Clinical Pharmacology in Research, Teaching and Health Care.

Considerations by IUPHAR, the International Union of Basic and Clinical Pharmacology

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Addendum II
Abbreviations and Glossary

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<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ADR</td>
<td>Adverse Drug Reaction</td>
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<tr>
<td>ADME</td>
<td>Absorption, Distribution, Metabolism and Excretion</td>
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<td>AIDS</td>
<td>Acquired Immunodeficiency Syndrome</td>
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<td>CME</td>
<td>Continuing Medical Education</td>
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<td>CP</td>
<td>Clinical Pharmacology</td>
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<td>CRO</td>
<td>Clinical Research Organisation</td>
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<td>CPT</td>
<td>Clinical Pharmacology and Therapeutics</td>
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<td>CYP</td>
<td>Cytochrome P450</td>
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<td>DDD</td>
<td>Defined Daily Dose</td>
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<td>EMEA</td>
<td>European Medicines Agency</td>
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<td>EU</td>
<td>European Union</td>
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<td>FDA</td>
<td>Federal Drug Administration (in the USA)</td>
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<td>GCP</td>
<td>Good Clinical Practice</td>
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<td>GLP</td>
<td>Good Laboratory Practice</td>
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<tr>
<td>GMP</td>
<td>Good Manufacturing Practice</td>
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<tr>
<td>GXP</td>
<td>A combination of GCP and GMP.</td>
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<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
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<td>HTA</td>
<td>Health Technology Assessment</td>
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<td>IP</td>
<td>Intellectual Property</td>
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<td>IUPHAR</td>
<td>Internation Union of Basic and Clinical Pharmacology</td>
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<tr>
<td>NICE</td>
<td>National Institute for Health and Clinical Excellence</td>
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<td>NIH</td>
<td>National Institutes of Health (in USA)</td>
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<td>NMRA</td>
<td>National Medicines Regulatory Authority</td>
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<td>NPV</td>
<td>Net Present Value</td>
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<tr>
<td>NSAID’s</td>
<td>Non Steroidal Anti-Inflammatory Drugs</td>
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<td>OTC</td>
<td>Over The Counter</td>
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<td>PASS</td>
<td>Post Authorisation Safety Study</td>
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<td>PK</td>
<td>Pharmacokinetics</td>
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<td>PD</td>
<td>Pharmacodynamics</td>
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<tr>
<td>R&amp;D</td>
<td>Research and Development</td>
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<td>RCT</td>
<td>Randomised Control Trial</td>
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<td>RMP</td>
<td>Risk Management Plans</td>
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<td>RUD</td>
<td>Rational Use of Drugs</td>
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<td>TDM</td>
<td>Therapeutic Drug Monitoring</td>
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<td>WHO</td>
<td>World Health Organisation</td>
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Glossary

’in-silico’ The use of computers to simulate biological studies.

Note that the words ”drug” and ”drugs” are used interchangeably with ”medicine” and ”medicines” respectively.
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1. **Executive Summary.**

   a. **Definition** (see page 10) Clinical Pharmacology is the scientific discipline that involves all aspects of the relationship between drugs and humans. The term ’clinical pharmacologist’ is also used in the professional sense to refer to those physicians who are specialists in clinical pharmacology. They have undertaken several years of postgraduate training in many aspects of the above relationship involving teaching, research and health care. 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.

   Dr. Pisonthi’s comment:

   Many clinical pharmacologists are involved in several government and hospital policies on rational drug use, which also requires a skill and understanding of the cost-effectiveness issue of a treatment, besides the safe and effective use of medicine.

   b. **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. We hope they will realise the great benefits that expertise in clinical pharmacology can bring to the delivery of better health care for all populations.

   b. **Clinical Care.** Clinical pharmacology has developed a number of ways in which the clinical care of patients can be improved (pages 25–28). The prime aim is to improve the rational use of drugs both for individual patients and for patient populations wherever they may reside. The clinical pharmacologist will be expert in the critical evaluation of new and old therapies, and will use 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 will provide, in association 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 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 of patients.

   Dr. Pisonthi’s comment:

   It might be appropriate to mention the role of clinical pharmacologists in the area of rational use of antibiotics and the combat against drug resistance issues. Also worth mentioning are the roles of CP in the community such as in the dissemination of unbiased information on drugs and therapies, for example the notions about glucosamine (registered as drug in Thailand), Anti-Altzheimer’s, NSAIDs, polypharmacy etc.

   d. **Research** (pages 16–19) is a vital part of the training and everyday work of a clinical
pharmacologist. 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 patient populations. Clinical Pharmacological research has always been translational in the sense that the discipline aims to take new scientific data on drugs into rational patient care.

Clinical pharmacologists could be even better equipped to undertake ‘translational’ research, especially the design and execution of the early phase of drug studies in man (Phase 1). (see pages 15 and 17). Too few contemporary clinical pharmacologists are actively engaged in the design, Conduct, and improvement of clinical trials (see page 15)

e. Teaching is a vital part of the work of a clinical pharmacologist (see pages 20-24 and addenda I and II) Perhaps the most important area currently is the training of new prescribers which is primarily new physicians since pharmacists and nurses do comparatively little prescribing when looked at in a world-wide sense. The ability of new young physicians to prescribe safely and effectively has been criticised in recent years and new systems are being developed so that much more attention is paid to these skills in the training of medical students. Since assessment drives learning, the assessment systems are being improved too. Specialist training of 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.

Dr. Pisonthi’s comment
The summary above is truthful, yet unrealized by the majority of the members of the Faculties of Medicine. Young prescribers are unskilled (and likely to be incompetent in antibiotics prescriptions) and the probability of being proficient is dimmed, due to the fact that the practices in the real world are much worse than the controlled environment of the teaching hospitals. Prescribers have to be fully competent when they graduated. All essential knowledge, skills, and attitude have to be injected and augmented in sequences, until a protective immune response against the unhealthy prescribing behaviour has been achieved. This responsibility is truly the utmost essential role of a CP who teaches. Unfortunately, teaching is governed by the curriculum design and subject priorities. Hopefully, this manuscript will help shape the curriculum design and objectives, for those who are reluctant to change.

f. Pharmaceutical companies (see pages 29-32) have been at the forefront of helping to train clinical pharmacologists. While many of the skills acquired in such companies are useful for the general training of a clinical pharmacologist, (eg clinical trials) a long term career in such a company requires a new set of skills for which training is needed.

Pisonthi’s comment
In several countries, the speciality of pharmaceutical physicians is a recognised sub-speciality for example, the Faculty of Pharmaceutical Medicine sits under the umbrella of the Royal College of Physicians (UK) and sets exams for physicians looking to specialise in Pharmaceutical Medicine training.

Pisonthi’s suggestions are highlighted in blue.

g. Governments (see pages 33-36) need clinical pharmacologists to help deliver the goal of ensuring safe and effective drug therapy ensuring safe, effective and affordable drug therapy for their populations, whether the clinical pharmacologists are working in
hospitals, regulatory agencies, government policies’ task forces or in Health Technology Assessment. (HTA) 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.

i. Clinical pharmacologists have a crucial role (see pages 42-47) 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 [62]. The policies aim to ensure:

* The quality, safety and efficacy of medicines
* Equitable access to medicines for all the population, through the drug selection process of the hospital PTC or the National Essential Drug List committee
* The rational/quality use of medicines
* A viable and responsible local pharmaceutical industry.

Clinical pharmacologists could do much more to meet 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. Training of clinical pharmacologists to meet these needs will have to be rather different from that envisaged in 1970 when the first WHO report was published [1].

2. Introduction

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 drugs 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 ( £600 million, €700 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 (e.g. 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. Moreover, a therapy with acceptable cost effectiveness ratio needs to be evaluated further for the budget impact to the payers when introducing such therapy to the whole population, hence affordability is the final hurdle in the selection process of the national reimbursable drug list.

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 [2] 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 [3,4]. A specific group of drugs, especially those with higher usage, contributed more to the incidence of ADR such as antibiotics, NSAIDs and cough & cold remedies for small children. Many of these ADRs are predictable and could be prevented if the process of educating prescribers was taken more seriously and the emphasis on safety before efficacy in drug prescribing has been instigated. 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 [5]. These problems do not only affect resource-rich countries, although the scale of the problem may be less in resource-poor countries.

In countries where the drug registration processes are inadequate, many approved medicines, usually registered in the late 1970 to 1980, are of questionable efficacy and safety. The burden of re-evaluating and withdrawal of these drugs are enormous and usually exceeds the capacity of the clinical pharmacologists populace who have expertise in drug evaluation processes. Consequently, medication such as multi-purposes antidiarrheal e.g. furazolidone + iodoquinol + neomycin + sulfonamides + kaolin is still widely available and popular in some developing countries. Many drugs that have been banned or restricted in the developed world are conveniently accessed through drug stores. Injection is perceived as instant cure for a large proportions of patients in developing world, analgesics and antipyretics comprise of dangerous chemicals and in some countries, do not even exist in the pharmacopeia yet are used widely in clinics and small hospitals.

It is clear then the time has come to modernise the original WHO report in the hope that lessons will have been learned and the problems addressed. We hope that WHO itself will do this over the next year or so by a modification of this IUPHAR report. After a period of expansion in the last 20 years of the twentieth century, clinical pharmacology, as a discipline, declined somewhat in many countries despite the increasing problems in inappropriate drug use. However during the last few years there have been signs both of new growth in and new enthusiasm for the discipline [6], 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 [7].
This document aims to set the scene for clinical pharmacology in the early part of the 21st century using the concept of the original WHO report and updating it for IUPHAR, the International Union of Basic and Clinical Pharmacology. We have gathered a group of distinguished clinical pharmacologists who have written the individual sections which are designed to address the role of clinical pharmacology in health care, research and teaching 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 Drugs policy. However this document is primarily aimed at decision makers in a variety of organisations, particularly 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. Last but not least, educators involving in curriculum development in Medical Schools are also the targeted audience. We hope they will realise the great benefits that expertise in clinical pharmacology can bring to the delivery of better health care for all populations.

3. Definition of clinical pharmacology

Clinical pharmacology is the scientific discipline that involves all aspects of the relationship between drugs and man. Its breadth includes the development of new drugs, the application of drugs as therapeutic agents, the beneficial and adverse effects of drugs in individuals and society, and the deliberate misuse of drugs. Clinical pharmacology is a science that may be of significant interest to a variety of professions including physicians, pharmacists, nurses and scientists in many different disciplines.

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 (see Addendum II) focusing on important aspects of clinical pharmacology including clinical trials theory, drug evaluations, pharmacoepidemiology, pharmacoeconomics, pharmacogenetics, pharmacovigilance and clinical drug toxicology. Such clinical pharmacologists have as their primary goal that of improving patient care, directly or indirectly, by promoting the safer and more effective use of drugs.
4. History of clinical pharmacology

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 [8] 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 and academic subject clinical pharmacology is young having originated from the middle of the 20th century. It is difficult to find who first coined the name since 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 [8,9] is commonly quoted as the person who first introduced the name clinical pharmacology in the early 1940s. However, in 1914 a text book was written by Hans Horst Meyer and Rudolf Gottlieb 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[10]. According to Shelley and Baur his contributions escaped the attention of the English-speaking world[10].

In the English literature there is a long tradition of “materia medica”, particularly in Scotland. In 1884 John Mitchell Bruce wrote his text book 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 USA[11,12]. Important landmarks are the first edition of Goodman and Gilman’s “The Pharmacological Basics 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 1960’s 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[10,11]. In 1966 Lasagna published a brilliant, still valid, account in Science of the present status and future development of clinical pharmacology [11]. The birth of clinical pharmacogenetics can be ascribed to the pioneering contributions of Werner Kalow and A.G. Motulsky [13,14]. 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 usually are mentioned in this context are Sir John Gaddum, Sir Horace Smirk and Sir Austin Bradford Hill [8]. Chairs in clinical pharmacology were created at the end of the 1960’s 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 [15].

IUPHAR took early initiatives to develop clinical pharmacology. A section of clinical pharmacology was formed in the early 70s and a division in the 1990’s. 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 Raskowa in Czechoslovakia, who all realized 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[16]. For the first time the potential usefulness of the discipline for the rational use of drugs in primary health care was emphasized.

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 “practised” clinical pharmacology during their efforts to introduce new pharmaco-therapeutic principles into clinical medicine.
5. **Global Medicine Scene**

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. The uncontrolled and unwised uses of the miracle drugs “Antibiotics” lead to irrecoverable lost of their effectiveness in many parts of the world, the consequences of global magnitude are still to be seen in the near future.

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 health-care 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. For some medicines with marginal benefit, to prescribe those drugs routinely is considered “unaffordable” even for the higher income countries.

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 offer 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 organisations, 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 (eg in elderly patients). Added to this, many of the largest pharmaceutical companies are facing, by 2011, a reduction of 30-40% in turnover as their “blockbusters” come off patent.

There have also been spectacular withdrawals of some marketed medicines over the last few years 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 health technology assessment facilities, across Europe and North America, is because of the necessity to look ever more closely at the clinical and cost effectiveness of therapeutic strategies. In the developing world, other extreme measures such as compulsory licensing are also being applied by the governments in the struggle to cope with affordability and accessibility issues for the nation.

The Future Prospects

Despite this gloomy outlook, a number of relatively recent 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 USA [17] and the European Medicines Agency in the EU [18] 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. And, 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 organisations 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 either patients, healthcare systems or their shareholders [19]. 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. Some pharmaceutical companies together with other alliances have already set up special access programs for patients in need of their medicines at low cost or no cost at all. GSK’s flexible pricing program has cut down more than 50% of HPV vaccine price in Thailand. GSK, Merck, WHO and The World Bank have joined forces in the Global Alliance to Eliminate Lymphatic Filariasis to tackle this problem in 83 countries. Novartis’s Glivec donation program (GIPAP) allowed cancer patients in many developing countries full access to its medicines for free.

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,) made crucial contributions to healthcare 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 health technology assessment (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, those with rare diseases, and those with conditions that are endemic in the poorest parts of the world.
6. Roles of Clinical Pharmacology

6.1 Research

Introduction

In the first WHO report on clinical pharmacology in 1970 [1] the section on research emphasized the need for studies that explored the mechanisms of action of drugs and identified their pharmacokinetics in man. Improvement of the early studies of new drugs in man and conventional therapeutic trials were also prioritized. 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 on 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 priorities. All these research areas have great potential for supporting health care personnel in their rational use of drugs.

Rational use of drugs (RUD) implies that drugs should be chosen according to efficacy, adverse drug reactions 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). It also includes research on adverse drug reactions, pharmacogenetics and drug interactions. Research in clinical pharmacology is usually interdisciplinary and hence often carried out in collaboration with other professions: pharmacists, drug analytical chemists, molecular biologists, statisticians, computer specialists as well as clinical researchers from other medical specialties. Clinical pharmacologists have responsibilities to promote rational use of drugs in all levels of health care. While those who work in the training facilities such as medical schools and their affiliations, have a vital role to set the examples of safe, effective & low cost prescriptions for their trainees. These are pivotal elements that are much needed in this era.

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 metabolizing 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 (see glossary). 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 trials phases I - III**

Important research areas are to improve the methods used to evaluate drugs in man. 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 Randomized 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 [20]. 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 since 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 adverse drug reactions 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.

In some developing countries it is mandatory for a generic product to show bioequivalence to its original counterpart before it can be registered. The demand for clinical pharmacologists who have expertises in such activities are tremendous, especially when the generic drug policy is warranted by the government.

**Therapeutic drug monitoring**

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 given dose 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 CNS-active drugs or anti-infective agents used to treat localised tissue infections.
TDM research on 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.

Following the mapping of the human genome and the revolutionary developments in biotechnology and human molecular medicine, research at the beginning of the 21st century mainly aims at understanding the role of genetic variation in the capacity or function of drug metabolizing 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 3-5,000 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 adverse effects should be known and in particular those that are predictable from its basic pharmacological properties or readily explained in the context thereof. However, at marketing, serious or even lethal but very rare adverse drug reactions 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 adverse drug reaction reporting is carried out in order to detect unknown potential drug toxicity. The method consists of collecting individual case reports of clinical suspicions of adverse drug reactions. Data mining in adverse drug reaction research is the search for structures and patterns in large adverse drug reaction 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 utilization studies

Clinical pharmacologists play a key role in drug utilization 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 utilization by Defined Daily Doses, DDD, which by definition is the typical maintenance dose of the drug in an adult for its main indication. These drug utilization evaluations have been used as tools for hospital PTCs to restrict the irrational use of essential drugs, especially reserved antibiotics such as carbapenems and vancomycin.