CLINICAL PHARMACOLOGY IN HEALTH CARE, TEACHING AND RESEARCH

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FOREWORD AND ACKNOWLEDGMENTS

This position paper regarding the roles of clinical pharmacology in health care, teaching and research was composed and edited by representatives of the International Union of Basic and Clinical Pharmacology (IUPHAR), the World Health Organisation (WHO) and the Council for International Organizations of Medical Sciences (CIOMS). It is an updated and edited version of a recent publication entitled "Clinical Pharmacology in Research, Teaching and Health Care-Considerations by IUPHAR, the International Union of Basic and Clinical Pharmacology" which was published in the journal Basic and Clinical Pharmacology and Toxicology (BCPT) in 2010, Volume 107, pages 531 – 559. This document contains new chapters of special relevance to global health.

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CONTENTS

ABBREVIATIONS

ADR	Adverse drug reaction
ADME	Absorption, distribution, metabolism and excretion
AIDS	Acquired immunodeficiency syndrome
CIOMS	Council for International Organizations of Medical Sciences
CME	Continuing medical education
CNS	Central nervous system
CP	Clinical pharmacology
CPT	Clinical pharmacology and therapeutics
CRO	Clinical research organisation
CVS	Cardiovascular system
CYP	Cytochrome P450
DNA	Deoxyribonucleic acid
EMA	European Medicines Agency
EU	European Union
FDA	Federal Drug Administration (in the USA)
GCP	Good clinical practice
GLP	Good laboratory practice
GMP	Good manufacturing practice
GxP	The combination of GCP, GLP, and GMP
HIV	Human immunodeficiency virus
HTA	Health technology assessment
IP	Intellectual property
IUPHAR	International Union of Basic and Clinical Pharmacology
NIH	National Institute of Health (in USA)
NMRA	National Medicines Regulatory Authority
OTC	Over the counter
PD	Pharmacodynamics
PK	Pharmacokinetics
R&D	Research and development
RCT	Randomised Controlled Trial
RUM	Rational use of medicines
TDM	Therapeutic drug monitoring
TNF	Tumour necrosis factor
WHO	World Health Organization

Executive Summary 1

DEFINITION

Clinical Pharmacology is the scientific discipline that involves all aspects of the relationship between drugs and humans. It is a multidisciplinary science that encompasses professionals with a wide variety of scientific skills including medicine, pharmacology, pharmacy, biomedical science and nursing. The term 'clinical pharmacologist' is commonly used in the professional sense to refer to physicians who are specialists in clinical pharmacology. They have undertaken several years of postgraduate training in many aspects of the above relationship involving health care, teaching, and research. Such clinical pharmacologists have as their primary goal that of improving patient care, directly or indirectly, by developing better medicines and promoting the safer and more effective use of drugs.

AIMS

This document aims to set the scene for clinical pharmacology in the early part of the 21st century following the concepts of an earlier report by the World Health Organisation in 1970 (1). This document is aimed primarily at decision makers in a variety of organisations, particularly in Governments and their health care ministries, in addition to chief executives and board level directors of primary and secondary care systems and directors in pharmaceutical companies. It lays out in detail the great benefits that expertise in clinical pharmacology can bring to the delivery of better health care for all populations.

THE CLINICAL PHARMACOLOGIST IN PATIENT CARE

Clinical pharmacology has developed a number of ways in which the clinical care of patients can be improved (see chapter 6). The prime aim is to improve the Rational Use of Medicines both for individual patients and for patient populations wherever they may reside. Clinical care of paediatric and geriatric patients needs special attention from the clinical pharmacologist and these special interests are addressed in chapters 7 and 8. The clinical pharmacologist is expert in the critical evaluation of new and old therapies, and uses drug utilisation studies and pharmacoepidemiological services to help in this task as well as skills such as pharmacogenetics. Clinical pharmacologists have an important role on Drug and Therapeutics Committees where they help the rational introduction and use of new and expensive medicines into the delivery of health care. Clinical pharmacologists provide, in collaboration with other health care staff such as pharmacists, drug information services to a wide variety of prescribers. Specialist services may include therapeutic drug monitoring, involvement in clinical drug toxicology and pharmacovigilance. Adverse reactions to drugs still cause many problems for patients, and health care systems could do more to prevent these since most of them are predictable through a knowledge of pharmacology.

The concept of personalised medicine is one where drug therapy can be based on the pharmacogenetic or other characteristics of a particular patient. While in its infancy as a discipline there are now good examples whereby adverse effects can be minimised and drug efficacy enhanced by a knowledge of the genetic makeup or other characteristics of the individual patient.

TEACHING CLINICAL PHARMACOLOGY

The teaching of clinical pharmacology is a vital part of the work of a clinical pharmacologist (see chapter 9 and addenda I and II). Perhaps the most important area is the training of new prescribers,

primarily medical students and new physicians. With the increasing trend for nurses and pharmacists to prescribe, usually in particular areas, attention needs to be paid also to their training in prescribing. The ability of new young physicians to prescribe safely and effectively has been criticised in recent years, and new systems are being developed to enhance these skills in the training of medical students. Since assessment drives learning, the assessment systems are being improved too. Specialist training of physician clinical pharmacologists is addressed in Addendum II, since there is a world wide shortage of such specialists. However the needs, the resources, and the regulatory arrangements available in different countries mean that the approach suggested is a general one.

RESEARCH DOMAINS OF CLINICAL PHARMACOLOGY

Research is a vital part of the training and everyday work of a clinical pharmacologist (see chapter 10). The endeavour of a pharmacologist working in the clinical environment is to develop methods and strategies that improve the quality of drug use in individual patients and in patient populations. Clinical pharmacological research has always been translational in the sense that the discipline aims to translate new scientific data on drugs into rational patient care. An increased engagement of clinical pharmacologists in the design, conduct and execution of clinical trials, particularly early phase I studies, would be advantageous. However, enhanced training in these areas may be required.

CLINICAL PHARMACOLOGY AND THE PHARMACEUTICAL INDUSTRY

The pharmaceutical industry has been at the forefront of helping to train clinical pharmacologists (see chapter 12). While many of the skills acquired in such companies are useful for the general training of a clinical pharmacologist (e.g clinical trials) a long term career in such a company requires a new set of skills for which training and experience is needed.

GOVERNMENTS: ESSENTIAL ROLES FOR CLINICAL PHARMACOLOGY

Governments need clinical pharmacologists to help deliver the goal of ensuring safe and effective drug therapy for their populations, whether the clinical pharmacologists are working in hospitals, regulatory agencies or in Health Technology Assessment (HTA) (see chapter 13). With a few notable exceptions the discipline of HTA has emerged in the absence of contributions from clinical pharmacology.

Clinical pharmacologists have a crucial role to play in helping to deliver the WHO agenda of "Guidelines for the Development of National Drug Policies" to which more than 150 countries are now signed up (2). The policies aim to ensure:

- The quality, safety and efficacy of medicines
- Equitable access to medicines for all the population
- The rational/quality use of medicines
- A viable and responsible local pharmaceutical industry.

Clinical pharmacologists are paying increasing attention to the health needs of those peoples who have in the past been marginalised. They include children, those with rare diseases, and those with conditions that are endemic in the poorest parts of the world. The training of clinical pharmacologists to meet these needs is rather different from that envisaged in 1970 when the first WHO report was published (1).

Introduction 2

Some forty years ago the World Health Organisation brought together a group of experts in Clinical Pharmacology and Therapeutics to define the discipline of Clinical Pharmacology, and to outline how it could help to improve the use of drugs in the delivery of health care (1). In the last four decades the importance of drug therapy has changed markedly in terms of the potency of the drugs we use, in the number and diversity of drugs that are available, and in the number of diseases that can be treated. In addition the discipline of molecular biology has had an increasing impact on the development of drugs, but solid knowledge about the pharmacological principles that underpin the Rational Use of Medicines (RUM) is just as relevant now as it was in 1970.

Since the production of the 1970 report the cost of developing drugs has risen substantially and the cost of taking a new chemical entity to market can easily be in excess of $US 1000 million (£638 million, €764 million). As a result newly developed drugs are very expensive, making it more difficult for resource poor countries to fund drug therapy for their inhabitants although there are welcome exceptions in the provision by Big Pharma of modern drugs at a very low or no cost (eg ivermectin for onchocerciasis). Even resource rich countries have limitations in financing drug therapy and this has led to new concepts such as the cost effectiveness of drug therapy and to the discipline of pharmacoeconomics.

While clinical pharmacology is learning to face these new problems we are still dealing with problems in drug therapy that were recognised in the 1970s. We knew then that adverse reactions to drugs (ADRs) were among the more common causes of admission to hospital (3) and this problem has not decreased in importance over the decades largely because little is done about it. In addition the problem of ADRs is worsened by the increasing use of combination therapies and the higher proportion of elderly patients in the population. We know that ADRs (the formal study of which has now given rise to the discipline of pharmacovigilance) cause some 7% of admissions to hospital and they are also a not uncommon cause of death, particularly in elderly patients (4,5). Many of these ADRs are predictable and could be prevented if the process of educating prescribers was taken more seriously. Another problem that has not improved significantly over the years since 1970 is the errors made during the prescribing process in spite of the widespread availability of computers and the internet providing easy access to appropriate information and knowledge (6). These problems are more written about in resource rich countries but are just as relevant in resource-poor countries.

It is clear then that the time has come to modernise the original WHO report in the light of lessons that have been learned and problems addressed. This updated report arises from a partnership between the World Health Organisation (WHO), the International Union of Basic and Clinical Pharmacology (IUPHAR) and the Council for International Organizations of Medical Sciences (CIOMS). After a period of expansion in the last 20 years of the twentieth century, clinical pharmacology as a discipline declined somewhat in many countries. However during the last few years there have been signs both of new growth in and new enthusiasm for the discipline (7), although the importance of clinical pharmacology to pharmaceutical companies has never been in doubt. A recent report on the relationship between the pharmaceutical industry and the National Health Service (NHS in the United Kingdom) has stated that re-building clinical pharmacology as a core discipline in the NHS is of vital importance for the future of health care in the UK and this is likely to be true in many other countries (8).

This document aims to set the scene for clinical pharmacology in the early part of the 21st century by updating the concept of the original WHO report. We have gathered a group of distinguished clinical pharmacologists who have written the individual sections which are designed to address the essential role of clinical pharmacology in health care, teaching and research as well as describing the discipline's link with industry and governments. We hope that the document will prove useful to many people, perhaps particularly young doctors who are looking to establish themselves in a clinical specialty and who have a particular interest in improving drug therapy and making it safer and more effective as exemplified in the WHO's Rational Use of Medicines policy (9). However, this document is particularly aimed at decision makers in a variety of organisations, in Governments and their health care ministries as well as chief executives and board level directors of primary and secondary care organisations and directors in the pharmaceutical industry. The document details the great benefits that expertise in clinical pharmacology can bring to the delivery of better health care for all populations.

Definition of Clinical Pharmacology 3

Clinical Pharmacology is the scientific discipline that involves all aspects of the relationship between drugs and humans. Its breadth includes the discovery and development of new drugs, the application of drugs as therapeutic agents, the use of drugs, the beneficial and harmful effects of drugs in individuals and society, and the deliberate misuse of drugs. Clinical pharmacology is a multidisciplinary team science that encompasses professionals with a wide variety of scientific skills including medicine, pharmacology, pharmacy, biomedical science and nursing. Other professionals who are important in various aspects of clinical pharmacology include social and behavioural scientists, dentists, economists, epidemiologists, geneticists, toxicologists, mathematicians and computer scientists.

The descriptor 'clinical pharmacologist' is normally used in a professional sense to refer to physicians involved in the medical care of patients who are specialists in clinical pharmacology. They have usually undertaken several years of postgraduate training (see Addendum II) focussing on important aspects of clinical pharmacology including clinical trials, drug evaluations, pharmacoepidemiology, pharmacoeconomics, pharmacovigilance and clinical drug toxicology. Some countries have accreditation programmes for clinical pharmacology as a physician specialty but many do not. The present document refers essentially to medical clinical pharmacologists.

History of Clinical Pharmacology 4

Clinical pharmacology is both old and young. The practice of drug therapy goes back to ancient times and the discovery of drugs such as quinine, reserpine and artemisinin which were first used as herbal medicines. William Withering's publication on the use of foxglove in the treatment of heart failure (see10) may very well be considered the first scientific account of the discipline but it took 200 years before the pharmacology of digitalis was explored with accurate, clinical pharmacological methods. As a scientific discipline, clinical pharmacology is young having originated from the middle of the 20th century. It is difficult to find who first coined the name as opinions differ between countries. Several distinguished pharmacologists active in the middle of the century brought pharmacology and clinical know-how about drugs together and helped to transform drug evaluation from the trial and error state to a scientific discipline. In the Anglo-Saxon literature, Harry Gold at Cornell (10,11) is commonly quoted as the person who first introduced the name clinical pharmacology in the early 1940s. However, in 1914, a textbook was written by Hans Horst Meyer and Rudolf Gottlied in German the title of which was translated as 'Pharmacology, Clinical and Experimental'. In addition, also in the German literature, Paul Martini, professor of medicine in Bonn, published his monograph in 1932 entitled 'Methodology of Therapeutic Investigation' and he is considered by some as the first clinical pharmacologist (12). According to Shelley and Baur, his contributions escaped the attention of the English-speaking world (12). In the English literature, there is a long tradition of 'materia medica', particularly in Scotland. In 1884, John Mitchell Bruce wrote his textbook entitled 'Materia Medica and Therapeutics. An Introduction to the Rational Treatment of Disease' and this, in its 20th edition, became Dilling's 'Clinical Pharmacology'. This book was published in 1960, the same year as Desmond Laurence's textbook entitled 'Clinical Pharmacology'.

There is no doubt that the most vigorous attempts to develop clinical pharmacology as an academic discipline were made in the United States (13,14). Important landmarks are the first edition of Goodman and Gilman's 'The Pharmacological Basis of Therapeutics' and the successful attempt (1960) by Walter Modell, also at Cornell, to launch the first scientific journal in the subject entitled 'Clinical Pharmacology and Therapeutics'.

In the early 1960s, the United States became the world centre for the training of clinical pharmacologists. The NIH chief James Shannon and his colleagues Bernard B. Brodie and Julius Axelrod introduced biochemical pharmacology as a science and drug measurements in body fluids as tools in clinical pharmacology. Several centres of excellence in clinical pharmacology offered training to potential clinical pharmacologists from all parts of the world. The efforts to improve clinical drug evaluation by Louis Lasagna, a pupil of Harry Beecher at John Hopkins Hospital, should be especially recognised (13,14). In1966, Lasagna published a brilliant, still valid, account in Science of the present status and future development of clinical pharmacology (14). The birth of clinical pharmacogenetics can be ascribed to the pioneering contributions of Werner Kalow and A.G. Motulsky (15,16).

Parallel developments occurred in Europe, particularly in the UK, where the strong infrastructure in basic pharmacology and clinical medicine formed an excellent basis for a rapid growth of the discipline. Names that are usually mentioned in this context are those of Sir John Gaddum, Sir Horace Smirk and Sir Austin Bradford Hill (10). Chairs in clinical pharmacology were created at the end of the 1960s in Germany, the UK and Sweden, although chairs in Materia Medica had long been established in Scotland. Academic growth of the discipline also took place in France (17). IUPHAR took early initiatives to

develop clinical pharmacology. A section of clinical pharmacology was formed in the early 1970s and a division in the 1990s. Several IUPHAR executives strongly supported the discipline, particularly the first president Börje Uvnäs in Sweden, but also Sir Arnold Burgen in the UK and Helena Raskova in Czechoslovakia, who all realised that pharmacology had to reach out to the bedside in order to develop. WHO brought together a Study Group in 1970 (1) to write a report on the scope, organization and training of clinical pharmacology, led by the late Sir Derrick Dunlop (UK), and containing, amongst others, the late professors Louis Lasagna (USA), Franz Gross, (Germany) and Leon Goldberg, (USA). In 1991, WHO Europe put together a booklet and a series of papers in the European Journal of Clinical Pharmacology about the roles of clinical pharmacology in teaching, research and health care (18). For the first time, the potential usefulness of the discipline for the RUM in primary health care was emphasised. Several Nobel Prize laureates in medicine can be considered as representatives of clinical pharmacological research at its best such as Sir John Vane, Sir James Black, George Hitchings, Gertrude Elion and Arvid Carlsson. They all 'practiced' clinical pharmacology during their efforts to introduce new pharmacotherapeutic principles into clinical medicine.

The Global Medicine Scene: The Place of Clinical Pharmacology

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Modern drug therapy has unquestionably transformed the health of peoples in developed countries over the last 50 years. Conditions such as poliomyelitis, diphtheria and pertussis have largely been eliminated in wealthier nations. Many lethal communicable diseases can be cured by modern antimicrobial agents. And complex surgery, beyond the imagination of our forefathers, can be performed safely and effectively using modern anaesthetic agents. Those with chronic diseases have benefited immeasurably with the emergence of safe and effective treatments for asthma, hypertension and hypercholesterolaemia.

Nevertheless, there remains massive unmet clinical need in developing, emerging and developed countries. There is, for example, a pressing need for effective vaccines against HIV/AIDS, malaria and tuberculosis. We have nothing to prevent the inexorable decline in neurological function in people with neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease or Huntington's disease. And, when effective vaccines and treatments have been developed, they are too often unavailable to those in the poorer parts of the world. During most of the second half of the 20th century, research-based pharmaceutical companies were, for practical purposes, the sole source of new medicines. They discovered, developed and delivered products – often with considerable ingenuity – for healthcare systems that were able to afford the costs required to maintain the industry's infrastructure.

People in poorer countries, unable to meet these costs – as well as lacking an appropriate healthcare infrastructure – only rarely benefited. The prospect for satisfying unmet medical need has, in some senses, never been brighter. Advances in molecular techniques offer the promise of identifying drug-sensitive targets that might attenuate or cure many miserable and life threatening conditions. The massive chemical libraries available to most pharmaceutical companies, coupled with high throughput screening and combinatorial chemistry, offer unimaginable rewards for us all. In addition, the emergence of an array of biotechnological techniques offers unique approaches to the development of innovative medicines.

Yet, despite the promise from the science, the outlook is not favourable. Despite record investment in biomedical research by the public sector and not-for-profit organizations, as well as by pharmaceutical and biopharmaceutical companies, the number of new active molecules registered by drug regulatory authorities has fallen dramatically. The costs of bringing a new product to the market are increasing at a rate of 10% per annum, due in part to the failures of products during development, but also to the extended requirements for evidence-based documentation from regulatory authorities (e.g. in elderly patients). Added to this, many of the largest pharmaceutical companies face large reductions in turnover as their 'blockbusters' come off patent.

There have also been spectacular withdrawals of some marketed medicines because of safety concerns. As a consequence, drug regulatory authorities have become increasingly risk averse and place ever greater demands on manufacturers to demonstrate the safety of their products before and after marketing. While this may have some benefits for drug safety, these measures are likely to increase the cost of medicines unless they are implemented with considerable care. Moreover, healthcare systems across the world are struggling to meet the apparently high prices that pharmaceutical companies seek to charge for new products that do reach the market. Those responsible for meeting the health needs of the populations they seek to serve are under increasing pressure to provide affordable care. The increasing numbers of elderly and very elderly people (many

with long-term chronic diseases requiring multiple drug therapy), the greater availability of effective screening measures (especially in the elderly), and the growing expectations of the public, all mean that resources are constrained. One of the reasons for the rapid emergence of HTA facilities, across Europe and North America, is because of the necessity to look ever more closely at the clinical efficacy and cost-effectiveness of therapeutic strategies.

THE FUTURE PROSPECTS

Despite this gloomy outlook, a number of initiatives suggest that remedial action is being taken:

1. Drug regulatory authorities themselves recognise the need for change if people are to have access to innovative medicines. Both the Food and Drug Administration in the United States (19) and the European Medicines Agency (EMA) in the EU (20) have published plans for expediting the regulatory process of innovative medicines that are appropriately safe and effective.
2. The process of drug discovery, confined for most of the 20th century to the laboratories of research-based pharmaceutical companies, has become much more pluralistic. In particular, academic scientists working in universities have become 'drug hunters' and some have been spectacularly successful. Whereas 25 years ago, major pharmaceutical companies were unwilling to even contemplate developing products that had not been discovered in their own laboratories, they are now prepared to do so with enthusiasm. Indeed, companies are pursuing truly collaborative projects with academic scientists to the extent that they are allowing access to their chemical libraries.
3. An increasing number of not-for-profit organizations such as the Bill and Melinda Gates Foundation (in Seattle) and the Hereditary Disease Foundation (in New York) are supporting drug discovery and development in co-operation with both academia and pharmaceutical companies.
4. Some major pharmaceutical and biopharmaceutical companies are increasingly recognising that their traditional models of discovery, development and pricing no longer meet the needs of patients, healthcare systems or their shareholders (21). Changes include moving away from seeking 'blockbusters'; expanding sales to include the emerging markets in Asia; and discussing, with healthcare systems themselves, what future products would bring most value for money.

CONCLUSIONS

These changes in the global medicines scene require the contributions of appropriately trained clinical pharmacologists if innovative new medicines are to reach those in need:

1. Clinical pharmacologists should be better equipped to undertake 'translational' research, especially the design and execution of Phase 1 studies.
2. Too few contemporary clinical pharmacologists are actively engaged in the design and conduct of clinical trials. The founding fathers of the discipline (such as Lou Lasagna (13)) made crucial contributions to health care by undertaking clinical trials – often in relatively small patient populations – that characterised a compound's properties (especially dose–response relationships).
3. With a few notable exceptions, the discipline of HTA has emerged in the absence of contributions from clinical pharmacology. This needs to change if HTA is to meet its full potential.
4. Clinical pharmacologists could do so much more to meet the health needs of those peoples who have in the past been marginalised. They include children, the elderly, those with rare diseases and those with conditions that are endemic in the poorest parts of the world.

INTRODUCTION

The Clinical Pharmacologist in Patient Care

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The ways in which clinical pharmacological services could be integrated in healthcare systems were first outlined in 1970 in a WHO Technical Report referred to earlier (1).

The quality and outcome of drug therapy in patient care can be greatly improved by using cost-effective and evidence-based treatment with drugs adapted to the needs of patient populations and individual patients. Advances in drug development provide patients with new drugs, novel drug combinations, expensive biological drugs and targeted drug therapy adapted to the molecular characteristics of the disease (22,23,24). Increasingly cost-effective generic drugs are available and should be used as first-hand therapies to balance the economic pressures on all healthcare systems today (25). The rate of implementation of this strategy varies widely across health care systems (25). Easy access to evidence-based drug information will assist physicians and healthcare staff in monitoring the effectiveness and safety of drug therapy and optimal allocation of limited resources (26,27).This is a priority since patients and patient organizations are eager to explore what new therapies can offer in terms of health benefits compared to existing treatments, but new drugs and drug combinations may not be affordable for all patients and healthcare institutions. It needs also to be considered that newly registered drugs are rarely innovative (24,27). As a result, great emphasis must be placed on the overall cost-effectiveness and safety of new drug therapies from a societal perspective in order to guide drug selection and reimbursement decisions (22,28). The use and value of new drug therapies have to be monitored within the healthcare institutions as part of a systematic introduction and follow-up of new therapies by involving drug experts across medical specialties and systematic use of clinical outcome data (24,28). Such a procedure will diminish the gap between documented efficacy in controlled clinical trials and observed effectiveness in clinical care (24,28). Clinical pharmacology with its emphasis on critical drug evaluation, scientific methodology, drug development and involvement in the work of drug and therapeutics committees is strategically positioned to bridge the knowledge gap between stakeholders including patients, clinicians, pharmacists, administrators, politicians and pharmaceutical companies within and outside healthcare institutions (26,27).

The quality of drug therapy can be improved in all healthcare settings irrespective of the resources of the country or of individual health care facilities. Patients can be provided with effective and safe therapy if well-documented drugs are prescribed, and the drugs are used according to medical, social, environmental and financial circumstances. The gap between knowledge about drugs and their use in clinical practice needs to be reduced in order to promote the principles governing the Rational Use of Medicines (RUM). These principles have to be communicated, learnt and practiced by students, doctors, healthcare staff and patients in their daily clinical practice (24,27,29,30). An optimal strategy for eliminating the knowledge–practice gap in drug therapy is to apply a multifaceted approach including practice-governed quality assurance programmes combined with interactive continuous medical education and prompt electronic access to evidence-based guidelines (24,27,31). The principles of RUM have to be integrated with healthcare planning and with resource allocation given the scarcity of resources that healthcare institutions are facing. Clinical pharmacologists with their focus on drug evaluation and on the principles of RUM are needed in patient care (22,27,28,29). They should train healthcare staff in the principles of drug evaluation and promote the use of guidelines and drug recommendations based on scientific evidence. At the level of individual hospitals and

healthcare institutions, limited resources cannot be used effectively and safely without a local knowledge and the practice of the principles of critical drug evaluation among clinicians and pharmacists (26,27). Decisions on drug use and reimbursement for specific indications can rationally be adapted to local circumstances in health care facilities by involving key medical opinion leaders at a local level supported by clinical pharmacologists and pharmacists trained in critical drug evaluation (27,29,30,31). In doing so, unbiased decisions free from improper influence by special interest groups is particularly important in view of the relentless increase in the promotion and cost of new drugs (27).

KEY CLINICAL PHARMACOLOGY SERVICES IN PATIENT CARE

The form these services take may vary from country to country and facility to facility depending on the professional and financial resources available. The key bodies providing overall coordination and control of these services are the Drug and Therapeutics Committee (DTC) and Clinical Pharmacology Departments at hospitals or in primary care. Therefore, all health care facilities should have a well-developed DTC with clear instructions, resources and a comprehensive approach (27,32).

(a) Critical evaluation of new and old therapies is fundamental for patient care. It should be a core activity in clinical consultations, in the provision of drug information, in services to DTCs, in consultations with clinical colleagues/clinics, in drug selection and in the design of clinical trials. Critical drug evaluation is the cornerstone for RUM and is important in rich as well as in resource-poor settings. The role of critical drug evaluation is particularly important when new and expensive drug therapies and drug combinations are introduced (see also Chapter 12).

Critical drug evaluation assists the practicing physician in rating the strength of documentation about efficacy, safety and cost-effectiveness for a specific drug therapy as compared with alternative therapies. The method of critical drug evaluation requires medical, clinical pharmacological and scientific skills (13, 26, 27). Applying critical evaluation methods in local health care settings is complementary to evaluations by drug registration bodies. Key elements of critical drug evaluation include assessment of the quality and completeness of a clinical drug study. By using a rating scale (0, 1, 2) this methodology can assist healthcare staff to assess the value of a specific drug therapy in clinical practice (33). In short, an evaluation of a clinical drug study should preferably include rating of the following aspects:

- *aims of the trial*
- *relevance of the trial for health care*
- *the quality and precision of criteria for diagnosis and selection of patients*
- *the type of controls used in the study*
- *the quality of the design of the study*
- *adequacy of randomisation to treatment*
- *the quality of pharmacokinetics data*
- *drug-drug interactions problems if any*
- *how adequately drug effects were recorded*
- *how well adverse effects were monitored and evaluated*
- *the quality of statistical planning and analysis*
- *the precision of conclusions of study results and shortcomings*

By applying this procedure it is feasible to rate the quality of a drug study with a maximum of 24 points that will help to guide the clinician about the strength of a specific clinical drug study and drug therapy. It will be possible to choose between suggested drug therapies by comparing outcomes of ratings of several clinical drug studies.

(b) Drug and Therapeutics Committees (DTC) All institutions, no matter what size, should have some appropriate version of a DTC. It should preferably recruit both hospital based specialists and primary care physicians in order to provide the same type of recommendations irrespective of the level of healthcare (26,27). The membership will vary depending on local circumstances and resources but may include physician clinical pharmacologists, relevant medical staff, clinical and other pharmacists and other staff as appropriate. Where available, physician clinical pharmacologists provide a leadership role bridging medical, pharmacy and other staff (26,27). DTCs should issue recommendations for drug use within the facility based on scientific evidence and medical needs at the local level. This will usually take the form of a local formulary or *"Wise List"* with the WHO Essential Drug concept being a useful model (27,34).

(c) Drug utilisation studies and pharmacoepidemilogical services are closely linked to the work of DTCs and to quality assurance of drug therapy in clinics and in hospitals (30, 35). Ideally, a multi-professional approach is preferred involving experts in clinical specialties, pharmacoepidemiology, pharmacoeconomics and clinical pharmacology. These services are important for a systematic introduction and monitoring of new drug therapies in the facility and can then be linked to forecasting future drug use in healthcare organisations. Knowledge about the use of drugs is a prerequisite for follow-up studies of the adherence of prescribers to drug recommendations and of the effectiveness of drug information and educational activities (27,30,35).

(d) Drug information services are primarily targeted to guide clinicians in evaluating and solving drug problems in patients. The services provided are usually both descriptive and problem oriented. The latter, addressing problems at a patient level are appropriately provided by physician clinical pharmacologists or clinical pharmacists depending on the availability of staff at the particular facility. Drug information services build on systematic literature searches in databases and reference books combined with an evaluation of the literature on patient-related diagnostic problems. This service should assist DTCs in literature searches as the foundation of evidence-based drug recommendations. A drug information service is also helpful for provision of unbiased drug information in academic drug detailing, which is well documented to improve adherence to drug recommendations and guidelines and should be part of the activities of the DTCs (36).

(e) Services in pharmacovigilance may include the responsibility to be a coordinating centre for reports of adverse drug reactions (ADRs) from clinicians and other prescribers at a regional or national level (37). ADR reports should be evaluated systematically and the conclusions fed back to the reporting clinicians and the DTC. Regional clinical pharmacology centres for pharmacovigilance have been successfully implemented in countries such as France and Sweden (37). Pharmacovigilance should be given priority in resource poor settings when implementing population based therapies to control major infectious diseases such as HIV/AIDS, malaria and tuberculosis (38).

(f) Continuing medical education. The focus should be on major pharmacotherapeutic areas, on the principles of RUM and on new drug therapies and drug combinations. Interactive models for learning such as integration of e-learning tools in academic drug detailing and open access internet should be considered and will help to improve the quality of knowledge in drug therapy in remote healthcare institutions in resource poor countries. Continuing medical education should preferably be interactive as this will foster the best involvement of clinical colleagues.

(g) Therapeutic drug monitoring (TDM) and pharmacogenetic services ideally involve the participation of a Division or Department of Clinical Pharmacology. TDM services should always involve clinical interpretation of the data taking diagnosis, drug-drug interactions, kidney function and pharmacogenetics into consideration. An important service, particularly for elderly patients, is to ensure that drug dosages are adapted to the reduction in kidney function that occurs with age (see also Chapter 8). An example of successful translation of the scientific development of pharmacogenetics into the clinic is the abacavir hypersensitivity syndrome which now can be prevented (39). Moreover, the discipline of personalised medicine is rapidly growing, particularly in the field of cancer.

(h) Measurement of drug concentrations for the diagnosis and prevention of drug abuse and other toxicological services. In many hospital settings, clinical pharmacologists are involved in toxicological services such as diagnosis and treatment of drug intoxication. Although the availability of causal treatment with antidotes is limited, a correct diagnosis of the drug involved through drug analysis is important for follow-up and future prevention. A new function in some countries is to participate in the prevention of the abuse of doping agents such as anabolic steroids among athletes and in society at large (40).

(i) Direct Patient Services. Clinical pharmacologists provide care for patients in a variety of ways. In some countries, physician clinical pharmacologists take responsibility for the direct care of patients with particular clinical problems (e.g. intensive care), in patients with particular organ diseases such as hypertension or areas such as paediatrics and geriatrics. In some countries, clinical pharmacologists are mainly used for their skills in the evaluation of clinical drug problems such as therapeutic polypharmacy. Clinical pharmacologists can assist in the development, implementation and evaluation of efficacy and safety of combination therapies in the treatment of major infectious diseases such as HIV/AIDS, tuberculosis and malaria. In both rich and poor countries, drug abuse problems cause considerable harm (41). Preventive programs as well patient care require access to clinical pharmacological expertise supported by adequate drug analytical resources.

(j) Electronic Pharmacological (e-Pharmacological) Services. Evidence-based databases for rational drug prescribing are now available through websites in many countries (42,43). They can be integrated into electronic medical journals and linked to lists of prescribed drugs. E-pharmacological services include tools, knowledge databases on drug recommendations, drug–drug interactions, drugs to be used in pregnant or lactating women, ADRs and tools for the solution of drug related problems. E-pharmacological services provide a link between published evidence and clinical practice. These services are predicted to become of particular importance with the accelerating spread of mobile phones and internet access in lesser developed countries and will, in the future, require extension to the public and to patients (24). This multidisciplinary field will be of great importance in resource poor settings where the clinical pharmacological community with a natural global professional network can help to provide electronic drug information from different countries. The contents of e-pharmacological services are heavily dependent on expertise in critical drug evaluation.

Drug Therapy in Paediatric Patients 7

The well-known paediatric therapeutic disasters of the late 1950s (eg sulfisoxazole, chloramphenicol) revealed the need and gave the impetus for the development of paediatric clinical pharmacology. Despite the fact that training of paediatric clinical pharmacologists has been going on for decades, training capacity remains very small. Consequently the number of trained paediatric clinical pharmacologists in the world is relatively small, with the majority of countries having only a handful if any (44). In this context, paediatric clinical pharmacologists are physicians with training in both paediatrics and clinical pharmacology. However, over the past two decades, professionals outside the discipline of medicine but who possess specialised expertise that is germane to the field of paediatric clinical pharmacology have entered the discipline and participate in a variety of settings (eg academic, regulatory, clinical and industrial).

The need for more and better development, scientific study, regulatory assessment and appropriate use of paediatric medicines is recognised in the US, EU, and WHO paediatric medicines initiatives. Implementation of all the paediatric studies mandated by these initiatives requires well trained investigators and other experts (eg research trained nurses, pharmacists, laboratory scientists) which in many countries do not exist in numbers sufficient to embrace the demands associated with paediatric drug development. Accordingly, building enhanced capacity and strength in paediatric clinical pharmacology across the world is essential to ensure the success of these initiatives.

DEFINITION OF PAEDIATRIC CLINICAL PHARMACOLOGY

Paediatric clinical pharmacology is a scientific discipline that involves all aspects of the relationship between drugs and humans during growth, development and maturation. Its breadth includes the continuum between discovery, development, regulation and utilisation of medicines (as regards compounds and formulations) intended to benefit the paediatric population. As well, paediatric clinical pharmacology is concerned with the response to and the adverse effects of medicines, their use and misuse, and the economics of drug therapy. As the great majority of scientific research and drug development is for many reasons first done in adults, paediatric clinical pharmacology adds the translational element of adapting scientific methods and translating scientific information from adults to paediatric patients (45).

By virtue of the comprehensive scope of paediatric clinical pharmacology, it involves numerous professional groups whose training and skills are relevant to one or more of the scientific and/or clinical facets of the discipline of paediatric clinical pharmacology (eg physicians, biomedical scientists, and non-physician health care providers such as nurses and pharmacists). Paediatric clinical pharmacology is therefore a scientifically driven field of endeavour that depends on a variety of skilled professionals with a training or special interest in appropriate aspects of paediatric drug therapy.

SCOPE OF PRACTICE IN PAEDIATRIC CLINICAL PHARMACOLOGY

Practice environments for paediatric clinical pharmacology are diverse and can include patient care, research, teaching, drug development and drug regulation. Paediatric clinical pharmacologists may participate directly in the care of paediatric patients as either primary care givers or consultants, or may work in scientific and/or administrative capacities to improve the quality of medicines use irrespective of

the health care setting or the wealth of the country. At the country level, paediatric clinical pharmacologists can provide valuable service in the development of National Medicines Policies that consider the special issues of the paediatric population. These issues include the Rational Use of Medicines (RUM) in paediatric drug therapy and measures to protect the basic human rights of paediatric patients who participate in medicines research. Their involvement often extends to the regulatory assessment of paediatric medicines, the development of national treatment guidelines, proposing inclusion of paediatric medicines in reimbursement lists, and monitoring of the performance of medicines in different clinical settings after regulatory approval (eg through the application of pharmacoepidemiology, pharmacovigilance and pharmacoeconomic principles) to assess impacts on health outcomes.

It should also be recognised that, globally, more than a third of the population in developing countries, and almost half in the least developed countries are in the paediatric age range (less than 18 yrs). Close to 9 million children die every year before their 5th birthday from diseases that are usually amenable to treatment. In the area of priority diseases like HIV/AIDS, malaria and tuberculosis, children lag far behind adults in their access to appropriate medicines, especially where the large part of the burden of disease is borne by the paediatric population (eg malaria). Recognising that children represent the hope of 100% of the world for its future, it is essential that their special needs with respect to the development and implementation of safe and effective drug treatment be fully embraced. To this end, the enhanced availability of the expertise and services that can be provided by paediatric clinical pharmacologists represents a critical need on a global level.

TRAINING IN PAEDIATRIC CLINICAL PHARMACOLOGY

Paediatric clinical pharmacology is a sub-discipline of clinical pharmacology and paediatrics. It is a recognised paediatric medical sub-specialty in at least the UK (46) and Australia. Individuals in other professional groups can also receive training and certification in specific areas related to paediatric drug therapy through their professional associations. Finally, it must be emphasised that training in paediatric clinical pharmacology must extend beyond the development of specialist paediatric clinical pharmacologists. It is vital that educational curricula for all health care professionals involved in the treatment of infants and children contain appropriate components of the principles of paediatric clinical pharmacology. Similar educational components should also be included in undergraduate medical programs and in paediatric medical and surgical sub-specialty postgraduate training programs. The continued development of programs and practitioners of paediatric clinical pharmacology is essential for these broad educational goals to be accomplished throughout the world.

Drug Therapy in Geriatric Patients 8

The most rapidly expanding age group world-wide is those 80 years and older (47). Multiple concurrent illnesses that may benefit from drug treatment are the rule, not the exception, in this group. The likelihood of adverse drug reactions increases markedly as the number of concurrently administered drugs rises. This combined with the age-related decline in physiological functions (decreased cardiac reserve, impaired baroreflex function, decreased immunological response, decreased renal function) that in younger patients may reduce the severity of an adverse drug reaction, make the older patient particularly at risk for polypharmacy related adverse drug reactions (48). However the benefits for the treatment of hypertension, coronary artery disease, congestive heart failure, diabetes, arthritis, and other chronic illnesses associated with advancing age are well established. Clinical pharmacologists who focus their research, teaching and clinical service toward older individuals have the opportunity to improve RUM for this increasingly important segment of the world's population.

During the past 30 years, clinical pharmacologists have conducted the research that has defined the pharmacokinetics of aging (49). This work, particularly in the area of drugs (or their metabolites) that undergo renal clearance, has contributed importantly to patient safety and well being. For many drugs it is essential to assess renal function in order to choose the appropriate dosage. Looking to the future, the research opportunities to define drug pharmacodynamics and altered drug harm/benefit relationships in older patients are abundant. Similarly, teaching RUM for older patients and placing this into a geriatric medicine perspective is an important role for the clinical pharmacologist. The number of physicians trained as geriatric clinical pharmacologists is inadequate to meet either the research or educational needs, and attracting physicians and training them to do geriatric clinical pharmacology is a continuing challenge.

Clinical pharmacology has an important role to foster the linkage of the principles of geriatric medicine and disease-based therapeutics. In geriatric medicine, advances in understanding the interplay of multiple concurrent illnesses and how these may result in a common path to patient disability and death have allowed definition of the frailty syndrome (50). In addition, the concept of competing morbidity such that in the older patient successful treatment of one illness may result not in restoration of health, but in the more obvious clinical presentation of another concurrent illness, has advanced clinical decision making and end of life care. The clinical pharmacologist has an important role in teaching about the changing balance of harm and benefit for specific drug therapy intervention in the context of the individual older patient and their specific concurrent illnesses. The research opportunities in this area for the clinical pharmacologist are both challenging and exciting. Research efforts by clinical pharmacologists that have been translated into improved clinical practice for older patients include the development of expert opinion developed lists of drugs to use such as the "Wise List" (27) and the Beers criteria (51). In addition, based on extensive drug usage data, clinical pharmacologists in Europe have developed "Unwise Lists" of drugs that are best avoided in older patients. Geriatric clinical pharmacologists also develop research tools such as the "Drug Burden Index" (52) that link anticholinergic and sedative drug exposure to important clinical functional outcomes in older patients.

Disease-based therapy focuses on the development and implementation of treatment guidelines to

optimise treatment for a specific illness. Clinical pharmacologists and geriatric medicine specialists have pointed out that implementation of treatment guidelines for each of the diseases of an older patient leads to extreme polypharmacy when multiple diseases are present. Often concurrent implementation of multiple therapy guidelines result in conflicts, contradictions, and the simultaneous use of drugs that are known to have harmful pharmacokinetic and/or pharmacodynamic interactions (53,54).The geriatric clinical pharmacologist brings the appropriate training and knowledge base to either resolve these therapeutic dilemmas, or to conduct the research needed to achieve optimal patient care.

The multidisciplinary health care team is championed by geriatric medicine as the optimal means of providing care for the complex older patient with multiple concurrent illnesses. The clinical pharmacologist has a key role on this team, working closely with the primary geriatric medicine clinician, the clinical pharmacist, and other members of the team to individualise and modify complex drug therapy regimens as the clinical status of the older patient evolves over time.

As the population ages in developing countries, the role of the clinical pharmacologist assumes even greater importance. Therapeutic decision-making for older patients with multiple illnesses that may benefit from drug therapy must be considered in the context of limited resources and the desire to provide effective and cost-effective treatment. Here too there are excellent opportunities for the clinical pharmacologist to team up with specialists in geriatrics and other health care team members to provide the best pharmacological care to the largest number of older patients.

Teaching Clinical Pharmacology 9

INCREASING DEMANDS ON PRESCRIBERS OF DRUGS

For most physicians, drug therapy is the main tool at their disposal to influence the health of their patients. New graduates are typically expected to start prescribing drugs regularly as soon as they begin their first medical post. The prescribing demands placed on this group in healthcare systems have progressively increased because of many important trends:

- The number of drugs available continues to rise so that physicians often have to prescribe drugs with which they are less familiar.
- Patients are taking more drugs, increasing the complexity of their treatment regimen and the potential for drug interactions.
- Medication errors and ADRs, many of which are avoidable, constitute a major challenge to public health.
- Patients who receive drugs are older and sicker, and more vulnerable to adverse events.
- Patient throughput is increasing (matched by a similar increase in prescribing episodes) imposing higher workloads on individual prescribers.
- The expansion of evidence-based medicine and HTA has enabled the beneficial and harmful effects of drugs to be quantified more accurately, and this knowledge has expanded the number of clinical guidelines that define norms of acceptable drug use.
- Patients increasingly expect their physicians to provide information about the drugs they are being given to inform their own choices about treatment.
- Poor access to trained medical staff in developing and emerging countries.
- Increasing problems with poor quality drugs and combination therapies for chronic diseases such as HIV /AIDS and tuberculosis in developing and emerging countries, in particular in Africa.
- There are more sources of opinion and 'disinformation' available to patients and prescribers, largely as a result of increasing access to the internet.
- The marketing activities of pharmaceutical companies remain a potential threat to cost-effective prescribing decisions and are complicated by direct-to-consumer advertising in some countries.

Prescribing drugs is a skilled task that always carries a risk of significant harms as well as benefits. Although newly qualified physicians are usually protected from the requirement to undertake high-risk practical procedures, they are often expected to prescribe powerful drugs from their first day of clinical work. Indeed, these inexperienced doctors typically write most hospital prescriptions in many healthcare systems. It is clear that all medical graduates should have a firm grounding in the principles of practical prescribing, as underpinned by the science of clinical pharmacology, at the point of graduation, as the basis for rational prescribing.

The primary determinant of the effectiveness of a prescriber in most areas of practice will be the education and ability of a prescriber to respond to changes in pharmacotherapy. The increasing support of other healthcare professionals, such as pharmacists, and the availability of prescribing support systems and electronic prescribing will help the prescribers in their task but they are no substitute for education and training.

Several studies have shown that lack of training and familiarity with drugs among prescribers is an important factor in serious medication incidents (6,55). New graduates rate prescribing as the most challenging aspect of their profession and the one for which they are least well prepared. Importantly, educational interventions such as the 'WHO Guide to Good Prescribing' have been shown to improve prescribing performance.

UNDERGRADUATE EDUCATION

A key aim of undergraduate medical education should be to provide the learning opportunities that will enable all students to acquire the requisite knowledge, skills and attitudes, and also to put in place appropriate assessments to ensure that these outcomes have been achieved. As the rate of drug development increased in the 1960s, Clinical Pharmacology and Therapeutics (CPT) emerged as a new teaching discipline and many medical schools incorporated it into their curricula as a distinct course. Most medical schools provide some teaching in both basic and clinical pharmacology, the former during the early years and the latter during the later clinical years of the medical curriculum. When students start clinical training, they have usually passed examinations in basic pharmacology and are expected to understand the principles of drug action (56-59).

The core content of a curriculum in CPT can be conveniently divided into knowledge and understanding, skills and attitudes with emphasis on critical drug evaluation (see Addendum I). Most of these outcomes are generic requirements for the safe and effective use of drugs in all areas of clinical practice. These core CPT learning objectives can be linked to a number of specific drugs and therapeutic problems which might be used to provide relevant clinical examples of the principles of CPT in practice. Teaching about specific drugs is organised in different ways in different countries.

One model is to focus teaching on a selected list of the most commonly prescribed 50–100 drugs that will be influenced by the pattern of disease in the country concerned. These should be selected in such a way that their pharmacological properties reflect the important pharmacodynamic and pharmacokinetic principles on which rational drug use should be based. The list could be close to a National Drug List (2), a regional list for 'Wise Drug Prescription' (27) or the WHO Essential Drug List (34) but will normally contain far fewer drugs than such lists. An extensive list of drugs should be avoided as the professional prescription of drugs will be practiced several years later when the prescribers have chosen their specialty. Specific lists of drugs that should be familiar to the prescribers will then differ between, for example general practitioners, internists, psychiatrists and oncologists. Postgraduate and continuing education in clinical pharmacology rather than undergraduate education will thus determine the drugs that are commonly prescribed. However, an understanding of the basic principles of CPT should allow physicians to take a logical approach to learning about any of the drugs they will encounter during their practice.

The principal recommendations for the delivery of CPT in the undergraduate medical curriculum are summarised below:

- CPT and prescribing (or equivalent) should be identified as an important component of the curriculum, visible to students in all years, either as an identified course itself or a theme that integrates with other modules.
- Core learning objectives in CPT should be clearly identified including knowledge and understanding about drugs, skills related to the prescribing of drugs and attitudes towards pharmacotherapy.
- The factual burden posed by the large number of drugs should be eased by prioritising learning around a core list of commonly used drugs (a 'student formulary'), similar to the process used by the WHO in developing their 'Essential Drugs' policy.
- There should be an identifiable and robust assessment that indicates whether the main learning objectives have been met. This might form part of an integrated assessment but it should not be possible to compensate for a poor performance in this area by a good performance in other items.

STUDENT FORMULARY

Medical students are often overwhelmed by the large number of drugs that they encounter during their training. This can be demoralising and lead to a lack of clarity and objectivity in learning. As suggested above, a potential solution is to develop a list of core drugs that could be considered as the 'student formulary' that helps to prioritise study and provide learning objectives that are realistic and attainable. This has already been done in a number of medical schools in Europe, the US, and elsewhere. The list should contain 50–100 drugs that are commonly prescribed and used to treat common diseases. For each drug or group of drugs, students might be expected to have an understanding of the mechanism of action, recognise the appropriate indication and contra-indication, know about potential interactions and adverse effects, know how to monitor effects and be able to explain the salient features of all the above to the patient. The students should also learn about the principles for stopping irrational drug therapy. The list of core drugs can be organised by organ system and set alongside the common therapeutic situations in which they are used. This arrangement emphasises the suitability of a problem-based approach to develop learning about CPT and the ease with which CPT can be integrated within a system-based curriculum.

DELIVERING THE CORE CPT CURRICULUM

Variability in the structure of medical courses will require local solutions for delivery of the CPT curriculum. Where there are traditional arrangements, there may be a preclinical phase containing scientific disciplines that include pharmacology and later courses in 'CPT' or 'pharmacotherapy' and this model is straightforward. Delivery is more challenging when the traditional barriers have been removed in the production of a truly integrated curriculum, often with an emphasis on problem-based learning. In these circumstances, CPT learning objectives must compete simultaneously with many others, usually dispersed across many different modules and through several years of the course. This poses practical difficulties for CPT teachers coordinating learning opportunities across many modules over which they have limited influence. Nevertheless, the importance of CPT should be emphasised in all clinical modules in which there are continuous opportunities to observe and appraise critically the patient drug charts, see the beneficial and harmful effects of drugs and practice relevant skills (e.g. prescribing, dose calculations, drug preparation and administration, and searching for good quality information to inform prescribing decisions).

CPT LEADERSHIP

A key factor in the successful implementation of the CPT core curriculum, particularly in an integrated course, will be strong and enthusiastic leadership. All medical schools should be able to identify an individual who will oversee delivery and ensure that the generic principles of safe and effective use of drugs are highlighted throughout the course. This role should ideally be undertaken by a senior individual with a background and training in CPT, helped by colleagues in the discipline some of whom may be trainees in CPT. In medical schools without CPT departments, other specialists with an enthusiasm for ensuring that principles of CPT are prominent throughout the curriculum should be identified.

The coordination of CPT learning opportunities can be devolved to many teachers across the course, often within organ-based specialties. They too should be encouraged to emphasise these principles

and remind students about the effects of drugs beyond individual organ systems. Simply providing a link between drugs and clinical conditions is insufficient to develop an appreciation of the complex considerations that surround the decision to initiate a prescription.

All schools should ensure that, in each case, students are helped to tackle the practical issues of weighing the harms and benefits of drug therapy, prescribing the drug and monitoring the impact of therapy. Clinical pharmacists who are usually available in greater numbers than physician clinical pharmacologists also have an important role to play in reinforcing learning during clinical attachments, working with other pharmacotherapeutic experts.

LEARNING STYLES

The successful delivery of the core curriculum may involve a variety of learning styles (e.g. lectures, problem-based tutorials) depending on local preference but the content should increasingly be based around inquisitive rather than passive learning. There should be an appropriate balance of teaching in large groups and small groups, practical classes and opportunities for self-directed learning. The core curriculum in CPT is well suited to take advantage of the increasingly popular style of problem-based learning.

Most prescribing episodes are a direct attempt to solve a clinical problem and require the appropriate knowledge, skills and attitudes outlined in Addendum I. Several schools have developed a series of 'therapeutic case discussions' that offer students a case vignette and pose direct problems relating to prescribing and therapeutics. These can be undertaken in live time, even within relatively large groups, or researched and discussed at intervals over several weeks. Other approaches to CPT involve writing case reports containing discussion about therapeutic aspects (e.g. portfolio cases), discussing prescribing decisions with patients as part of communication skills, critiquing clinical trials involving drugs, appraising claims for new drugs and searching for information about drugs.

E-LEARNING

Many CPT departments have now embraced web-based approaches as an opportunity to deliver learning opportunities and self-assessment in CPT. Certainly, it is important that students should be exposed to and trained in the principles of electronic retrieval of reliable drug information. Computer-assisted learning packages are constantly accessible. As the change from paper to electronic prescribing spreads worldwide, aided by advances in virtual reality environments, this approach will be able to provide increasingly realistic simulation of real-world therapeutics (60). An e-learning approach is foreseen to be of high relevance in resource-poor countries with chronic lack of educated staff. Innovative teachers should be able to use the academic high-speed networks for provision of distance learning, interactive teacher–student contact. This may also be applicable in many developing countries.

ASSESSMENT

Assessment drives learning and is critical in emphasising the importance of CPT in the course and ensuring that graduates are fit to practice. All medical schools should have validated and reliable schemes of assessment in place to ensure that students demonstrate that they have achieved the curricular outcomes. It is important too that assessments should not simply be knowledge-based but test the acquisition of practical skills

(e.g. writing a prescription, offering information to a patient about a drug and spotting potentially dangerous prescriptions). The objective structured clinical examination (OSCE) is an ideal format for this kind of assessment. Relatively few schools now have a traditional CPT examination as changes to the curriculum bring the assessments of diverse learning objectives together in integrated examinations. Where this is the case, there should be a clear, identifiable and robust component devoted to the knowledge and skills that support rational prescribing. Furthermore, whether assessment is integrated or part of a collection of discipline-based assessments, it is normally not appropriate for students to be able to compensate for a poor performance in prescribing or therapeutics with good performances in other assessments. Students should also be provided with formative assessments and the chance for self assessment at regular intervals during the medical course.

QUALITY ASSURANCE

All schools should have some form of external quality assurance to ensure that the CPT learning opportunities and assessments they provide are fit for purpose, i.e. deliver graduates with sufficient knowledge and skills. Such reviews might examine whether the goals outlined earlier in this section have been met. The appointment of external examiners with CPT expertise might also help to ensure that appropriate standards are met.

POSTGRADUATE EDUCATION

Education in CPT and prescribing should be a continuing process in postgraduate medicine, not only because of the constant emergence of new medicines but also rapid changes in the knowledge base of those that are already established in clinical practice (see Addendum II).

The previous section outlines the importance of developing a firm platform on which to build postgraduate training. There should be a progression from undergraduate training for broad-based, supervised prescribing through to progressively specialised and less supervised work during subsequent years. Curricula for specialist training and related assessments will be critical in promoting the importance of CPT principles and knowledge. In the case of specialists in primary care or hospital-based disciplines, arrangements for continuing medical education (CME) (often known as Continuing Professional Development) will be important in updating knowledge and skills and fostering reflective practice. The emergence of new prescribing groups (e.g. pharmacists, nurses) in some countries offers a further opportunity for CPT education to be used to enhance health care.

There are several important challenges for postgraduate CPT education. Perhaps the greatest is to find the necessary time in already busy clinical schedules. However, this problem is being increasingly circumvented by the development of more flexible web-based learning solutions and recognition within the relicensing/revalidation process that all doctors require protected time for CME. Another important challenge is to provide good quality non-promotional education. Recent years have seen pharmaceutical companies play a well-resourced highly influential role in the delivery of unbiased postgraduate education. Clinical pharmacologists should embrace the opportunity to contribute to the planning of non-promotional educational events.

Research Domains of Clinical Pharmacology

10

INTRODUCTION

In the first WHO report on clinical pharmacology in 1970 (1), the section on research emphasised the need for studies that explored the mechanisms of action of drugs and identified their pharmacokinetics in humans. Improvement of the early studies of new drugs in humans and conventional therapeutic trials were also prioritised. Research in clinical pharmacology has now taken new paths and this satisfies many principles of translational medicine defined as taking scientific data on drugs into rational patient care.

However, we should be aware that not all research into drugs falls within the remit of translational medicine. The endeavour of a pharmacologist working in a clinical environment is to develop methods and strategies that improve the quality of drug use in individual patients and patient populations. Research in drug evaluation, drug utilization, pharmacovigilance and pharmacoepidemiology – areas that were only superficially mentioned in the 1970 document are now the priority. All these research areas have great potential for supporting healthcare personnel in their RUM. Rational use of medicines implies that drugs should be chosen according to efficacy, ADRs and cost as potentially equally important parameters. Research in clinical pharmacology therefore also includes studies that elicit new data about drugs in use, such as new indications and treatment of neglected patient populations (children, elderly - see chapter 7 and 8). It also includes research into ADRs, pharmacogenetics and drug interactions. Research in clinical pharmacology is usually interdisciplinary and hence often carried out in collaboration with other professionals: pharmacists, drug analytical chemists, molecular biologists, statisticians, computer specialists as well as clinical researchers from other medical specialties.

PHARMACOKINETIC, PHARMACODYNAMIC AND PHARMACOGENETIC STUDIES IN HUMAN VOLUNTEERS

This research should lead to a fundamental understanding of the mechanisms involved in the actions of the drugs on the organism or the actions of the organism on the drugs. The research is particularly focused on intra- and interindividual differences in pharmacokinetics and pharmacodynamics, an area in which clinical pharmacologists have made important contributions in the past. The mechanisms in such variability usually involve inherited individualities in the genes encoding drug targets, drug transporters and drug metabolising enzymes. The perspective of the research should not only be in understanding the molecular mechanisms but also in designing genotyping or phenotyping tests, which may be applied to forecast drug response and to differentiate between genetic and non-genetic modifiers of the outcome of drug treatment . *In vivo* research is often combined with experimental studies *in vitro* and *in silico.* The research aims to identify the routes of metabolism and excretion of drugs.

There are two separate approaches in pharmacokinetic research, one based on several drug measurements over a fixed time schedule in a few subjects and the other being based on sparse measurements in each subject of a large population of individuals (population pharmacokinetics). Such data may help to identify subpopulations with impaired or enhanced elimination capacity. The population approach can also be applied to pharmacokinetic–pharmacodynamic evaluation.

CLINICAL DRUG EVALUATION AND CLINICAL TRIAL PHASES I–III

Important research areas are to improve the methods used to evaluate drugs in humans. The first examination of the effects of a new drug in humans (Phase I) is done with great care and in great detail, few subjects being tested. These Phase I studies are often done by clinical pharmacologists working in industry or in specialised clinical trial units. When the time comes to examine the effect of the drug in patients with the disease to be treated (e.g. hypertension), again small numbers of patients will be studied in detail (Phase II studies). The training that clinical pharmacologists undergo gives them the skills to do such studies.

The randomised controlled trial (RCT) or its extension to meta-analysis or systematic reviews of several RCTs is considered to be the gold standard for documenting the efficacy of drugs. The RCT has advantages but also disadvantages and other methods for the evaluation of clinical interventions are needed (61). Clinical pharmacologists have been the pioneers in introducing the RCT and in particular in introducing the placebo as control. The RCT is now mastered by clinical intervention researchers in practically all medical specialties and is no longer solely the province of clinical pharmacologists. The RCT is a method with which all clinical pharmacologists should be familiar as it still forms the basis of most drug evaluations. One area in which clinical pharmacologists could make a difference is the detection of relatively frequent ADRs that are predictable and understandable on the basis of the mode of action of the drug. Another area is the evaluation of biomarkers as measures of drug action in clinical trials. In the case of new drugs, the studies described above are part of the Phase I clinical trials.

THERAPEUTIC DRUG MONITORING (SEE ALSO CHAPTER 6)

Therapeutic drug monitoring (TDM) is a scientific medical technology where clinical pharmacology has made major contributions. The measurement of drug concentrations in blood or plasma will often help to achieve better understanding of the nature of individual drug exposure, how this relates to expected exposure values at the given dose, and recommended target ranges in plasma at which there is an optimal therapeutic effect or an increased risk of ADRs. Therefore, the clinical use of TDM is obvious for drugs that have a narrow therapeutic window and for which individual exposure is difficult to predict from the particular dose used owing to extensive interindividual differences in pharmacokinetics. It may provide direct guidance for individual dose adjustments in cases of ADRs or therapeutic failure. TDM is based on the assumption that the plasma concentration of the drug reflects the concentration at the drug target, although this may not always be the case, for instance with some central nervous system (CNS)-active drugs or anti-infective agents used to treat localised tissue infections.

TDM research into clinical routine samples has been important for a safer use of specific drugs in subgroups of patients at risk: the elderly, children and patients with renal or hepatic failure. TDM research has also helped to detect and manage drug–drug interactions and to understand the clinical impact of genetic polymorphisms in drug elimination pathways.

The mapping of the human genome and the revolutionary developments in biotechnology and human molecular medicine have been of fundamental importance in this regard. Research at the beginning of the 21st century mainly aims at understanding the role of genetic variation in the capacity or function of

drug metabolising enzymes, drug transporters and receptors and their relationship to the clinical effects of drug treatment. Many TDM laboratories now offer genotyping services, in addition to TDM, and medical input is crucial for an individualised, clinical interpretation.

Clinical pharmacologists need to understand the principles of the laboratory methods that are used, although they may not necessarily be able to perform them. In experimental studies on TDM or pharmacogenetics, the main responsibility of the clinical pharmacologist is to formulate a clinically relevant problem, design the study that will help to bring further understanding to this problem, be medically responsible for the study volunteers and translate the results into clinical practice.

PHARMACOVIGILANCE

When a new drug enters the market, it has been tested in only 3–5000 patients. There ought to be solid documentation that its actions are superior to placebo or comparable to or even better than the existing treatment. Its most common harmful effects should be known, in particular those that are predictable from their basic pharmacological properties or readily explained in the context thereof. However, at marketing, serious or even lethal but very rare ADRs that cannot be explained by the basic pharmacology of the drug and that occur in, say, 1 out of 10,000 patients or even less commonly, may not have occurred or been recognised. Spontaneous ADR reporting is carried out in order to detect unknown potential drug toxicity. The method consists of collecting individual case reports of clinical suspicions of ADRs. Data mining in ADR research is the search for structures and patterns in large ADR databases, manual inspection no longer being possible. Data mining involves the development, testing and implementation of computer methods, routine algorithms and tools for finding such associations and patterns of associations between drug intake and adverse events.

DRUG UTILISATION STUDIES

Clinical pharmacologists play a key role in drug utilisation research, which can be defined as an eclectic collection of descriptive and analytical methods and theories for the quantification, understanding and evaluation of the processes of prescribing, dispensing and consumption of medicines. The subject is also concerned with the testing of interventions to enhance the quality of these processes. It is common to quantify drug utilisation by defined daily doses, which by definition is the typical maintenance dose of the drug in an adult for its main indication.

PHARMACOEPIDEMIOLOGY

Sometimes an RCT is either unethical (e.g. in detecting harmful effects on the foetus) or impossible because hypothesis testing or signal generation will require very large numbers of patients. Clinical pharmacologists have been pioneers in establishing pharmacoepidemiology, which may be defined as the science of studying the utilisation and actions of drugs in large populations. Pharmacoepidemiology uses methods from both clinical pharmacology and epidemiology. The purpose of the research may be to detect a signal, to estimate the risk of an ADR or to test a hypothesis. The results of the research can be used to give advice to healthcare organisations and individual patients or to formulate a policy regarding the optimal use of the drug.

Cohort studies are carried out by registering a drug effect (cure, death, ADR) in a sample of patients treated with a particular drug. A sample of patients not treated with the drug is used as a control group. Random allocation and blinding are not applied

and that presents problems with confounding and bias but methods have been developed to at least partly overcome this. In case-control studies, drug use in patients with a symptom suspected of being an ADR is compared with drug use in a sample of patients without the symptom. Thus, the odds ratio for developing an ADR can be calculated. Linkage studies are carried out by linking data from individual level prescription databases to health outcome databases. Pharmacoepidemiology is an important new development in clinical pharmacology. For the sake of the continued development of the scientific discipline, it is important that part of pharmacoepidemiology be anchored in clinical pharmacology.

PHARMACOECONOMICS

Pharmacoeconomics is the scientific discipline that evaluates the clinical, economic and human aspects of pharmaceutical products, services and programmes as well as other healthcare interventions. The aim is to provide healthcare decision-makers, providers and patients with valuable information for optimal outcomes and the allocation of healthcare resources. Pharmacoeconomics incorporates health economics, clinical evaluations, risk analysis, technology assessment and health-related quality of life, epidemiology, decision sciences and health services research in the examination of drugs. Clinical pharmacologists are important in the field of pharmacoeconomics as they are best placed to formulate research questions of medical importance and to translate the research findings into effective treatment with sensible outcome measures for the average patient. The main role of a clinical pharmacologist in this discipline is to assess the quality and suitability of clinical trials data for inclusion in the overall analysis, in order to determine whether a new drug has any clinical advantage over the existing treatments. It is necessary to arrive at an objective quantitative evaluation of 'benefit' or 'effectiveness' to put into cost-effectiveness models that health economists have developed. The clinical pharmacologist is uniquely able to do this evaluation which may end up not conforming to the appraisal or claim submitted by manufacturers.

Emerging Roles of Clinical Pharmacology: Biologics and Biosimilars

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BACKGROUND

The growing importance of biopharmaceuticals, is one area in which the remit of the clinical pharmacologist has expanded very significantly since the original WHO document appeared in 1970. In the last three decades, drugs produced or extracted from biological sources (e.g. recombinant products, monoclonal antibodies and recombinant vaccines) such as insulin, somatotropin, interferon, granulocyte-stimulating factor, erythropoiesis-stimulating factors like epoetin and tumour necrosis factor – alpha (TNF-alpha) and inhibitors like infliximab have been developed and approved for therapeutic use. Biopharmaceuticals are a rapidly growing segment of newly developed drugs, with sales amounting to about $40 billion in 2006 in the United States (62) . Today, 20–30% of drugs are produced by biotechnological methods. The patent on human insulin was filed in the early 1980s and expired in 2002. Other patents have also ended or are about to expire. Currently, about 400 biopharmaceuticals are under clinical development about half of which are used in treating cancers. As many of them are expensive, it is important that generic products can be provided to make cost-effective treatment accessible to all those who need them.

In contrast to classical drugs, which are typically manufactured by chemical synthesis, biologics (or biopharmaceuticals) are manufactured in a living system such as a micro-organism or plant or animal cells. Owing to their production process and mechanism of action, biologics have a different pattern of potential adverse effects compared with chemically synthesised drugs, and these adverse effects deserve special attention (63).

Most biologics are very large, complex molecules or mixtures of molecules. The production is usually based on recombinant DNA technologies and the process is often commercial-in-confidence (62). Changes to the production process such as cell lines used, vectors, culture media and conditions can lead to the formation of protein isoforms, alteration of glycosylation patterns and/or changes in the tertiary protein structure. Therefore, unlike classical drugs, a medicine produced by such a process in order to mimic an already licensed biologic (the reference drug) is a product that is similar to but not the same as the innovator drug. Therefore, such a product is not called 'generic' but 'biosimilar' or 'follow-on biologic'.

Because of the complex science involved, the EMA recognised that the usual approach to generic medicines is scientifically not appropriate for these products. Clinical pharmacologists working in this field posess or need to acquire knowledge and skills in molecular and cell biology rather different from those needed previously.

BIOSIMILARS – PROBLEMS IN EVALUATION

As biosimilars are different from existing biologics in terms of their raw materials and manufacturing processes, biosimilars have the potential to cause, for example, immunogenicity problems that were not detected in clinical trials and did not occur with the original manufacturer's product. Therefore, EMA has stipulated that a regulatory framework should be established to minimise the risk to patients by requiring extensive testing before approval in order to ensure that biosimilars are safe and effective. Moreover, biosimilars have to undergo post-marketing monitoring like that required for new biologics. Accordingly, EMA has taken a case-by-case approach to similar biological products, typically requiring new clinical trials. The FDA is given some flexibility in deciding how much data and testing are enough to establish the key standards of safety and efficacy – similarity and interchangeability - for follow-on biologics (64). In particular, the manufacturer of a

biosimilar has to provide a detailed pharmaceutical dossier, including data on the manufacturing process, manufacturing facilities, implementation of non-clinical bioassays, toxicity studies, local tolerability studies, and Phase I to Phase IV studies compared with the reference product. Thus, for biosimilars of epoetin, EMA stipulated two double-blind studies in a parallel group design to investigate the efficacy of the new erythropoiesis-stimulating agent in patients with anaemia following renal damage. Generally, it is permitted to extrapolate results on efficacy in a specific therapeutic area to others, e.g. from renal anaemia to the symptomatic treatment of chemotherapy-associated anaemia. However, this may vary between agencies and from time to time.

As mentioned above, immunogenicity is a major problem of biologics. As they are proteins, an immune response such as the formation of antibodies is more likely than in conventional pharmaceutical products. Thus, in patients treated with epoetin alpha, an isolated erythroblastopenia (pure red cell aplasia) has occurred as a consequence of the generation of neutralizing antibodies against erythropoietin (65). In general, the immunogenic potential of biopharmaceuticals depends on the production process, and also on the mode of application, dosage, duration of treatment and specific characteristics of the individual patient. Therefore, careful pharmacovigilance is needed, as immunological reactions may be without clinical consequences, or may sometimes lead to a loss of efficacy, without causing severe adverse reactions. According to EMA guidelines, at least 300 patients must be observed over at least 12 months in order to assess possible immunogenicity and the profile of adverse events of a biosimilar compared with the reference substance (66).

As the safety data from pre-authorization studies are never sufficient to get a complete profile of the immunogenic potential of a biosimilar, post-authorization safety studies and the preparation of risk management plans are obligatory for biosimilars. To illustrate the differences of approval for biosimilars of epoetin, Abseamed (Medice, Iserlohn, Germany) and Binocrit (Sandoz, Kundl, Austria) were approved in Europe except for subcutaneous injection in patients with chronic renal failure, as data on immunogenicity were considered to be insufficient for this indication. This exception does not exist for the biosimilar Epoetin alfa Hexal (Hexal, Holzkirchen, Germany).

CONCLUSIONS

The extensive requirements of regulatory authorities concerning preclinical and clinical studies of biosimilars impose substantially higher developmental costs than those for usual generic drugs. It is therefore expected that biosimilars may save only 15–20% of costs compared with the biopharmaceutical original (67).

In summary, the assessment of the harm benefit ratio of biologics and biosimilars is a challenge for physicians, manufacturers and regulatory authorities and requires translational efforts to consider the needs of drug innovation on the one hand and patient safety on the other hand (68). It requires the expertise of molecular biologists, immunologists and clinical pharmacologists in order to take advantage of these challenging new medications. The opportunities for clinical pharmacologists in this field are considerable provided the necessary training in molecular and cell biology is taken on board in addition to the standard training that clinical pharmacologists undergo.

Clinical Pharmacology and the Pharmaceutical Industry

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OVERVIEW AND THE INDUSTRY ENVIRONMENT

Pharmaceutical companies have until recently driven the discovery, development and marketing of new and established drugs. They include a range of organisations varying from 'big pharma' global companies such as Pfizer and GlaxoSmithKline, to smaller, usually disease-focused, specialised companies, large (e.g. Genentech) and small biotechnology companies, and companies focused on generic, over-the-counter (OTC) or complementary medicines. The clinical pharmacologist has a broad perspective of all aspects of drug discovery and use, and all of the 'sub-specialities' of clinical pharmacology from pharmacokinetics / pharmacodynamics to pharmacoepidemiology, pharmacovigilance (benefit/harm management) and pharmacoeconomics are critical. More importantly, the clinical pharmacologist can integrate knowledge of the drug target, disease pathophysiology, context and management and preclinical and clinical data to guide drug development in an ethical, informed and efficient manner.

Globally, pharmaceutical companies operate in a complex environment where evolving economic, regulatory, social and political influences constantly force change. Investment in R&D increases rapidly, but is not matched by the rate of emergence of new products onto the market. The high expectations of innovation models that involve combinatorial chemistry, high-throughput screening, rational drug design, pharmacogenomics, bioinformatics and disease and pathway modelling have not been met despite the high level of investment. The risks in a business model that concentrates on a few 'blockbuster' drugs are also apparent as patents expire or are challenged vigorously by generic companies, and new drug pipelines to replace them are meagre. There have also been highly visible failures of potential blockbusters at a late stage in development and a number of high-profile safety-related post-marketing drug withdrawals that have resulted in an increased regulatory focus on risk management during the drug development process. At another level, consumers, health insurers and governments are increasingly focusing on paying for health outcomes rather than drugs, and sales and marketing approaches used in the industry are being questioned with a resulting reduction in trust. What changes are being driven by these factors?

At the discovery level, there is recognition that diseases are complex and that a focus on single targets may not be the optimal approach, resulting in a move back to disease models rather than target-based R&D. The separate silos of discovery, preclinical development and clinical development are increasingly integrated vertically into development teams that include functions from early discovery through to pharmacoeconomics and marketing. Companies are emphasising translational research to facilitate the efficient transition from ***in vitro*** and preclinical animal research to human applications, and medicines are developed for more tightly targeted patient groups who are identified as likely to respond using biomarkers and/or pharmacogenomic approaches, thus improving the cost-effectiveness of the treatment (so-called 'personalised medicine'). Companies increasingly market medicines coupled with related services and diagnostics to identify responsive patients, and there is recognition of developing markets and neglected diseases as targets for drug development and marketing. The focus of payers on cost-effectiveness drives companies towards development of medicines that produce real health benefits, and the biotechnology paradigm replaces the chemical, with biologicals providing

high benefits coupled with high value and cost. 'Big Pharma' is accessing biotechnology medicines through in-house R&D, licensing, sponsored R&D, partnerships and the acquisition of small, vigorous, fast moving and innovative biotechnology companies that have often been started by academics.

Despite the problems facing the industry, the demand, and therefore the market, for medicines is likely to rise during the second decade of the 21st century owing to ageing populations and the emergence and growth of new markets particularly in developing countries. Companies are consolidating through mergers and acquisitions and this trend is set to continue. Paradoxically, they may become less homogeneous, with niche market, biotechnology and generics companies all emerging as significant players.

ROLES FOR CLINICAL PHARMACOLOGISTS IN INDUSTRY

Clinical pharmacologists can work in a wide range of roles across companies, but will need to develop skills and expertise beyond those normally associated wit the discipline in the academic or hospital setting. The types of roles available, and the knowledge, skills and attitudes required are discussed below.

Traditional roles: The clinical pharmacologist in industry customarily has been involved at the early stages of clinical drug development – planning, design, conduct, analysis, interpretation and reporting of Phase I and Phase II studies in humans. These activities include:

- First in human trials, involving the first exploration in humans of dose, tolerability and pharmacokinetic and (where appropriate) pharmacodynamic parameters. The clinical pharmacologist works with preclinical, translational medicine/biomarker, drug metabolism/PK, and toxicology partners to synthesise all the available data, to plan the optimal Phase I strategy for clinical development, and eventual filing for marketing approval.
- Phase II proof of concept clinical trials to establish efficacy in a restricted patient population
- Follow-up on PK/PD studies exploring issues such as drug interactions, effects of disease states, bioavailability and / or bioequivalence of dosage forms used during early and late development, and special patient groups such as the elderly or children.

Specialised roles: Clinical pharmacologists have diverse areas of special interest within the discipline, and many of these roles and skills are needed by the pharmaceutical industry (69-71). Given their broad training and background, clinical pharmacologists are well placed to integrate their special area of interest across functional and therapeutic area groups. Some examples are:

- Preclinical development
- Pharmacogenetics
- Pharmacoepidemiology
- Pharmacovigilance (benefit/harm management)
- Pharmacoeconomics
- Late clinical development – Phase III confirmatory trials.

Other activities: Clinical pharmacologists in industry contribute to greater or lesser extents in a range of other activities which may include:

- Regulatory – preparation of submissions, interactions with regulatory authorities and regulatory strategy planning.
- Outsourcing – managing CRO and academic contracts.

- Advisory – arranging and managing scientific and clinical advisory boards, interactions with key scientific and clinical advisers to ensure appropriate product development.
- Intellectual property management – assisting with the preparation of patents, liaising with patent lawyers and responding to queries from patent offices around the world; involvement in IP protection strategies including decisions to patent, retain as in-house know-how or put in the public domain; scientific and clinical advice for patent defence.
- Due diligence activities – involvement in scientific and clinical analysis of data and the scientific, clinical and market potential of products or companies.
- Management and financial activities – human and physical resources – planning most efficient development paths – quicker development gives higher net present value.

Roles in small pharmaceutical or biotechnology companies:

The clinical pharmacologist is needed in this setting to fulfil a much broader role, being involved in overall discovery, development and marketing. The company will often function in a specific therapeutic area with a small number of products in development and / or on the market. The role will usually involve a broader strategic planning, management and financial focus. Clinical pharmacologists are needed to contribute to many aspects of the overall business, including raising funding on the financial markets, development strategies in relation to funds available, and making decisions about developing to market stage, or licensing or sale of the product at an earlier development stage.

Industry roles and needs. Pharmaceutical companies usually have distinct scientific and management career streams. Clinical pharmacologists will normally start in the scientific stream, but are well placed because of their broad background to contribute in both areas. Clinical pharmacologists are needed in roles including managing a project or product development team, leading a therapeutic area such as CNS or cardiovascular system (CVS), or leading a functional area such as clinical pharmacology, benefit / harm management or pharmacoepidemiology. The broad perspective of clinical pharmacologists is ideal for higher management roles with involvement in the company's overall discovery, development and marketing strategies.

Knowledge, skills and attitudes. The clinical pharmacologist in industry normally has basic training as a physician with specialist training in clinical pharmacology. Companies provide training in-house, or externally, for necessary industry-specific skills such as project management, but much is gained through hands-on experience. The areas involved may include:

- Intellectual property and knowledge management.
- Strategic planning and project management.
- Regulatory requirements – international, regional and country-specific.
- Regulatory compliance – GxPs, electronic and hard record data and information management.
- Leadership and decision-making in complex organizations and cross-functional teams.
- Core business skills – including the structure of the industry, a broad understanding of the business issues and models in the industry, the differences between industry sectors, and how product value is created and measured.
- Ethical and societal perspectives and broad industry issues – attitudes and ethical practices in a company or industry sector, medical versus marketing department perspectives, values and activities.

The goal of drug development is to convert intellectual and scientific creativity into medicines that are valuable in terms of both benefits to patients and a sustainable business model for the company. The clinical pharmacologist has the background to influence industry practices along appropriate ethical, societal and medical lines, even though this may be difficult in the context of a large, financially driven organisation.

Governments: Essential Roles for Clinical Pharmacology

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The clinical pharmacologist is an individual who has had systematic training in the evaluation of drug therapy and drug products. This makes the specialty suitable and valuable in a number of government-based public activities that relate, for example, to drug approval, post-marketing surveillance, drug therapy selection, reimbursement decisions and ethical review of research projects. Governments should be involved in the ethical, scientific and developmental aspects of medicines. Activities in all these three dimensions are complementary and underpin the most important role of any government: to protect its citizens through support and promotion of public health.

Governments and their respective institutions have to take all necessary measures to make sure that clinical research involving its citizens is not doing them harm or ignoring their basic human rights. This challenging task involves making sure that the research to decide which medicines (or other healthcare interventions) are authorised for use in human beings provides enough grounds to ensure safety. It also involves the task of assessing whether planned clinical research follows scientific principles that can justify both the harms and the expected benefits from this research. This forms the ethical dimension of the role of governments.

HISTORY

Following the two world wars, several initiatives were taken around human rights and these were embodied in the World Medical Association's Declaration of Helsinki in1964. In particular, the Council for International Organizations of Medical Sciences (CIOMS) was founded under the auspices of WHO and the United Nations Educational, Scientific and Cultural 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, could be effectively applied, particularly in developing countries, given their socioeconomic circumstances, laws and regulations, and executive and administrative arrangements. The most important of the publications of CIOMS is its International Ethical Guidelines for Biomedical Research Involving Human Subjects, first published in 1993. The updated version was published in 2002 (72) and is designed to be of use, particularly to resource-poor countries, in defining the ethics of biomedical research, applying ethical standards in local circumstances, and establishing or redefining adequate mechanisms for the ethical review of research involving human subjects. Although mainly targeting ethics committees sponsors and investigators, the CIOMS guidelines, to which several clinical pharmacologists have contributed, have influenced the thinking of governments concerning clinical research, especially in resource-poor settings. Another important facet of research in human subjects is good clinical practice (GCP) which is a 'standard for the design, conduct, performance, monitoring, auditing, recording, analysis and reporting of clinical trials. GCP provides assurance that the data and reported results are credible and accurate, and that rights, integrity and confidentiality of trial subjects are protected'. Many GCP guidelines are based on, or refer to, the Declaration of Helsinki, including WHO GCP Guidelines published in 1995 (73) and the International Conference of Harmonization (ICH) GCP (E6) from 1996 (74).

ETHICS COMMITTEES AND REGULATORY BODIES

A fundamental requirement for the application of ethical considerations is submission of a research proposal to independent evaluation by an ethics review committee. Nowadays, many governments define procedural aspects of the work of ethics committees in detail. For example, the European Commission has laid down strict timelines for processing research applications which affect the work of ethics committees in all European Union Member States. Clinical pharmacologists are particularly valuable as members of ethics review committees because of their knowledge of medicines-related clinical research. In addition, governments have to ensure that only effective, safe, good quality medicines are used to treat their citizens. Nowadays, all medicines are subject to marketing authorization approval before they are prescribed. The approvals are based on assessment of the quality, safety and efficacy of the products. The safety monitoring of medicines during their whole life cycle (from marketing authorisation to potential withdrawal from the market) is also a task for governments. Usually, these and other medicines-related regulatory functions are carried out by specialised governmental agencies – national medicines regulatory authorities (NMRA) such as the US Food and Drug Administration (US FDA) and in Europe, the EMA. In a broad sense, the role of the NMRA is to cover multiple dimensions and is derived from their mission. WHO Policy Perspective on Medicines No. 7 'Effective Medicines Regulation: Ensuring Safety, Efficacy and Quality' (75) states the following: "A clear mission statement, which includes the national regulatory authority goals, is necessary to guide its work. Goals usually include the protection and promotion of public health by ensuring the safety, efficacy and quality of medicines, and their appropriate use; and ensuring the appropriateness of medicines information provided to the public and health professionals."

The EMA which coordinates the work of the various national experts in Europe and has very far reaching responsibilities, has a broader mission statement (76):

'' To foster scientific excellence in the evaluation and supervision of medicines, for the benefit of public and animal health" by

- developing efficient and transparent procedures to allow rapid access by users to safe and effective innovative medicines and to generic and non-prescription medicines through a single European marketing authorization;
- controlling the safety of medicines for humans and animals, in particular through a pharmacovigilance network and the establishment of safe limits for residues in food-producing animals;
- facilitating innovation and stimulating research, hence contributing to the competitiveness of EU-based pharmaceutical industry; and
- mobilising and coordinating scientific resources throughout the EU to provide high-quality evaluation of medicinal products, to advise on research and development programmes, to perform inspections for ensuring fundamental GxP (GxP means 'good clinical practice' (GCP), 'good manufacturing practice' (GMP) and 'good laboratory practice' (GLP) collectively) provisions are consistently achieved, and to provide useful and clear information to users and healthcare professionals''.

These are two examples of mission statements. The one from EMA addresses the three aspects described above, namely ethical, scientific and

developmental concerns. It is very important that regulators involved in the evaluation of safety and efficacy of medicines have the best possible scientific education and background. They should also be able to make a critical scientific evaluation of the clinical data and to understand what, at the time of the assessment, is known and what remains unknown about each drug under review. Some NMRA also have units focusing on clinical pharmacology. For example, the U.S. FDA has in its Centre for Drug Evaluation and Research (CDER), the Office of Clinical Pharmacology. Nowadays, safety surveillance and pharmacovigilance are also the responsibility of the regulators.

CLINICAL PHARMACOLOGISTS IN GOVERNMENT

In most countries, governments, directly or through their specialised agencies, are also involved in taking decisions about the selection of medicines for public procurement, developing national treatment guidelines and proposing inclusion of medicines in reimbursement lists. This work may also involve composing and updating national Essential Medicines Lists as promoted by the WHO. Clinical pharmacologists are usually closely involved at the government level in developing and delivering a National Medicines Policy. It is important that such individuals work in an environment that has political support but also where there is a good prospect of continuity of support when governments change.
The monitoring of the performance of drugs in real life after regulatory approval, including cost-effectiveness assessment in the wider context of Health Technology Assessment (HTA) needs highly qualified specialists. However, all these activities are linked to promotion of the rational use of medicines, sometimes also called 'quality use' (77). An example of governmental institutions involved in such activities is the National Institute for Health and Clinical Excellence in the United Kingdom. The activities of such bodies should be based on the best possible scientific methods and knowledge and are part of the scientific dimension of the government's obligation to its citizens. Clinical pharmacologists have proved themselves to be well prepared to meet the challenges of the complex assessment of medicines.

Working at the government level, clinical pharmacologists are well trained to work in the area of HTA. Many of the assessments are very much in the field of new drug assessments, especially the new molecular biology drugs, as well as in the administration of drugs by new technologies. Recent history gives evidence that not all the research necessary for developing and promoting public health by medicines is possible using only private sector initiatives and funding. Thus, governments may also be involved in delivering financial support for clinical research involving medicines. Clinical pharmacologists are well positioned to make judgements about the scientific value of proposals for government funding of research projects. An important emerging issue is electronic patient health records which have been implemented or are on their way in many countries.

Although these may be perceived as mostly administrative tools, they include a huge scientific potential for monitoring the safety and quality of drug therapy. There is already evidence that electronic health records can offer greatly added value for research in pharmacovigilance (78). Clinical pharmacologists should be actively involved in designing and using electronic patient health records because of the enormous potential for future clinical research including monitoring of rational drug use and safety.

FUTURE CHALLENGES

A government's efforts to create a research-friendly environment in its country should be composed of functional legal and other systems which will make government offices well informed about the necessary scientific background, and thus help their effective functioning.

Owing to the relative lack of new therapies and pressure from patient groups and industry, governments have been pushed into granting 'early market approvals' under certain pre-conditions. However, effective methods for pharmacovigilance and safety studies in the context of early market access need to be created and tested and clinical pharmacologists have an important role to play (79,80). Clinical pharmacologists also contribute to the topic of pharmacoepidemiology. This discipline is being increasingly used and sometimes is the only available approach to assess the benefits and harms of long-term pharmacotherapy. Similarly, pharmacoeconomics attempts to give a financial cost and value to everyday drug use which may become the basis for rational reimbursement systems.

In order to implement these various dimensions, governments have to create laws and regulations, the necessary infrastructure in terms of governmental institutions and necessary resource allocations to support the infrastructure. One of the key resources is properly trained specialists, capable of taking decisions based on the best possible scientific methods and evidence. All these dimensions are inter-related and interdependent. Good ethics cannot do without good science; good science can be ethical, whereas bad science can never be.

CONCLUSIONS

The clinical pharmacologist is a specialist who, working at government level, serves the public interest by helping to ensure that only safe and effective medicines are authorised for use, as well as facilitating cost-effective prescribing and improving the RUM. The training of clinical pharmacologists is ideal for these purposes and can be tailored to meet the needs of various government services in order to ensure that the best scientific knowledge is used to make decisions in public health. In particular the governments of emerging economies and developing countries will benefit from the applied expertise of clinical pharmacologists. However, few have given the necessary priority to the development of the discipline of clinical pharmacology, and many have difficulty in creating positions that compete for funds with disciplines that may be seen to be more 'mainstream'.

The Clinical Pharmacologist and Traditional Medicines

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"Traditional medicine" is a comprehensive term used to refer to various forms of indigenous medicine - including traditional Chinese herbal medicine, African traditional medicine, Ayurvedic and Unani medicine, homeopathy, naturopathy and other administered treatments derived from natural sources (81). It also covers manipulative physical treatments which are not considered here.

Clinical pharmacology arose in the universities of the western world where modern prescription and over-the-counter medicines were the sole entities studied and where the expectation was that trained clinical pharmacologists would teach, investigate, and have clinical expertise in, the use of such medicines. Most clinical pharmacologists in practice today will have had little or no exposure to traditional medicines unless they have sought it out for themselves.

In the 40 years since WHO published its first Technical Report on Clinical Pharmacology (1), the use of traditional ('complementary', 'alternative') medicines has grown rapidly in developed countries many of which have now created national regulatory bodies to set standards for their quality and safety.
Although access to conventional medicines in developing countries has improved, it is still estimated that a third of the world's population, which is almost exclusively in developing countries, has inadequate access to "Essential Medicines". Therefore, in the developing countries the majority of the population still relies on traditional medicines and its practitioners.

However, the involvement of clinical pharmacologists in traditional medicines has so far been quite small despite the remarkable increase in their use in both developed and developing countries.

From a clinical pharmacologist's perspective there are several issues surrounding traditional remedies. Preparation from natural ingredients plant, animal or mineral, is not necessarily standardised and quality may vary between suppliers and seasons. Safety of traditional medicines cannot be taken for granted and several have demonstrated significant toxicity even after many years of use, e.g., nephrotoxicity and carcinogenicity of *Aristolochia* found in some traditional Chinese preparations (82). Many of the claims for efficacy have not been substantiated in adequate clinical trials although the spectacular anti-malarial activity of medicines derived from *Artemisia* species should caution against dismissing activity until the evidence has been fully investigated. Moreover, the taking of traditional and conventional medicines together predisposes to potential adverse interactions, e.g., the co-administration of St John's Wort (an enzyme inducer) may reduce the efficacy of medicines metabolised by the cytochrome P450 3A4 enzyme sub-type (83).

All physicians need to be aware and knowledgeable about the side effects or toxicity of some common herbal remedies. Patients often use traditional medicines without being aware of the potential side effects or interactions with their other current medications, and fail to disclose this to their physician. In fact, it is up to the physician to be proactive by inquiring about the use of traditional medicines. In one report, approximately 20% of hospitalised patients used traditional medicines concurrently with conventional medicines without informing their physicians (84). The reasons for non-disclosure included patients' anticipation of the physician's disinterest or negative response, a misconception that the physician would be reluctant or unable to contribute useful information, and

complete ignorance of the potential risk of using traditional with conventional medicines (85).
It is clear from these observations that the training of clinical pharmacologists, and indeed of all physicians, needs to be reviewed to ensure that traditional medicines are included.

THE UNDERGRADUATE MEDICAL CURRICULUM

There is a need for instruction about traditional medicines at some point in all undergraduate medical curricula. This should provide an understanding of the commoner traditional medicines that are used in the particular society and that are therapeutically or toxicologically important in patient care. The aim is to enable the young doctor to advise and/or manage patients using these medicines, and to be vigilant for any potential interaction with conventional medicines. Also, an opportunity to engage students in research involving traditional medicines might stimulate some to pursue working in this field at a later stage.

THE POSTGRADUATE CLINICAL PHARMACOLOGY CURRICULUM

Research: It would be appropriate to provide training in clinical research and evaluation of one or more of the common traditional medicines in the community for quality, safety and efficacy, using scientifically acceptable guidelines for conduct and evaluation of human studies.

Service: Adequate instruction is needed to ensure that the clinical pharmacologist is competent to advise on the value, potential risk and management of patients using traditional medicines. However, to have a broader influence on prescribing by traditional healers or practitioners, it is desirable that the clinical pharmacologist undertakes further training in traditional medicine or even becomes a fulltime traditional medicine practitioner with specialisation in the clinical pharmacology of these medicines- though at present this would be a rare occurrence.

RESOURCES

In recent years, there has been a rapid expansion of evidence-based texts about traditional medicines (86-88) and the scientific basis for these preparations will continue to be strengthened. The Cochrane library contains many systematic reviews of efficacy of traditional medicines (89) and several excellent websites provide information with its accompanying evidence (90-93). Clinical pharmacologists should be aware of, use and promote these resources.

Collaboration with Other Drug Experts

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The rise in clinical pharmacology in the 1960s was in a large part due to the realisation of basic pharmacologists that their discipline was too far removed from the practice of medicine, but also due to the desire of prominent clinicians specialising in pharmacotherapy to develop their science and improve the quality of drug therapy. Clinical pharmacologists at the time had to have fruitful collaboration with both pharmacology and internal medicine and usually had considerable training in both disciplines.

Clinical pharmacology at its best now requires a much broader view of all aspects of medicine in which drugs are used be it internal medicine, paediatrics, psychiatry, anaesthesiology, geriatric medicine or oncology. The role of clinical pharmacology in all these areas should be to educate physicians, to perform collaborative research and to disseminate information about the principles of drug evaluation and RUM. These roles are facilitated by having access to diversified methods for monitoring and improving drug therapy. As the field has evolved and clinical pharmacists and Ph.D. scientists trained in clinical pharmacology have increased in numbers, contribution and collaboration among these somewhat differently trained individuals has strengthened and extended the contribution of medically trained clinical pharmacologists. This is particularly the case for multi-disciplinary Drug and Therapeutics Committees and drug information services. In pharmacoepidemiology and pharmacovigilance, collaboration with epidemiologists is necessary.

In TDM, collaboration with drug analytical experts is vitally important to maintain accreditation of the analytical methods used. Such experts are usually trained in chemistry or pharmacy. Collaboration with persons knowledgeable in molecular biology is of increasing importance, particularly in pharmacogenetics. Many clinical pharmacologists depend on their collaboration with trained nurses who fulfil valuable roles in areas such as drug utilization measurement and evaluation and assisting with clinical trials.

Organisation: Structural Models for Clinical Pharmacology

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INTRODUCTION

Historically, clinical pharmacology developed either from departments of pharmacology or from departments of internal medicine. Clinical pharmacology is now an independent medical specialty in many countries. In countries where it is not a separate medical specialty, clinical pharmacology should be recognised as a scientific and clinical discipline in its own right. Clinical pharmacology is usually organised in separate units headed by a clinical pharmacologist. Depending on local and national circumstances, the unit could either be a division of clinical pharmacology in a clinical or in a pharmacology department. While internal medicine is historically the base clinical department, increasingly clinical pharmacology units are developing from other clinical specialties such as paediatrics (see chapter 7), geriatrics,(see chapter 8), anaesthesiology or psychiatry.

Irrespective of which model is used, the optimal setting is in a university hospital as it supports all three major functions of clinical pharmacology: health care, teaching and research. County (or district) hospitals and primary health care also need experts in clinical pharmacology. Such expertise can be provided from the university hospital if the local availability of clinical pharmacologists is limited. In some cases, the discipline of clinical pharmacology may justify only a small organisation and here the terminology of 'Unit' may be more appropriate than 'Division'. There are several models of organisation, described below.

INDEPENDENT DEPARTMENT OF CLINICAL PHARMACOLOGY IN A UNIVERSITY HOSPITAL

In some countries, clinical pharmacology has developed to such an extent that a separate department in a university hospital has been created. Such departments have sufficient staff for the manifold interests of clinical pharmacology in research, teaching and clinical service. Such staff will comprise both clinical pharmacologists and other multidisciplinary staff such as pharmacists and drug analytical staff and will often include basic pharmacologists.

The department may have beds, and the physician clinical pharmacologists are then fully responsible for the treatment of patients. The advantage of this arrangement is that the physician clinical pharmacologist is fully integrated in the clinical work of the hospital making it easier for them to relate to clinical colleagues. The disadvantage is that the involvement of physician clinical pharmacologists in direct health care will reduce their time availability for other important clinical pharmacology activities (see chapter 6). Thus, in many countries, physician clinical pharmacologists are not directly responsible for patient care. As there are advantages and disadvantages in both models (see above) the model chosen should reflect the national and local traditions, circumstances and needs.

Collaboration between basic and clinical pharmacologists enables achievements to be made that are rare when the disciplines work on their own. Finally, the department will need staff with other skills such as nurses, computer experts, statisticians, laboratory technicians and secretaries to fulfil its role properly.

DIVISION OR UNIT OF CLINICAL PHARMACOLOGY IN A CLINICAL DEPARTMENT

In many countries, this model for clinical pharmacology is more appropriate. It is likely to be the pattern where it is impractical to have a fully independent department and this is the model most likely to be relevant in resource poor environments. This may be the case where the range of clinical services required is significantly smaller than as listed in chapter 6 or where the number of staff employed only permits the provision of a limited range of such services. In either case, the long-term aim should be to grow so that a full range of services, relevant to the needs of the community, can be provided. This may result in the creation of an independent department in due course.

DIVISION OR UNIT OF CLINICAL PHARMACOLOGY IN A PHARMACOLOGY DEPARTMENT

In some cases, a clinical pharmacology unit (or division) has been organised in close association with (or has developed from) a department of basic pharmacology. The advantages of such an arrangement have been discussed above. There will be a considerable disadvantage if the basic pharmacology department is sited some distance from the hospital.

DEVELOPMENT OF CLINICAL PHARMACOLOGY ORGANIZATIONS

Many clinical pharmacology organisations start small, but as they grow over the years in response to the healthcare needs of their communities, they develop new skills and require different staff groups. Thus, there are examples of clinical pharmacology organisations that have developed from basic pharmacology but now have individual clinical pharmacologists who provide direct or consultative health care to patients, e.g. by looking after patients who have taken a drug overdose, running a unit for clinical trials, or evaluating patients with pharmacotherapeutic problems such as therapeutic failure or ADRs.

Equally, there are clinical pharmacology organisations that have developed from providing direct patient care to become more involved in the basic science of pharmacology – for example the use of molecular biology skills to understand pharmacogenetic variability and thereby to provide a more personalised approach to drug therapy. The training available for clinical pharmacologists will need to reflect this changing world (see Addendum II).

The Central Place of Clinical Pharmacology in Global Public Health

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BACKGROUND

Since the first edition of the WHO Technical Report in 1970 (1), the medical world has changed dramatically. New diseases have arisen (HIV/AIDS), developments in molecular biology have generated new biotherapeutic agents, communications have been revolutionised by the Internet and many of the historically important diseases of the developing world are receding and being replaced by non-communicable disease – with the notable exceptions of malaria and multidrug- resistant tuberculosis.

However, more than 50% of countries that replied to a WHO survey in 2003 had no policies in place to improve the use of medicines despite data showing around 50% of all medicines worldwide are being used inappropriately (38.) A prominent example is the excessive use of antibiotics which is a major factor in the high prevalence of resistance to previously first-line antibiotics for dysentery, pneumococcal pneumonia and hospital-acquired infections (38). The World Health Assembly, recognising these problems, urged 'member states to establish or strengthen multidisciplinary national bodies for monitoring medicine use, and to implement national programmes for the rational use of medicines' (WHA resolution 60.16, May 2007).

With this as background, it can be argued that the most important single development that has expanded the role of clinical pharmacologists in global public health has been the recognition by many developed and developing countries of the value of a National Medicines Policy. The initiative came to a focus in the WHO 'Guidelines for the Development of National Drug Policies' published in 1988 (2). More than 150 countries now have their own policies in varying stages of implementation.

These policies aim to ensure:

- The quality, safety and efficacy of medicines
- Equitable access to medicines for all the population
- The rational / quality use of medicines
- 'A viable and responsible local pharmaceutical industry' (quotation from the Australian National Medicines Policy, 2000). Clinical pharmacologists have clear and demanding roles in the implementation of each of these key ingredients.

QUALITY, SAFETY AND EFFICACY OF MEDICINES

Quality of medicines is threatened by counterfeiting, poor manufacturing practice or the unscrupulous marketing of time-expired products – each of these is a contemporary problem, especially in the developing world (94). In many countries, clinical pharmacologists contribute substantially to drug regulation. The pre-marketing assessment of the quality, safety and efficacy of a new medicine demands critical skills possessed by the trained clinical pharmacologist, including a capacity to evaluate clinical trials performed in many different clinical areas. The ability to assess the relevance and possible problems of a new medicine for a particular population also requires an understanding of local epidemiology (if only to establish whether or not the country 'needs' this particular medicine – based on an assessment of the prevalence and severity of any particular medical condition) and possible racial variations in, for example, the metabolism of medicines.

Increasingly, pharmaceutical companies are conducting clinical trials in developing countries in

the expectation that this will be a cost- and time-efficient way of recruiting large numbers of patients. The trial results feed into the regulatory system at the point of pre-marketing assessment. Clearly, this provides an opportunity to obtain country-specific data, but it also raises the question of who takes clinical responsibility for critically assessing trial protocols, who manages the necessary initial research ethics application and clearance, and who takes responsibility for the clinical supervision of patients. These are standard roles for clinical pharmacologists in developed countries and there is a strong case for providing positions in less developed countries for the same purposes.

Safety cannot be fully appraised at the point of marketing and only some form of post-marketing surveillance will permit the timely detection of less common adverse effects not detected in the limited pre-marketing data. For many developing countries, limited resources mean that most new medicines approved for marketing have already been used for years elsewhere, and there is a greater probability that their safety has been more fully characterised, allowing for differences in pharmacogenetic variations from country to country. In whichever context, the clinical pharmacologist has a major role in the setting up of spontaneous reporting systems, in reviewing (and suggesting action on) reported adverse events, and in providing data not only to guide decisions in the home country but also to contribute to the global database (95).

EQUITABLE ACCESS

The individual's right to the 'best possible standard of health' is set out in the Universal Declaration of Human Rights (96). When challenged in the courts of several countries, the right of access to essential medicines has been upheld as an extension of the right to health (97). Despite this assertion of principle and intent, WHO estimates that as many as two billion people worldwide do not currently have access to essential medicines. For the poorest populations, lack of finances may be the major cause. An estimate of annual per capita income adjusted for within-country cost of living, expressed in 'international dollars' (so-called ''Purchasing Power Parities'') was $41,674 for the United States in 2005, $3487 for Sri Lanka and $1892 for Nigeria (98). With no regular acceptance of the need for medicine prices to be proportional in some measure to national per capita income, the costs of many medicines are beyond the limited resources of the poorer countries as the figures above predict.

Many countries have or are developing systems for pre-marketing economic evaluation of medicines. While the economic model chosen will influence the outcome, the starting point is always evaluation of the clinical trials data from which the estimate of potential benefit is derived, to set alongside cost in the cost-effectiveness calculation. This requires clinical pharmacological skills and involvement of clinical pharmacologists as part of the pharmacoeconomic team to address these issues specifically. In countries where the cost of medicines to the individual is subsidised by government, a list of selected medicines is maintained.

This may be the same as the country's 'Essential Medicines List', and this is the case in many low and middle income countries. However, subsidy of this type – whether funded entirely by government, partly by the patient as a co-payment or through some form of insurance scheme – requires a rigorous examination of not only the quality, safety and efficacy of medicines but also measures of cost-effectiveness and affordability.

Clinical pharmacologists are commonly involved in this selection process in developed countries but much less so at present in the developing world, partly because there are so few of them. Buying only medicines that are cost-effective and affordable locally is a potent way of ensuring that limited resources are used to best advantage.

RATIONAL USE OF MEDICINES

Having medicines of high quality that are accessible to all does not guarantee that they will be used in the best possible way. More money can be saved and health objectives met by ensuring the highest standard of use. Over the past two decades, methods for measuring and evaluating the quality of use of medicines have been developed and implemented.

Drug utilisation reviews

One of the first steps in improving the way medicines are used in any community is definition of the potential or actual problems. Measuring medicine use and relating it to clinical indication in a community, hospital, clinic or at a national level is not the easy task it would be if there were databases that could be linked (with proper attention to confidentiality of the records). Supply is not the same as utilisation, although in some circumstances, especially in resource-poor settings, it may be the only surrogate available. Commonly, utilisation has to be measured prospectively by data collection in a defined area for an adequate time, to ensure representative results. In many countries, this task has fallen to pharmacists who have had special training in the methods. However, when the results are being interpreted, clinical input is required. Clinicians with specialty training are needed in order to judge whether prescribing has been appropriate. Ideally this role is best filled by a clinical pharmacologist with broad clinical training and experience. Standard treatment guidelines (below) that have been endorsed for a country, hospital or community serve as the reference standard and help to define inappropriate practice. The clinical pharmacologist should be a member of the evaluating team and also in the design and implementation of interventions to mitigate problems that are identified.

Standard treatment guidelines

The introduction of evidence-based treatment guidelines is one of the interventions that has a large potential to improve the quality of use of medicines (99). To have the necessary authority, the guidelines should contain the best available evidence, be put together with representative input from all end-users and be sensitive to local conditions (e.g. storage and transport problems for particular formulations of medicines in remote countries with difficult climates such as the isolated island communities of the Pacific region). The guidelines should also be endorsed by local opinion leaders (including government and professional associations) and be revised regularly to maintain currency. Clinical pharmacologists commonly have a central role in developing guidelines and their broad training fits them for this task.

Essential medicines lists

The essential medicines list should reflect, and derive from, the national standard treatment guidelines. Ideally, guidelines should be prepared first and the essential medicines list produced from their recommendations. Whatever the sequence, the two documents should always be harmonised at each updating and review.

Objective information about medicines
(see also chapter 6)
In many developing countries, there is a dearth of objective information for health professionals about medicines, the gap being filled by information provided by pharmaceutical companies with, not unexpectedly, a promotional bias. Many developed and some developing countries produce regular drug information journals. These deal with topical issues about the use of medicines, review the profiles of newly introduced medicines and discuss adverse effects. Clinical pharmacologists play a major role in the editorial processes and as authors for such publications. In some developed countries, drug information centres staffed by clinical pharmacologists, pharmacists and other health professionals have been set up to provide patient-focused information. Increasingly, medicines information is being produced for consumers, written in non-technical language and in some countries issued with all first prescriptions for medicines.

Education of health professionals and of consumers (see also chapter 9 and Addenda I and II)
Clinical pharmacologists working within the health system always have a responsibility to be involved in undergraduate, postgraduate and continuing education. Much evidence suggests that doctors prescribe less well than they might (6,38). Undergraduate training, with continuation into post-graduate and continuing education, has the potential to lift the level of prescribing beyond the mediocre and provide a pattern for life-long learning as new medicines, or new uses for old ones, are introduced. Whose business is the education of consumers? Peer education is a powerful technique and several studies have demonstrated its effectiveness in improving understanding and use of medicines. If this is the strategy chosen, the clinical pharmacologist may not be the primary educator but often becomes the adviser who helps to translate the information from medical to everyday language. Work in a Drug Information Centre and Drug and Therapeutics Committees may be a natural extension of the tasks listed above – especially in larger teaching hospitals.

THE CLINICAL PHARMACOLOGIST'S JOB DESCRIPTION FOR GLOBAL PUBLIC HEALTH

There is a wide 'job description' for the clinical pharmacologist working predominantly in the health system. It is good that we can now demonstrate that many of the strategies listed above have strong evidence that they are effective in increasing knowledge, improving prescribing or the consumer's use of medicines (99). However, while it appears intuitive, there is virtually no evidence to link improved prescribing and use of medicines uniquely to improved health outcomes although there is the honourable exception of improved compliance / adherence, reflected in better disease control – especially most recently in the treatment of HIV/AIDS – and some instances where antibiotic choice and adherence play the crucial role in patient recovery.

The list of tasks above (and in chapter 6) reflects the clinical pharmacologist's usual pre-occupation with prescription medicines. A further, emerging role is in the evaluation and investigation of traditional medicines (see chapter 14) which provide first-line treatment for up to 80% of the world's population. Largely neglected by Western clinical pharmacology, these traditional preparations have the potential to provide surprises. For example, it is arguable that the most important advance in the pharmacotherapy of malaria in the last decade has been the introduction of the *Artemisia* derivatives – which come directly from the Chinese herbal tradition.

Several developed and developing nations

have recently set up a regulatory framework for traditional / complementary medicines. The concerns that prompted these initiatives were the need to ensure quality control in the manufacture of these products and to evaluate the potential for unexpected toxicity (as demonstrated, for example, by aristolochic acids in some traditional medicines as a cause of renal impairment and renal cancer (82)). There is also the difficult problem of assessing the efficacy of products that have had little or no scientific study in the past, and which are produced by an industry that has only limited options for patent protection.

In addition, there are only limited funds available for the necessary clinical trials work and thus many problems remain to be solved. However, research money is beginning to flow from both pharmaceutical companies and from government sources in some countries.

In several instances, clinical pharmacologists have been members of the national advisory committees making recommendations to government regulators, and in both Australia and the UK these committees have been chaired by a clinical pharmacologist. Some preparations that have been in use for many centuries warrant investigation and evaluation – a further role for the clinical pharmacologist in relation to global health.

The recognition that medicines are used for treatment or prophylaxis on such a scale in many populations that they assume the same importance as other factors that influence public health has led to the use of epidemiological methods to explore the impact of medicines on populations as a whole. The exploration of ADRs has led to fresh approaches for the linkage of events with medicines use. Case–control studies (100) and health database linkage have raised hypotheses, and sometimes provided hard causality evidence about events stemming from drug exposure. Record linkage is at present only feasible in countries that have the necessary accessible databases but will undoubtedly spread more widely as the technology comes within the reach of less well resourced countries.

CONCLUSIONS

The discipline of clinical pharmacology arose from the two imperatives of the need to be able to measure the efficacy of medicines in patients and the equally urgent need to be able to monitor adverse effects. However, the list of ingredients in a contemporary clinical pharmacologist's work provides a menu too full for a single individual. In reality, and especially in resource-poor countries, clinical pharmacologists will make the biggest contribution, working as part of a team, whether in the hospital, the community or in an administrative position. Training of clinical pharmacologists to meet these needs will have to be rather different and much broader than envisaged in 1970. It is covered in chapter 9 and in Addenda I and II.

CHAPTER 3. THE DEFINITION OF CLINICAL PHARMACOLOGY

Clinical Pharmacology is the scientific discipline that involves all aspects of the relationship between drugs and humans and involves the delivery of health care, teaching and research as well as helping to frame policy and giving information and advice about drugs. It is a multidisciplinary science that encompasses professionals with a wide variety of scientific skills including medicine, pharmacology, pharmacy, biomedical science and nursing. The term 'clinical pharmacologist' is also used in the professional sense to refer to those physicians who are specialists in clinical pharmacology. They have usually undertaken several years of postgraduate training focussing on important aspects of clinical pharmacology including clinical trials, drug evaluations, pharmaco-epidemiology, pharmacoeconomics, pharmacogenetics, pharmacovigilance and clinical drug toxicology. The primary goal of clinical pharmacologists is the improvement of patient care, directly or indirectly, by promoting the safer and more effective use of drugs.

CHAPTER 4. THE HISTORY OF CLINICAL PHARMACOLOGY

Clinical Pharmacology is a relatively new medical discipline having been developed extensively in the middle of the 20th century. However it has its roots in a much older tradition of 'materia medica' going back for centuries. After a period at the end of the 20th century when the discipline was seen to contract in some countries there are now new signs of optimism (see introduction).

CHAPTER 5. THE GLOBAL MEDICINE SCENE –THE PLACE OF CLINICAL PHARMACOLOGY

Modern drug therapy has unquestionably improved the health of peoples in developed countries over the last 50 years and yet there is much more that could be done in these countries quite apart from the needs of developing and resource poor countries.

CHAPTER 6. THE CLINICAL PHARMACOLOGIST IN PATIENT CARE

The prime function of a clinical pharmacologist in patient care is to deliver safe and effective drug therapy in what is often termed the Rational Use of Medicines (RUM). In some cases this is done directly where a clinical pharmacologist has direct responsibility for patient care, but more commonly a range of services is offered to clinical colleagues and their patients. Clinical pharmacologists are trained particularly in the critical evaluation of both new and old therapies and so may function on drug and therapeutic committees or by delivering drug information services (often in collaboration with other health care professionals such as pharmacists). Special skills are available in drug utilisation, pharmacoepidemiology, and pharmacovigilance. In addition many clinical pharmacologists are involved in therapeutic drug monitoring services. These are often combined with pharmacogenetic services leading to a personalised medicine approach which can result in more effective therapy with fewer adverse drug reactions.

CHAPTER 7. DRUG THERAPY IN PAEDIATRIC PATIENTS

The treatment of paediatric patients needs special skills since children are not just small adults. After a number of drug disasters in children in the 1950's it was recognised that paediatric clinical pharmacology was a specialty in its own right which needed development for a number of reasons but particularly because of the high death rate of children from treatable diseases in under-developed countries.

CHAPTER 8. DRUG THERAPY IN GERIATRIC PATIENTS

The treatment of elderly patients is a real concern in today's world. The most rapidly expanding age group in the world is the over 80 age group. Elderly patients have particular problems in drug therapy as increasing age is associated with impairment of several physiological functions particularly renal function which affects the excretion of drugs and their metabolites. In addition therapy with multiple drugs leads to more problems from drug interactions. Thus some specialists in the care of the elderly patients have developed special skills in Geriatric Clinical Pharmacology.

CHAPTER 9. TEACHING CLINICAL PHARMACOLOGY

All clinical pharmacologists have a considerable role to play in teaching, whether this is at the undergraduate, postgraduate or continuing professional development level. Most attention is currently directed at the undergraduate medical level because of the increasing demands being placed on new prescribers and because of the evidence that new prescribers are more likely to prescribe less effectively and with more errors than their seniors. A number of different approaches to this problem are described and in a comprehensive Addendum (Addendum I) a Model approach to the required Core Knowledge and Understandings, Skills and Attitudes is suggested.

Postgraduate teaching of Clinical Pharmacology is also covered (see Chapters 9 and 12 and Addendum II) but the approach here is a more general one mostly because there is far greater variability in the availability of staff and resources as well as more varying needs around the world in the postgraduate scene than in the undergraduate one.

CHAPTER 10. RESEARCH DOMAINS OF CLINICAL PHARMACOLOGY

Research is a fundamental part of the training and the work of virtually all clinical pharmacologists. The endeavour of a pharmacologist working in a clinical environment is to develop methods and strategies that improve the quality of drug use in individual patients and patient populations**.** Research in drug evaluation, drug utilisation, pharmacovigilance and pharmacoepidemiology has become more important than at the time of the 1970 WHO report (1). The Rational Use of Medicines (RUM) implies that drugs should be chosen according to their efficacy, adverse drug reactions and cost as potentially equally important parameters. Research in clinical pharmacology includes studies that elicit new data about drugs in use such as new indications and treatment in neglected populations. It also includes research on adverse drug reactions, pharmacogenetics and drug interactions. Research in clinical pharmacology is almost always multidisciplinary.

CHAPTER 11. EMERGING ROLES OF CLINICAL PHARMACOLOGY: THE EXAMPLE OF BIOLOGICS AND BIOSIMILARS

Biologicals play an emerging role in clinical pharmacology. In contrast to common drugs, which are typically manufactured through chemical synthesis, biologics are made in a living system, so the usual generic approach is scientifically not appropriate for these products. Biosimilars require a special regulatory framework in order to ensure that biological therapies are safe and effective, and require post-marketing monitoring similar to that for new innovative biologics. Hence the assessment of the harm/benefit ratio of biologics and biosimilars is a challenge for physicians, manufacturers and regulatory authorities and requires expertise across multiple disciplines.

CHAPTER 12. CLINICAL PHARMACOLOGY AND THE PHARMACEUTICAL INDUSTRY

The clinical pharmacologist has much to offer the pharmaceutical and biotechnology industry at all levels. The clinical pharmacologist's broad knowledge of all aspects of drug use combined with the insights gained from clinical practice provides a unique platform to influence the effective and ethical development and marketing of therapeutic drugs. Clinical pharmacologists contribute at many levels from broad high level management positions to a focus on a special area of expertise within clinical pharmacology. They develop a range of skills and knowledge not often encountered in academic clinical pharmacology.

CHAPTER 13. GOVERNMENTS: ESSENTIAL ROLES FOR CLINICAL PHARMACOLOGY

Governments need to develop systems to serve the public by ensuring that only safe and effective drugs are authorised for use in their populations and the clinical pharmacologist is well suited to this purpose as well as facilitating cost effective prescribing and improving the rational use of medicines. The training of clinical pharmacologists is ideal to meet the needs of various government services in order to ensure that the best scientific knowledge is used in making decisions in public health. In particular, the governments of emerging economies and developing countries could benefit from the expertise of clinical pharmacologists, although few have given the necessary priority to the development of the discipline and many would have difficulty in creating positions that are seen to compete for funds with other medical disciplines.

CHAPTER 14 . THE CLINICAL PHARMACOLOGIST AND TRADITIONAL MEDICINES

Clinical pharmacologists conventionally have had little exposure to traditional medicines and yet these are widely used both in the developed and in the under-developed world. It is clear that use of traditional medicines can cause harm as well as benefits. Clinical pharmacologists should be better informed about traditional medicines and be more involved in work to increase the scientific knowledge around traditional medicines.

CHAPTER 15. COLLABORATION WITH OTHER DRUG EXPERTS

Clinical pharmacology is a multidisciplinary activity and close working relationships with a number of different professional groups is critical. Some of the disciplines involved in various aspects of clinical pharmacology include medicine, pharmacology, pharmacy, biomedical science, nursing, social and behavioural sciences, dentistry, economy, epidemiology, genetics, toxicology, mathematics and computer sciences.

CHAPTER 16. ORGANISATION: STRUCTURAL MODELS FOR CLINICAL PHARMACOLOGY

Clinical pharmacology services can be delivered through a variety of different organisational arrangements. There is little doubt that the most effective system is for the clinical pharmacology services to be delivered from a department or division based within a hospital, whether the hospital is a university hospital or a district general hospital. The needs of primary care are also important particularly where these services are delivered outside the hospital setting.

CHAPTER 17. THE CENTRAL PLACE OF CLINICAL PHARMACOLOGY IN GLOBAL PUBLIC HEALTH

The development of clinical pharmacology has been centred on the 'developed' countries of the world and yet the needs are arguably greater in the developing and resource poor countries. The skills and resources available in such countries necessitate a different approach to developing the rational use of medicines. The discipline of clinical pharmacology arose from the two imperatives of the need to measure the efficacy of medicines in patients, and the need to be able to monitor therapy and prevent adverse drug effects. However the list of ingredients in a contemporary clinical pharmacologist's work provides a menu that is too full for a single individual or discipline. In reality, and especially in resource poor countries, clinical pharmacologists make the biggest contribution, working as part of a team, whether in the hospital, the community or in an administrative position.

Training of clinical pharmacologists to meet these needs is rather different, and much broader, than envisaged in 1970 when the initial WHO report was published (1).

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Addendum I.
Model Core Curriculum for Clinical Pharmacology, Therapeutics and Prescribing for Medical Students

21

This addendum provides a list of knowledge and understanding, skills and attitudes relevant to the use of drugs that should be core content in the undergraduate medical curriculum. These represent key learning outcomes that will enable all graduates to prescribe safely and effectively at the point of graduation. These core objectives are generic and applicable to most areas of therapeutics. They should be considered in association with a relevant list of core drugs and therapeutic problems to which they apply. Medical schools should be encouraged to identify lists that are appropriate for their local circumstances. For each drug, graduates should be expected to have an understanding of the mechanism of action, recognise the appropriate indications for use, know the appropriate route(s) of administration, and know the important contra-indications and adverse effects. In some cases a drug class is listed with a commonly used member of the class as an example. The list of drugs chosen might be viewed as a 'student formulary'.

I CORE KNOWLEDGE AND UNDERSTANDING, SKILLS AND ATTITUDES REQUIRED TO SUPPORT RATIONAL PRESCRIBING

Core Knowledge and Understanding

Basic pharmacology

- the general mechanisms of action of drugs at a molecular, cellular, tissue and organ level
- the ways in which these actions produce therapeutic and adverse effects
- the receptor as a target of drug action and related concepts such as agonism, antagonism, partial agonism and selectivity
- the development of tolerance to drugs

Clinical pharmacokinetics

- the mechanisms of drug absorption, distribution, metabolism and excretion
- the concepts of volume of distribution, clearance and half-life and their clinical relevance
- how these factors determine the optimal route, dose, frequency, and duration of drug administration

Factors that determine inter-individual variation in drug response

- adherence to therapy
- pharmacodynamic variation
- pharmacokinetic variation
- pharmacogenetic variation
- environmental variation
- pharmaceutical variation

Monitoring Drug Therapy

- the importance of monitoring the effect of drug therapy
- the ways in which this can be achieved (e.g. measuring plasma drug concentrations or assessing pharmacodynamic responses)
- the variable relationship between drug dose, plasma concentration and clinical effect

Adverse drug reactions

- the different types of adverse drug reactions
- the frequency of adverse reactions in primary and secondary care
- recognition of common susceptibility factors and how risks of harms can be minimised
- the importance of reporting adverse reactions and other approaches to pharmacovigilance

Drug-drug interactions

- the potential for drugs to interact to cause beneficial and harmful effects
- the mechanisms by which drugs interact (pharmaceutical, pharmacokinetic, pharmacodynamic)
- the ways in which interactions can be predicted and avoided

Medication errors

- the different types of medication errors
- the common reasons medication errors occur in practice
- the ways in which individual prescribers can reduce the risk of medication errors

Clinical drug toxicology

- the assessment, recognition and treatment of common intoxications (e.g. paracetamol)
- the principles of removing or counteracting the effects of toxic substances after ingestion
- toxicokinetics and toxicodynamics

Prescribing for special patient groups with altered physiology, pharmacokinetic handling and pharmacodynamic responses

- elderly patients
- children
- women who are pregnant, breast-feeding, or of child-bearing potential
- patients with renal or liver disease

Legal aspects of prescribing drugs

- categorisation of drugs as over-the-counter preparations, prescription-only medicines, controlled drugs
- the prescribing of 'unlicensed' preparations
- the responsibilities associated with prescribing controlled drugs

Developing new drugs

- drug development including clinical trials (Phase I to Phase IV)
- the approval process and major regulatory authorities in the relevant country
- the requirements of good clinical trial design
- consent, ethics, bias, statistics, dissemination of information

Understanding the principles and pitfalls of clinical drug trials

- Aims of the trial
- Relevance of the trial for health care
- Selection of patients, diagnostic criteria and sampling procedure, criteria for inclusion and exclusion
- Controls: crossover, separate control group, untreated, other therapy, placebo
- Design: double blind, single blind, open
- Randomisation of treatment

Concentration-effect studies, biomarkers

- Drug interaction
- Recording of effects (subjective and/or objective)
- Recording of adverse effects
- Statistical planning
- The author's conclusion: adequate, questionable, irrelevant or impossible?

Managing the prescribing of medicines in the health service

- the role of local formularies
- the role of drug & therapeutics committees
- the influences that affect individual prescribing choices
- the rational assessment of new drugs based on safety, efficacy and cost-effectiveness

Ethics of prescribing

- informed patient consent and adherence to therapy

Commonly used drugs

- the mechanism of action, the indications for use, the appropriate route, frequency and duration of administration, and the important contra-indications and adverse effects of commonly used drugs

Common therapeutic problems

- the management of common acute and chronic therapeutic problems

Alternative therapies and traditional medicines

- the motivations that lead patients to seek alternative therapies
- some common indications and appraisal of the evidence for their efficacy
- how such therapies interact with prescription drugs that patients are receiving

Drug information retrieval

- Retrieval of drug information for prescribers and other health care staff
- Acquisition of knowledge and practice in how to assess the value and reliability of drug information sources

Core Skills

Taking a drug history

- taking accurate information about current prescription and non-prescription drugs
- making an assessment of adherence to a medication regimen
- recording current and past adverse drug reactions and allergies

Prescription writing

- choosing a safe and effective drug and an appropriate dose
- writing accurate, legible, and legal prescriptions including controlled drugs
- keeping accurate records of prescriptions and response
- calculation of drug doses based on patient weight or a nomogram
- calculation of the strength of an infusion based on the required rate of drug administration
- prescribing oxygen (flow rate, delivery) and intravenous fluids

Drug administration

- selecting the appropriate route of administration
- administering subcutaneous, intra-muscular and intravenous injections
- preparing drugs for parenteral administration including mixing and dissolving drugs
- preparing and administering drugs by an infusion pump
- preparing and administering nebulized drugs
- advising patients about special modes of drug delivery e.g. inhaled, topical, insulin

Prescribing drugs in special groups

- elderly, children, pregnancy and breast-feeding, renal and liver failure

Prescribing drugs to relieve pain and distress

- palliation of pain and other distressing symptoms

Adverse drug reactions and interactions

- assessing drugs as a possible cause of symptoms and signs
- recognising the potential for adverse interactions
- reporting adverse drug reactions and interactions

Drug allergy

- recognising allergic drug reactions and taking a history of allergic reaction
- treating allergic reactions, emergency treatment of acute anaphylaxis

Clinical pharmacokinetics

- using core knowledge of pharmacokinetics to inform safe prescribing

Monitoring Drug Therapy

- identifying which therapeutic effect to observe
- using measurements of plasma drug concentrations appropriately (which and when)
- acting appropriately with the results

Analysing new evidence

- practising evidence-based prescribing
- assessing the validity of evidence presented on new drugs or therapies
- reading, assessing and criticising clinical studies
- spotting methodological flaws including sources of bias
- recognising the difference between clinical and surrogate end-points

Obtaining accurate objective information to support safe and effective prescribing

- using National Formularies
- accessing reliable drug information from medical journals and medical databases
- accessing Poisons Information Services
- assessing the reliability of varying sources of evidence and opinion

Obtaining informed consent to treatment

- providing patients with enough information about drugs to allow them to make informed decisions about their treatment
- discussing benefits and harms of drug therapy with the patients
- exploring patients' own views and wishes in relation to drug treatment

Core Attitudes

A rational approach to prescribing and therapeutics

- identifying the correct clinical diagnosis
- understanding the pathophysiological processes involved
- knowing the drugs that might beneficially influence these processes
- establishing the end-points with which to monitor therapeutic response
- assessing the potential harms and benefits of treatment
- communicating with the patient in making the decision to treat

Assessing the balance of benefit to harm

- recognising that there are harms and benefits associated with all drug treatments
- recognising these may differ between patients depending on a variety of factors
- recognising that doctors should monitor the effects of the drugs they prescribe

Recognising the responsibilities of a doctor as part of the prescribing community

- avoidance of wasteful prescribing and consumption of limited resources
- recognising the need to report adverse drug reactions for the common good
- controlling the availability of restricted drugs
- adhering to therapeutic guidelines and drug formularies as appropriate
- avoidance of indiscriminate prescribing of antibiotics

Recognising personal limitations in knowledge

- recognising the need to seek further information about drugs when faced with unfamiliar prescribing problems

Responding to the future

- recognising the need to update prescribing practices
- ensuring that patients benefit when possible from advances in medical knowledge
- recognising the need to assess the benefits and harms of new therapies
- knowing the limitations of applying clinical trial data to individual patients

Recognising the Effect of Drugs on the Environment

Addendum II.
Model Curriculum for Medical Specialisation in Clinical Pharmacology

22

INTRODUCTION

A medical clinical pharmacologist is a physician with an advanced knowledge of pharmacology and the skills needed to achieve the rational use of medicines (RUM) in individual patients and in the population at large. The former may include the direct care of patients and also includes consultations on patients with complex drug problems such as therapeutic failure, adverse drug reactions and drug interactions. This pattern will vary from country to country. Improving drug therapeutics more broadly includes, but is not limited to, work on drug development, drug utilisation (both analysis of current practices and research on ways to improve it), teaching and providing information about drug therapy, working in Drug and Therapeutics committees from local (hospital formulary) to regional, national, and international organisations, and other problems that arise during the practice of clinical pharmacology (see below).

AIM

This Model Curriculum is designed to enable the aspiring clinical pharmacologist to obtain the knowledge and skills needed to carry out this professional activity in an efficient and satisfying way. It is deliberately set to be broadly based and thus applicable to as many countries as possible.

ADMISSION REQUIREMENTS

Physicians are usually admitted to a clinical pharmacology training program after they have completed the requirements for registration as a practising physician in their geographic area. In addition they will often have completed 2-3 years of work as a practising doctor under supervision in one of the specialties in which drug therapy is the major means of treatment.

However admission requirements will vary depending on national needs and agreements.

We recognise that the above scheme represents the ideal for the training of clinical pharmacologists but in many parts of the developing world it may be necessary, for practical reasons, to reduce the scope of the training in order to see health care delivered by health care professionals with a relevant knowledge of clinical pharmacology. Other entry requirements in the form of preparatory/orientation training for general Medical Officers or general physicians are determined according to local conditions.

OTHER INTERESTS

A physician starting the program after initial medical registration or licensure may wish to acquire additional specialty training. This can be interspersed with clinical pharmacology training by special arrangement with the directors of both programs or following the clinical pharmacology training.

Syllabus Overview

The formal clinical pharmacology training program is normally a 3 year activity but can vary from 2 – 5 years depending on the country concerned. The activities include:

1. Formal instruction for the trainee to acquire the specialist fund of knowledge of a clinical pharmacologist which often involves working closely with basic pharmacology.
2. Clinical experience caring for patients with drug problems.
3. Research experience that advances therapeutics more broadly. In some countries CPT is a research intensive discipline entailing the production of a thesis.

1. *Formal instruction should include:*

- A review of the broad field of pharmacology including the topics covered in a medical school pharmacology course but at an appropriately high level. It is often of great benefit for the trainee to spend time in a basic pharmacology department and to experience work in such a laboratory including work with animals.
- Pharmacological topics of special relevance to the discipline are:

i. Critical evaluation of drug effects, both desired and adverse;
ii. Principles of research methods in humans, both experimental and observational ,eg clinical trials methods;
iii. Informed voluntary consent and ethics of research in humans;
iv. Data management and biostatistics;
v. Absorption, distribution, metabolism and excretion (ADME) of drugs in humans;
vi. Pharmacogenetics;
vii. Additional sources of variation among people in their dose-response, such as age, gender, pregnancy, liver and renal disease, drug interactions and environmental factors;
viii. Drug concentration measurement and techniques for monitoring drug therapy;
ix. Drug intoxications and poisoning, both intentional and accidental;
x. Drug tolerance, dependence and addiction;
xi. Pharmacovigilance and pharmacoepidemiology (including drug utilisation);
xii. Pharmacoeconomics;
xiii. The process of drug discovery, development and regulation;
xiv. Adherence to medication regimens;
xv. Drug information;
xvi. Other topics of local relevance.

The specific subject matter should be covered at the appropriate time in the complete curriculum.

2. *Clinicalexperiencecaringforpatientswithdrug problems*

The trainee should get substantial clinical experience consulting about or caring for patients with serious or complex drug problems with increasing responsibility as the trainee's knowledge and skill levels increase. Ideally, experience with infants and children as well as elderly patients should be included. This experience may be concentrated in one part of the program or spread throughout it.

3. *Researchexperiencethatenhancesknowledgeof drug therapy more broadly*

The trainee should be encouraged to identify, by the end of their first year of training, an area of drug therapy in which information could be improved, with benefit to future drug therapy. The trainee will then plan the research to be done, write the protocol, and obtain any necessary ethics committee approval for the work to proceed. This work will be done under supervision and the results reported in such a way that they can then be communicated to others, preferably by publication in a learned journal or monograph. Trainees with talents in research should be encouraged to complete a PhD thesis (or equivalent) in clinical pharmacology.
This research experience has been discussed in the broadest terms and should be applicable anywhere. What is important is for the trainee to develop the attitude that gaining new knowledge to improve drug therapy for an identifiable group of patients, no matter how few in number or how small the geographic area in which these patients live, is part of the practice of clinical pharmacology.

REQUIRED TRAINING RESOURCES

A clinical pharmacology training program must have resources for the curriculum to be carried out. This requires an adequate number of trained and committed staff, a sufficient number of patients with a variety of illnesses for adequate clinical pharmacology experience for the trainee, supporting clinical services including the ability to measure concentrations of drugs in human body fluids, and research facilities for the resident to carry out a research project.

A training program can be at a single institution with all the resources needed or through a consortium of institutions committed to the training program, their combined resources being adequate.

Further details of training programmes can be found in the literature (see references 101-106).

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