mg iodine. Although one injection may suffice for 3–4 years, oral administration of iodide is preferable because of the risks of transmissible disease. Oral doses of 300–480 mg and 400–960 mg may be given every year to pregnant women and non-pregnant fertile women respectively, although smaller doses have been reported to be effective.

Table 3. Summary of IDD prevalence indicators and criteria for a significant public health problem

Indicator	Target population	Severity of public health problem (prevalence)		
		Mild	Moderate	Severe
Goitre grade > 0	SAC	5.0–19.9%	20.0–29.9%	$\geqslant$30%
Thyroid volume $>$ 97th centile	SAC	5.0–19.9%	20.0–29.9%	$\geqslant$30%
By ultrasound				
Median urinary iodine level (µg/l)	SAC	50–99	20–49	<20
TSH $>$ 5 mU/l whole blood	Neonates	3.0–19.9%	20.0–39.9%	$\geqslant$40%
Median Tg (ng/ml serum)*	C/A	10.0–19.9	20.0–39.9	$\geqslant$40.0

SAC = school-age children; C/A = children and adults; Tg = thyroglobulin.

*Different assays may have different normal ranges.

IV. ADRENAL DISEASE AND STEROID THERAPY

The adrenal glands are composed of adrenal cortex and adrenal medulla, the cortex producing corticosteroid hormones and the medulla producing catecholamines. The majority of clinical problems concern corticosteroid therapy and diseases of adrenal insufficiency. Corticosteroid excess (Cushing's syndrome) and diseases of the adrenal medulla are rare and these will be mentioned only briefly. The adrenal cortex secretes the glucocorticoid hormone hydrocortisone (usually termed cortisol), which has weak mineralocorticoid activity; the main mineralocorticoid secreted by the adrenal is aldosterone. Both of these hormones are essential for health and well-being, and deficiency is life-threatening. Glucocorticoids are widely used in medicine as anti-inflammatory agents, usually in high doses, for the treatment of diverse diseases such as asthma, inflammatory bowel disease, rheumatoid arthritis, dermatitis, and malignant disease.

IV.a. Glucocorticoids in Clinical Use

A series of agents are available for clinical use, with different anti-inflammatory potencies and varying glucocorticoid and mineralocorticoid activities. In comparison with the native hormone, hydrocortisone, the synthetic agents betamethasone, dexamethasone, prednisolone, prednisone and triamcinolone are more potent, but have relatively less mineralocorticoid effect, and they are therefore widely used as anti-inflammatory agents. Hydrocortisone is commonly used in emergency situations by intravenous injection, but has too much mineralocorticoid activity to allow its use in high doses, which can thus cause significant fluid retention. *Prednisolone* has mainly glucocorticoid activity and is the most widely used oral steroid therapy, with an anti-inflammatory potency roughly 4 times that of hydrocortisone. (Prednisone has similar activity but requires hepatic conversion to prednisolone, and is therefore now not widely used.) Betamethasone and beclomethasone are more potent (betamethasone about 25 times more potent than hydrocortisone) and can be used topically for skin and eye disease and for asthma. Dexamethasone is of roughly similar potency to betamethasone, and is often used for high dose therapy, for example for cerebral oedema.

IV.a.1. Side Effects of Corticosteroids

Corticosteroids (commonly abbreviated 'steroids') have been dramatically beneficial in clinical medicine since their introduction 50 years ago, but they have major side effects when used for long periods or in high doses. The side effects of glucocorticoids have been shown to be strictly dose dependent. Thus, as the dosage is escalated to improve efficacy, the side effects also increase. In addition, some side effects are known to be age and sex-dependent. The side effects of glucocorticoid therapy show different degrees of severity, likely due to the wide variety of physiological contexts in which glucocorticoids act. The list of side effects from long-term steroid use is long and includes suppression of the production of endogenous glucocorticoids (adrenal suppression) and other steroids (testosterone and oestrogen), dermal atrophy due to lack of remodelling of the skin, and impacts on behavior and mental state. A number of the more common side effects are detailed below.

IV.a.1.1. Osteoporosis. Long-term glucocorticoid treatment often results in some degree of osteoporosis. Susceptibility to fractures and the chance of aseptic necrosis of the femoral head increases within months of starting glucocorticoid therapy. Steroids reduce the quality of trabecular bone, resulting in an increase in fracture rate. Detrimental bone effects have been documented in several disease settings after glucocorticoid treatment, including RA, chronic obstructive pulmonary disease, asthma, and transplantation. Bone loss is highest in the first 6 months of therapy, after which patients continue to lose bone, but at a slower rate. When taken off steroids, patients appear to partially regain bone.

IV.a.1.2. Muscle wasting. Glucocorticoid-induced myopathy, resulting in decreased strength and muscle mass, likely contributes to the high fracture rate caused by steroids due to an increased likelihood of falls. The mechanism by which glucocorticoids affect muscle mass is partially due to hypogonadism observed in many patients. This is manifested as a decline in levels of the sex steroids estrogen and testosterone, two hormones that normally contribute to the maintenance of both muscle and bone mass.

IV.a.1.3. Hypertension. Excess glucocorticoids can lead to increased blood pressure. These effects contribute to increased risk of heart-related illness

and other complications. Glucocorticoids and mineralocorticoids exert effects at several different points critical for regulation of blood pressure. Glucocorticoids are in vast excess relative to mineralocorticoids in serum. Normally, the kidney is protected from the effects of these high cortisol levels through the oxidizing action of 11beta-hydroxysteroid dehydrogenase type 2, a tissue-specific enzyme capable of converting cortisol to the weaker 11-ketosteroid cortisone. However, aldosterone, with an aldehyde group at C18, as well as synthetic steroids such as dexamethasone (with a 9 alpha-fluoro group) are not susceptible to this activity and have major effects directly on the kidney through both the mineralocorticoid and glucocorticoid receptors. The effects in this tissue include increases in both transepithelial sodium transport and sodium reabsorption in the proximal tubule as a result of increased sensitivity to angiotensin II.

A similar system may operate in brain, best characterized in the rat; 11beta-hydroxysteroid dehydrogenase type 2 is expressed along with mineralocorticoid receptor (MR) in a few select areas involved in central regulation of salt, water balance, and blood pressure. There are however areas of the brain where MR is likely unprotected and may be exposed to cortisol.

IV.a.1.4. Glucocorticoid-mediated insulin resistance. The glucocorticoid effect on glycemic control is thought to target insulin signaling. Glucocorticoids affect insulin-mediated increases in blood flow to muscles and they decrease key insulin receptor signaling molecules and increase glucose output by increasing the rate-limiting enzyme in gluconeogenesis, phosphoenol pyruvate carboxy kinase. *Diabetes* or glucose intolerance may be induced by moderate doses of systemic steroids, and this may occasionally present as acute diabetic ketoacidosis. It is therefore very important to monitor blood glucose in patients receiving high doses.

IV.a.1.5. Truncal obesity and fat redistribution. Glucocorticoids induce fat redistribution and accumulation; fat is shed from limbs and accumulates in truncal and visceral areas. Facial, supraclavicular, and posterior cervical fat depots are particularly sensitive to glucocorticoids, resulting in the moon face and buffalo hump characteristic of long-term glucocorticoid treatment. This significantly affects the quality of life for glucocorticoid-treated patients by affecting their appearance and by predisposing them to obesity-related health issues.

IV.a.1.6. Inhibition of wound repair. Glucocorticoids increase the risk of infection by hindering wound healing. These effects are dependent on both the dose and timing of glucocorticoid administration. Glucocorticoids affect wound healing by several mechanisms. Inflammation itself is a natural and critical part of the wound healing process and as a consequence, the antiinflammatory effects of glucocorticoids are detrimental to wound repair. In addition, glucocorticoids inhibit both collagen synthesis and cross-linking, directly affecting the structural components of a healing wound.

IV.a.1.7. Mental disturbances. These are probably more common than usually realized, and include euphoria, depression and paranoia, with occasional acute ‘steroid psychosis’.

IV.a.1.8. Growth retardation. In children this may cause permanent short stature. It is a common problem with systemic steroid administration, but has also been observed in children taking high doses of topical steroids.

IV.a.1.9. Adrenal suppression. It results from inhibition of pituitary ACTH secretion, and some suppression of the normal adrenal response to stress may persist for years after stopping therapy. Rapid withdrawal of corticosteroid therapy can therefore precipitate dangerous acute adrenal insufficiency (‘Addisonian crisis’, with hypotension, vomiting, coma and ultimately death), and for this reason steroid treatment should always be reduced gradually, sometimes over many months, according to the dose and duration of therapy.

IV.a.1.10. Immunosuppression. An important effect of steroid therapy is immunosuppression and this may be an essential part of their anti-inflammatory action in some situations. However patients may therefore be at risk of serious illness as a result of normally minor infection. This is particularly important with diseases such as chickenpox and measles. In addition the usual clinical effects of such diseases may be masked, delaying their diagnosis.

IV.a.1.11. Mineralocorticoid side effects. These are common problems, causing sodium and water retention, hypokalaemia and hypertension. They are often marked with hydrocortisone, but may be seen with high doses of all of the therapeutic glucocorticoid drugs.

IV.b. Treatment of Adrenal Insufficiency

In terms of endocrine disease, glucocorticoids are mainly used for replacement therapy in cases of adrenal insufficiency, both primary adrenal failure and hypopituitarism. Autoimmune adrenalitis and tuberculosis are the leading causes of Addison's disease, the former being the most common in the developed countries. However tuberculosis is still an important cause of Addison's disease in the developing countries, particularly where tuberculosis is not uncommon. ACTH deficiency is most commonly induced by high-dose or prolonged steroid therapy, including topical therapy, while pituitary or hypothalamic lesions are much rarer. AIDS is an emerging but still unusual cause of adrenal insufficiency, though acute adrenal crisis has been reported.

IV.b.1. Glucocorticoid Replacement

For adrenal glucocorticoid replacement therapy hydrocortisone is normally the treatment of choice, and is given in a schedule designed to mimic the physiological circadian changes in serum cortisol. The dose schedules have been studied recently, and most evidence suggests that 20 mg per day is adequate for most patients. In addition, a thrice daily regimen (e.g. 10 mg on rising, 5 mg around midday, and 5 mg late afternoon) is preferable to a twice daily regimen, the higher dose should be taken in the morning, which commonly gives excessive peaks and suboptimal troughs in plasma cortisol levels.

IV.b.2. Mineralocorticoid Replacement

For replacement of deficient aldosterone secretion, the fluorinated steroid derivative fludrocortisone is used, usually in a dose of 100–200 μg per day. Replacement therapy is normally judged by monitoring blood pressure (lying and standing) and plasma electrolytes.

IV.b.3. Acute Adrenal Insufficiency

This is a medical emergency, and must be treated with intravenous hydrocortisone (50–100 mg 6-hourly) as intramuscular absorption may be unreliable. Patients are usually hypovolaemic and shocked, so mineralocorticoid deficiency must also be treated by using intravenous saline infusion, often requiring several liters of fluid, until the patient is well enough to take oral fludrocortisone.

IV.b.3.1. Precautions for patients. Patients taking corticosteroids will frequently have underlying adrenal failure or glucocorticoid-induced adrenal suppression. In view of the life-threatening nature of acute adrenal crisis, patients should be advised to carry cards or bracelets giving details of their steroid dose and underlying condition. Anaesthetists and surgeons must be aware of the need for increased 'steroid cover' for surgical stress. Patients may require parenteral steroid treatment if they develop intercurrent illness, and particularly if they are likely to absorb oral doses poorly, for example during diarrhoeal or vomiting illnesses. Some patients keep a supply of injectable hydrocortisone for emergency use.

IV.c. Adrenal Medulla and Phaeochromocytoma

Deficiency of adrenal medullary catecholamines appears to give no ill effects, and replacement therapy is therefore not used, but adrenal medullary tumours, phaeochromocytomas, secrete excess catecholamines often causing hypertension with dramatic episodes of headache, palpitations, pallor, sweating and anxiety. This condition is normally treated surgically, but preoperative preparation is mandatory to avoid catastrophic effects of surges of catecholamine release. A combination of alpha- and beta-adrenergic receptor blockade is normally used, with drugs such as phenoxybenzamine or doxazosin as alpha-blockers, and propranolol as a non-selective beta-blocker.

V. REPRODUCTIVE MEDICINE, SEX STEROID THERAPY AND CONTRACEPTION

V.a. Female Reproductive Medicine

The ovaries have two major functions, namely the production of female sex hormones, and the regular production of mature gametes ready for potential fertilization. Their function is controlled by the pituitary gonadotrophic hormones, luteinising hormone (LH) and follicle stimulating hormone (FSH). In normal women the ovaries undergo a regular 28-day cycle, in which a single dominant ovarian follicle containing an oocyte matures over 14 days under the influence of FSH, with feedback control on the pituitary exerted by rising levels of oestradiol and inhibin. At about 14 days there is a surge of pituitary

LH secretion which induces rupture of the follicle and release of the mature egg into the fallopian tube. In the ovary a corpus luteum forms, which secretes progesterone (maximal at about day 21) to prepare the endometrium for implantation of an early embryo. If pregnancy does not occur, the corpus luteum involutes, progesterone levels fall, and the thickened endometrium is shed giving rise to menstrual bleeding, which is defined as starting on day 1 of the next cycle.

V.a.1. Menopause and Hormone Replacement Therapy (HRT)

In normal women, the ovaries cease to function at age 45–55 years, and the complete cessation of menstrual periods is termed the menopause. In fact the menopause is not usually an abrupt change, but a gradual transition that may take as long as 10 years before periods finally stop. This can be detected by hormone measurement, as serum levels of oestradiol fall, eventually becoming unmeasurable, and FSH and LH rise. The fall in oestrogen levels causes the well known vasomotor symptoms of flushing and vaginal dryness, but post-menopausal oestrogen deficiency is associated with rapid loss of bone mineral density and increased risk of cardiovascular disease. As life expectancy has increased in many countries, a greater number of women expect to live for substantially longer after the menopause. Thus these risks have come to be of great public health importance as well as their significance to the individuals concerned. This has led to interest in the best ways of administering physiological doses of oestrogen replacement therapy (and indeed, the possible benefit of replacing small amounts of androgens).

A number of different ways of administering oestrogens have been widely used for post-menopausal replacement therapy, usually abbreviated HRT. Each of these is effective in prevention of vasomotor symptoms and protection from bone loss, and studies have shown significant reductions in risk of vertebral and hip fracture.

V.a.1.1. Oral HRT preparations. For oral therapy, there is a choice between conjugated equine oestrogens purified from urine, synthetic oestrogens such as ethinyloestradiol and tibolone, and oestradiol itself. In women with an intact uterus, the oestrogen should normally be given in conjunction with a progestagen in order to protect the endometrium from unopposed oestrogenic stimulation, as the resulting endometrial proliferation can predispose to endometrial carcinoma. In women who have had a hysterectomy, oestrogens can be given alone without risk. The progestagens currently available include progesterone and its analogues medroxyprogesterone acetate and dydrogesterone, testosterone analogues norethisterone and norgestrel, and the latter's derivatives, levonorgestrel, norgestimate, gestodene and desogestrel.

Different regimens of oestrogen replacement have proved effective. The traditional pattern is of cyclical oestrogen and progestagen administration, with monthly progesterone withdrawal to induce menstrual bleeding. However, many women prefer to reduce the inconvenience of frequent menstruation if possible, and 3-monthly patterns of administration have been used with success. In women with an established post-menopausal state, that is, no spontaneous menstruation for at least one year, continuous treatment can be given, using oestradiol or the synthetic oestrogen tibolone, which also possesses combined progestagenic and weak androgenic action.

V.a.1.2. Transdermal preparations. Adhesive patches applied to the skin can be used to deliver oestrogens transdermally, using either a reservoir of liquid or an oestradiol-containing matrix. These systems deliver adequate amounts of oestradiol to maintain plasma levels within the normal range for 24 hours, and some preparations now provide transdermal progestagen also, thus avoiding the need for additional tablets to be taken for part of the cycle.

V.a.1.3. Oestrogen and androgen implants. Subcutaneous implants of oestrogen-containing pellets, usually up to 800 mg, provide stable plasma oestradiol levels for at least 6 months in most patients. Some monitoring of plasma levels is useful to avoid progressive accumulation of oestradiol. Additional supplementation with a testosterone pellet of 100 mg has proved beneficial in some women. Subcutaneous implants have the advantage of infrequent dosing, but a minor procedure is necessary on each occasion, and there is a small incidence of implant extrusion.

V.a.1.4. Risks of HRT. HRT slightly increases the risk of DVT, pulmonary embolism, stroke, breast cancer (combined HRT), endometrial cancer (oestrogen-only HRT) and ovarian cancer (oestrogen-only HRT). Current estimates indicate

that women who have never used HRT have a cumulative risk over 10 years of about 62 cases of breast cancer per 1000 women by the age of 70, compared to a risk of about 68 cases per 1000 women who have used HRT for 10 years. This relative excess risk for breast cancer can also be expressed as 1 extra case of breast cancer per 167 women treated for 10 years.

V.a.2. Female Contraception

There are numerous choices of contraception for women, and the efficacy and costs of each must be balanced when giving advice, both to the individual and to the community at large. Hormonal contraception is still the most effective method of fertility control, and in this section only hormonal contraception will be considered. However the relative merits of other methods such as intrauterine contraceptive devices (IUCDs), condoms, and vaginal or cervical caps should be kept in mind as alternatives. Condoms in particular have important advantages in limiting spread of sexually transmitted disease.

V.a.2.1. Combined oral contraceptives. The combined oral contraceptive pill contains an oestrogen and a progestagen, and provides generally safe and effective contraception. The oestrogen content varies from 20–50 μg, and generally the lowest dose is chosen that provides adequate control of the cycle (i.e. no breakthrough menstrual bleeding) and minimizes side effects. Some preparations provide phasic changes in oestrogen dose during different parts of the month and most combined pill preparations are provided in calendar packs to simplify dosing schedules. The common side effects associated with the combined oral contraceptive include nausea, vomiting, headache, changes in body weight, fluid retention, changes in libido. The combined pill is contraindicated in pregnancy, in patients with severe risk factors for arterial disease or venous thromboembolism, ischaemic heart disease, migraine or transient ischaemic attacks, liver disease, and hormone responsive cancers such as breast or uterine carcinoma.

The progestagens in combined pills include desogestrel, gestodene, norgestimate, ethynodiol, levonorgestrel and norethisterone. The first two agents have more favorable effects on plasma lipids and cardiovascular risk but are associated with higher risks of venous thromboembolism (see below).

Patients taking the combined pill should be warned about loss of contraceptive effect due to missed pills (>12 hours late, especially early in the cycle), reduced absorption through diarrhoea or vomiting, or drug interactions.

Risks of venous thromboembolism: Combined oral contraceptives carry a small excess risk of venous thromboembolism. This risk in women not taking any form of contraceptive pill is estimated at 5 cases per 100,000 women per year, and rises to 15 cases per 100,000 woman-years with 'second generation' pills containing levonorgestrel and 25 cases per 100,000 woman-years with 'third generation' pills containing desogestrel or gestodene. (This risk remains much lower than that associated with pregnancy, namely 60 cases per 100,000 woman-years.) Most people feel that this low level of risk is acceptable for the vast majority of women, unless the patient has additional predisposing risk factors.

V.a.2.2. Progestagen-only contraceptives. These preparations are suitable for women in whom oestrogens are contraindicated, but are less effective than combined pills. Injectable long-acting progestagens, including 'Depo-Provera' (medroxyprogesterone acetate), which can be repeated at 12 week intervals, or 'Norplant' (levonorgestrel), whose effect lasts up to 5 years. These drugs are effective, but require full counselling of the patient before administration.

V.a.2.3. Emergency contraception. Emergency contraception (EC) has three possible ways in which it can work: (1) ovulation is inhibited, meaning an egg will not be released; (2) the normal menstrual cycle is altered, delaying ovulation; or (3) the lining of the uterus is irritated, so that if the first and second actions fail, and conception occurs, then implantation will not succeed. Combined preparations of 100 μg ethinyloestradiol plus 0.5 mg levonorgestrel (often termed the 'Yuzpe' regimen) can be used to prevent unintended pregnancy. Two doses are taken 12 hours apart, within 72 hours of intercourse. Timing is an essential element of the product's effectiveness. EC should be taken as soon as possible after unprotected intercourse. Treatment may be initiated up to five days (120 hours) of unprotected intercourse. EC effectiveness declines gradually over five days and EC use will not interfere with an established pregnancy. Levonorgestrel-only regimens (two doses of 0.75 mg) may be more effective with

fewer side effects. In the Cochrane database a systematic review of 15 trials is available which concludes that levonorgestrel and mifepristone seem to offer the highest efficacy for emergency contraception with an acceptable side effect profile. One disadvantage of mifepristone is that it causes delays in onset of subsequent menses which may induce anxiety. However, this seems to be dose-related and low doses of mifepristone minimize this side effect without compromising effectiveness. It is recommended that future studies should compare the effectiveness of mifepristone with levonorgestrel.

V.a.3. Induction of Ovulation

Couples presenting with infertility should be fully evaluated by specialists in reproductive medicine, in order to ensure effective and timely investigation, and appropriate treatment. This section will deal only with treatment of anovulatory infertility, and the management of tubal obstruction and male factor infertility are dealt with elsewhere.

Women with anovulatory infertility should be offered full endocrinological evaluation, considering potential diagnoses such as hypothalamic-pituitary disease, polycystic ovary syndrome and primary gonadal disease. Hyperprolactinaemia must be sought as a potential cause, and its treatment is outlined below. The main treatments available include the anti-oestrogens clomiphene and tamoxifen, and gonadotrophin therapy.

V.a.3.1. Anti-oestrogens. Clomiphene and tamoxifen are oestrogen antagonists which induce gonadotrophin release by the pituitary by disrupting the normal negative feedback of oestradiol on FSH secretion. They are mainly useful in patients with anovulation due to polycystic ovary syndrome. They are given for several days at the start of each cycle, and up to 6–12 cycles of treatment are normally given. Prolonged use of clomiphene is not advised because of the increased risk of endometrial and ovarian carcinoma. Patients should be monitored to reduce the risk of ovarian hyperstimulation (and the risk of multiple pregnancy). Visual disturbance should be reported in patients taking clomiphene, and the drug should be withdrawn if it occurs.

A systematic review of 4 studies in the Cochrane database concludes that clomiphene citrate (at doses between 50–250 mg per day) is an effective method of inducing ovulation and improves fertility in oligo-ovulatory women. However adverse effects include possible ovarian cancer risk and risk of multiple pregnancy.

A conventional treatment algorithm involving clomiphene citrate (CC) followed by FSH induction of ovulation may result in a 71% cumulative singleton live birth rate. In attempts to improve treatment outcome further and reduce complication rates, new compounds such as insulin-sensitizing agents or aromatase inhibitors (Letrozole) are currently used increasingly.

Women with the polycystic ovary syndrome are at increased risk for the metabolic syndrome and associated health risks and metformin, which also reduces hyperinsulinemia, might be effective in treating obese, infertile women with the polycystic ovary syndrome.

V.a.3.2. Gonadotrophins. Follicle-stimulating hormone (FSH) is given by injection to women who have hypopituitarism, or women with clomiphene-resistant anovulation due to polycystic ovary syndrome (see Nugent et al., 2000). It is used with LH, usually given as human chorionic gonadotrophin (hCG), which is given after adequate follicular development has occurred, in order to induce ovulation and release of the egg from the mature follicle. Use of gonadotrophins is expensive and arduous for the patient, as it requires daily injection and regular intensive monitoring. Careful monitoring of the ovarian response is mandatory, using ultrasound imaging and measurement of serum oestradiol. This is important both to judge the degree of follicular development and hence allow timing of the hCG injection, and also to avoid the potentially dangerous ovarian hyperstimulation syndrome. However, FSH injection is contraindicated in women who have a high FSH level indicating primary ovarian failure, uncontrolled thyroid and adrenal dysfunction, an organic intra-cranial lesion such as a pituitary tumor, the presence of any cause of infertility other than anovulation unless they are candidates for *in vitro*-fertilization, abnormal bleeding of undetermined origin, ovarian cysts or enlargement not due to polycystic ovary syndrome, prior hypersensitivity to FSH and in women who are pregnant.

V.b. Male Reproductive Medicine

V.b.1. Hypogonadism

V.b.1.1. Androgen replacement therapy. Although serum testosterone in men may decline with

age, there is no clear male equivalent of the female menopause, and most men therefore do not require any form of androgen therapy unless there is clear evidence of deficiency, due to pituitary or testicular failure.

Testosterone should be given to men with hypogonadism in order to restore sexual function (though it does not restore fertility), muscle strength and general energy and well-being. As with oestrogen replacement, various forms of therapy are available.

Intramuscular depot injection of mixtures of testosterone esters (e.g. Sustanon, Primoteston) are reliable and effective. A depot injection of 250 mg is normally given every 3–4 weeks, though lower doses at shorter intervals are sometimes used. Newer preparations are now available that allow 3-monthly depot injections, which can be helpful for patients, though the injection volume is larger. The main disadvantages are pain at the injection site, and fluctuations in mood, energy and libido due to swings in serum testosterone levels can be troublesome with shorter-acting preparations. Implants of testosterone pellets at 6-monthly intervals are reliable and give stable serum levels, but some patients dislike the repeated implant procedure. Transdermal testosterone administration can achieved by skin patches or by testosterone-containing gel; both are convenient and effective but slightly more expensive. Oral testosterone undecanoate is effective, but variably absorbed from the gut, and is therefore not an ideal choice for most patients. Finally, buccal tablets deliver testosterone through the mucosal lining of the gum, and are suitable for some patients.

V.b.1.2. Gonadotrophin treatment. Men with hypopituitarism normally require only testosterone replacement therapy, but if fertility is needed gonadotrophins are necessary to stimulate spermatogenesis. This therapy is expensive and often requires prolonged administration in order to achieve an adequate sperm count, and its use should be restricted to specialist centres.

V.b.2. Male Contraception

So far no simple equivalent of the oral contraceptive pill has been developed for men. Relatively large doses of testosterone do inhibit gonadotrophin secretion and hence spermatogenesis, and different schedules are under clinical trial at present.

VI. PITUITARY DISEASE

Clinically significant pituitary disease is rare, although small functionless pituitary adenomas are commonly seen as incidental findings at autopsy or on magnetic resonance brain scans. The main issues for clinical pharmacology concern replacement therapy for hypopituitarism, and treatment of hormone-producing pituitary adenomas.

VI.a. Hypopituitarism

Hypopituitarism may be idiopathic, congenital, or secondary to structural damage to the pituitary or hypothalamus, and all cases must be fully evaluated with imaging studies. The pharmacological treatment of hypopituitarism is based on detailed assessment of each of the pituitary-target organ axes. Thus the pituitary adrenal axis should be assessed by insulin stress testing or short tetracosactrin testing, the pituitary-thyroid axis by monitoring thyroid function tests (TRH testing is not usually necessary), and the pituitary-gonadal axis by measurement of testosterone or oestradiol and gonadotrophins. Growth hormone deficiency and diabetes insipidus are considered separately below.

Hormonal replacement therapy is required usually to replace the product of the target gland, as outlined in the different sections above. Thus for ACTH deficiency, hydrocortisone replacement is given as for primary adrenal failure, normally with no need for fludrocortisone as aldosterone secretion is primarily regulated by the renin-angiotensin system. Similarly, for TSH deficiency, thyroxine is given as for hypothyroidism. In the case of gonadotrophin deficiency, sex steroid replacement is satisfactory except when induction of ovulation or spermatogenesis are required, when gonadotrophin treatment is necessary.

VI.b. Growth Hormone Deficiency

Growth hormone deficiency is identified in children that present with growth failure and short stature, but in adults it is usually identified as a result of combined pituitary function testing in cases of established pituitary disease. There is debate about the best diagnostic tests to be used, which include the insulin hypoglycaemia stress test, the glucagon or arginine stimulation tests, and sometimes in children, multiple nocturnal sampling. Frequently the results of two different tests are required to formally confirm the diagnosis.

Growth hormone replacement used to be carried out using GH extracted from human pituitary glands removed at autopsy, but this practice ceased in 1985, when it was found to be responsible in a few cases for transmission of the spongiform encephalopathy, variant Creutzfeld–Jakob disease. Since that time, recombinant human GH has become available for clinical use, and the potentially unlimited supplies have led to expansion of its clinical role, with a wider range of indications than before. Whereas only some children with GH deficiency could be treated in the past, treatment can now be offered to children with short stature from other causes such as Turner syndrome, in which GH treatment can increase final height even though the patients are not GH deficient. There are now two studies clearly indicating that the two major factors guaranteeing a more successful treatment outcome are early onset of treatment allowing for longer duration of treatment and a higher dose of growth hormone.

GH therapy has been shown to benefit many adults with GHD. It is critical to identify appropriate candidates in whom the clinical context suggests that GHD may be present. Confirmation of GHD before beginning therapy is crucial and usually involves biochemical testing. The demonstrated benefits of GH therapy include improvements in body composition, exercise capacity, skeletal integrity, lipids, and quality of life. Although it has been suggested that GH treatment may reduce the increased vascular mortality associated with hypopituitarism, this has not yet been proven. It should be emphasized that long-term clinical outcome studies on hard endpoints such as fractures, clinical heart disease, cancer and mortality are still lacking at present. Dosing should be individualized with attention to avoidance of side effects. Periodic monitoring will be necessary for adverse effects and physiological benefit.

GH replacement therapy has important potential benefits, but it requires daily subcutaneous self-injection by the patients themselves, and the costs are considerable. Especially for adult GH replacement therapy this has so far limited its widespread use in some regions.

VI.c. Diabetes Insipidus and Vasopressin (Anti-diuretic Hormone)

Deficiency of pituitary vasopressin (arginine vasopressin or AVP, also termed anti-diuretic hormone, ADH) causes the syndrome of polyuria, thirst and polydipsia termed cranial diabetes insipidus. It is commonly caused by lesions in or near the hypothalamus, such as craniopharyngioma, sarcoidosis and some large pituitary tumours, and particularly may result from surgical damage to the pituitary stalk. The diagnosis is often straightforward, as the patient passes large quantities of dilute urine in the face of haemoconcentration with high plasma osmolality caused by dehydration. In more subtle cases, the diagnosis may need to be established formally by means of a water deprivation test, or occasionally by infusion of hypertonic saline and measurement of the plasma vasopressin response to the resulting hyperosmolality.

The vasopressin analogue desmopressin (desarginine, D-amino-arginine vasopressin, DDAVP) is in widespread clinical use, and has replaced earlier drugs such as pitressin and lypressin. It can be given intranasally using a dropper device or a metered nasal spray, or orally by tablets taken 3 times daily. The dose can be adjusted according to clinical symptoms which patients can usually judge easily provided their sense of thirst is intact. Inadvertent overdosage can be a problem, as the resulting haemodilution and hyponatraemia may not be immediately obvious to the patient, and some monitoring is therefore required on initiation of therapy and occasionally thereafter.

Nephrogenic diabetes insipidus is due to resistance to action of vasopressin, and therefore DDAVP is not indicated, but some benefit may be gained by using thiazide diuretics or chlorpropamide. The syndrome of inappropriate antidiuretic hormone (SIADH) can be treated by using the antibiotic derivative demeclocycline to induce a state of vasopressin resistance and partial nephrogenic diabetes insipidus.

VI.d. Pituitary Tumours

Pituitary tumours can be classified according to their hormonal product, and ‘functioning tumours’ give rise to the clinical syndromes of prolactinoma (prolactin-secreting tumours), acromegaly (GH-secreting), and Cushing’s disease (ACTH-secreting tumours). ‘Functionless’ tumours usually comprise gonadotroph cells that may secrete glycoprotein hormone subunits, but normally do not cause a clinical syndrome other than hypopituitarism. The treatment of pituitary tumours comprises several possible approaches, including surgery, irradiation, and endocrine therapy, and only the last of these will be dealt with here.

VI.d.1. Prolactinoma and Dopamine Agonist Drugs

Hyperprolactinaemia gives a clinical syndrome of galactorrhoea and amenorrhoea in women, and frequently presents as anovulatory infertility. It is frequently caused by small intrasellar pituitary adenomas, although larger macroadenomas can present with effects of a pituitary mass such as headache and visual failure. The normal inhibitory control of prolactin by dopamine has been exploited in the treatment of hyperprolactinaemia by the development of potent dopamine D2 receptor agonist drugs, notably bromocriptine, cabergoline and quinagolide. Each of these drugs suppresses plasma prolactin concentrations to normal in 85–90% of cases, suppressing lactation and restoring normal ovulatory ovarian cycles and hence fertility. In addition, they induce shrinkage of underlying prolactin-secreting adenomas, to such an extent that they can be used as sole therapy even in patients with very large pituitary tumours that threaten vision, thus avoiding the need for surgery.

Patients with hyperprolactinaemia must always be thoroughly investigated, with careful neuroradiological imaging of the pituitary gland to evaluate the size of a possible tumour. Hyperprolactinaemia can result either from a genuine prolactin-secreting adenoma, or from hypothalamo-pituitary disconnection, which can be caused by any lesion in the pituitary-hypothalamic area. Pituitary function should also be assessed in case associated hormonal deficiencies also require treatment. A full drug history should be taken, as numerous drugs raise plasma prolactin (for example phenothiazines and dopamine antagonists), and hypothyroidism should be excluded as an additional potential cause.

Dopamine agonists have frequent side effects, most commonly nausea and vomiting, postural hypotension and dizziness, headache and constipation. Depressive reactions may be also be seen in some patients. At least 20% of patients experience significant nausea while taking bromocriptine. However such side effects are minimized if the therapy is initiated at night. Newer dopamine agonist drugs include cabergoline and quinagolide, which have less marked side effects, but even cabergoline has to be stopped by a proportion of patients. Recently concerns have been raised that cabergoline may cause a cardiac valvulopathy when used in high doses in Parkinson's disease, but there is so far no evidence that this is a risk with the smaller doses used for hyperprolactinaemia. Recent studies have shown that dopamine agonist drugs may be stopped after a period of successful treatment without recurrence of the original prolactinoma in as many as 30% of cases, depending on tumour size and response. In other words, these drugs may in some cases cause a permanent remission in terms of both tumour function and size.

After therapy starts, the patient should continue to be monitored hormonally and radiologically, and female patients should be warned about their resumption of ovulation and resulting fertility. On the basis of its safety record in pregnancy, bromocriptine has so far been the treatment of choice when restoration of fertility is the patient's goal. The possibility of continuing tumour enlargement despite therapy should be considered. A functionless pituitary tumour causing disconnection hyperprolactinaemia may progress despite suppression of the serum prolactin, and the underlying diagnosis should remain under review.

VI.d.1.1. Pregnancy and dopamine agonists. Treatment of hyperprolactinaemia is often used to restore fertility and patients seeking pregnancy must be advised carefully. Dopamine agonists are usually stopped as soon as patient knows that she is pregnant, at about 6–8 weeks' gestation. If they are continued throughout pregnancy they will suppress lactation and prevent breast-feeding, but there is no evidence that they harm the fetus. However there is a small risk that an underlying prolactinoma may enlarge during pregnancy: the risk is greatest for large macroadenomas, which may expand to cause significant problems of headache and visual failure in up to 35% of patients; for microadenomas the risk of clinically significant enlargement is only 1–2% (see Davis, 2004). Patients should therefore be advised of these risks, and monitoring of serum prolactin, clinical well-being, and visual fields may be helpful during pregnancy.

VI.d.2. Acromegaly: Somatostatin Analogues and GH Antagonists

Acromegaly is almost always caused by a pituitary growth hormone (GH)-secreting adenoma, and transsphenoidal surgery is normally considered to be the first treatment of choice. A number of patients are not cured by surgery, however, and GH hypersecretion is nowadays treated actively, because of its known associated excess mortality.

Somatostatin analogues do not cause clinically useful shrinkage of somatotroph tumours, but they frequently reduce GH levels, if not to normal, at least to levels that appear to be 'safe' in terms of normalizing long-term mortality. The two drugs currently in use are octreotide and lanreotide, and both appear to have comparable efficacy. Octreotide can be given at 8-hourly intervals by subcutaneous injection, or by monthly intramuscular injection of a depot preparation of coated microspheres. Lanreotide is likewise given as a depot preparation once per month. Both drugs are generally well tolerated, but can cause pain at the injection site, impaired glucose intolerance and gall-stone formation. Their use requires regular monitoring of GH levels to adjust treatment, and routine monitoring of pituitary tumour size, as they cause only minor tumour shrinkage in some patients. The main practical problem at present is the expense of this therapy for long term use.

Dopamine agonists are also used for the treatment of acromegaly, but although they are much cheaper than somatostatin analogues, they are also less effective, and rarely normalize serum GH concentrations.

Growth hormone antagonists have recently entered clinical use, and though they have no known effect on the size or growth of the underlying pituitary tumour, they are effective in reducing IGF-1 levels towards normal. They are well tolerated, but still very expensive, which has limited their use.

VI.d.3. Cushing's Disease: Metyrapone

Cushing's disease (caused by a pituitary ACTH-secreting adenoma) or Cushing's syndrome from an adrenal tumour is normally treated by surgical removal of the primary lesion where possible. Cases of ectopic ACTH syndrome associated with carcinoma of the bronchus cannot be treated surgically, and often benefit from medical therapy to control adrenal steroid excess.

Metyrapone is a competitive inhibitor of 11beta hydroxylation in the adrenal cortex, and effectively inhibits cortisol production. It is used in low doses, titrated to achieve plasma cortisol levels as close as possible to normal day-time values. Occasionally it is used in higher doses combined with replacement corticosteroid treatment. Its main side effects relate to overdosage and resulting hypoadrenalism, but it can also cause hirsutism and hypertension, due to accumulation of precursor steroids. Ketoconazole is also sometimes used to suppress adrenal steroid production, but its potential for hepatotoxicity limits its use. Trilostane and aminoglutethimide are less effective than metyrapone and are now little used in Cushing's syndrome.

VII. BONE AND MINERAL METABOLISM

VII.a. Vitamin D Deficiency and Hypoparathyroidism

Vitamin D is synthesized in the skin in the presence of ultraviolet light, and it is unusual to become dependent on dietary intake except when exposed to inadequate UV light. The active form of vitamin D is 1,25-dihydroxycholecalciferol (1,25-OHCC), also termed calcitriol. For vitamin D synthesis, cholecalciferol (also termed vitamin D3) is synthesized in the skin from cholesterol via 7-dehydrocholesterol, and is 25-hydroxylated in the liver and 1-hydroxylated in the kidney. Dietary vitamin D is actually a mixture of sterols which includes 7-dehydrocholesterol, and is mainly found in fish and eggs.

Dietary causes of vitamin D deficiency are unusual except among the poor and malnourished, and in those with fat malabsorption. Reduced exposure to sunlight may then become a critical factor. Renal failure can impair 1-hydroxylation of cholecalciferol, and chronic liver disease can reduce 25-hydroxylation as well as contributing to malabsorption.

VII.a.1. Osteomalacia, Rickets and Hypoparathyroidism

Osteomalacia is the condition in which bone becomes demineralised due to deficiency of vitamin D. In this condition parathyroid hormone (PTH) acts on the bone to maintain serum calcium, resulting in demineralisation. Serum calcium is usually normal or slightly low; alkaline phosphatase levels are high, reflecting excessive osteoblast activity, and serum phosphate falls as an effect of PTH on the kidney. The same condition in children results in defects in long bone formation, and is termed rickets.

Deficient parathyroid hormone secretion most commonly results from neck surgery, and idiopathic forms are rare. The symptoms and signs are those of hypocalcaemia, with paraesthesiae of the hands and peri-oral area, non-specific muscle weakness, gastrointestinal upset and tiredness.

VII.a.2. Vitamin D Therapy

Vitamin D preparations that are available include ergocalciferol (also termed calciferol, or vitamin D2), cholecalciferol (vitamin D3), alfa-calcidol (1α-hydroxycholecalciferol) and calcitriol (1,25-hydroxycholcalciferol).

VII.a.2.1. Prevention. Vitamin D deficiency can be prevented by dietary supplementation with low doses of vitamin D, usually given as calcium and ergocalciferol tablets, containing only 10 µg (400 units) of ergocalciferol.

VII.a.2.2. Treatment. Treatment of established vitamin D deficiency requires much larger doses of vitamin D, such as calciferol tablets of 1 mg (40,000 units) daily. Newer but more expensive preparations such as alfa-calcidol and calcitriol are very effective, and are particularly valuable in patients with renal failure who are unable to hydroxylate calciferol. Patients treated with pharmacological doses of vitamin D preparations must be monitored by checking serum calcium at regular intervals because of the risk of inducing hypercalcaemia. This should always be suspected if patients develop thirst, nausea or vomiting. The newer hydroxylated preparations have a shorter effective half-life, and therefore problems of overdosage are quicker to resolve once identified.

VII.a.3. Hypoparathyroidism

Vitamin D preparations are also used to treat hypoparathyroidism, but they require even larger doses, often up to 2.5 mg (100,000 units) daily to increase the serum calcium back to normal. As in vitamin D deficiency, the dose must be carefully monitored.

VII.b. Paget's Disease

Paget's disease is a syndrome of excessive bone resorption, possibly caused by a virus, in which osteoblastic activity and bone remodelling are abnormal. The bone becomes misshapen as a result, and may be painful. The disease is very common in western countries, and most cases are in fact asymptomatic, but some patients develop bone pain or other complications that require treatment.

Bisphosphonate drugs have been very effective in relieving symptoms and reducing the rate of bone turnover in Paget's disease. The drug most commonly used is disodium etidronate, either by intravenous infusion or by mouth, but newer bisphosphonate drugs have been introduced, including pamidronate, risedronate, and tiludronic acid. The drugs are adsorbed onto hydroxyapatite crystals and inhibit osteoclast activity.

Calcitonin is also moderately effective in Paget's disease, but requires regular subcutaneous or intramuscular injection. Mithramycin has been used with some success, but is relatively toxic, and its use requires careful monitoring of blood counts to avoid marrow suppression, so it is rarely used in current practice.

VII.c. Hypercalcaemia of Malignancy

Hypercalcaemia is associated with a number of malignancies including breast and lung cancer and myeloma. Although it is often ultimately incurable, it can be substantially alleviated using bisphosphonates. Most patients presenting with 'humoral hypercalcaemia of malignancy' are dehydrated and it is essential to replace fluids, usually using several liters of normal saline, while initiating pharmacological therapy. Pamidronate, sodium clodronate, ibandronic acid or zoledronic acid are all highly effective in reducing serum calcium; they may also improve bone pain from osteolytic metastases. Calcitonin and corticosteroids used to be used for this indication, but are less effective.

VII.d. Osteoporosis

Osteoporosis denotes loss of bone matrix, and is distinct from osteomalacia, in which the bone matrix remains, but becomes poorly calcified. Bone density decreases with age in everyone, but falls especially fast in women after the menopause. Postmenopausal osteoporosis is a growing worldwide problem as women live progressively longer after the menopause, and is a growing burden on health economies in terms of morbidity and mortality from fractures, particularly of the femoral neck. Hormone replacement therapy (HRT) with oestrogens (see above) now has a proven benefit in maintaining bone mass and reducing fracture risk, and also appears to reduce mortality from cerebrovascular disease and myocardial infarction. The risks of oestrogen HRT have been described above.

An other class of drugs has been developed, termed selective oestrogen response modifiers (SERMs), the best known of which is raloxifene. These drugs may not carry the same excess risk of

breast cancer (though this remains to be firmly established), yet they still protect the patient from bone loss. However they are not effective at relieving vasomotor symptoms of the menopause, and their main indication so far is protection against osteoporosis. So far there are no direct comparisons of raloxifene with conventional HRT, which still remains the first choice for prevention of post-menopausal osteoporosis in most circumstances.

Finally, bisphosphonates have an important place in treatment of osteoporosis of all causes, including steroid-induced osteoporosis. Disodium etidronate, alendronate and clodronate all have potent effects to restore bone mass, and this effect persists for several years of therapy. Newer drugs such as zoledronic acid can be administered by infrequent (once-yearly) infusion, which can help compliance and reduce side effects.

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Abbreviations used in the index are: ACE = angiotensin converting enzyme; AIDS = acquired immune deficiency syndrome; AT_1 blockers = angiotensin II antagonists; COPD = chronic obstructive pulmonary disease; HIV = human immunodeficiency virus; MAOIs = monoamine oxidase inhibitors; NSAID = non-steroidal anti-inflammatory drugs; SSRIs = selective serotonin re-uptake inhibitors.

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