The Textbook of Pharmaceutical Medicine

EDITED BY

John P. Griffin

BSc, PhD, FRCP, FRCPath, FFPM
Director, Asklepieion Consultancy Ltd.
Formerly Director of the Association of the British Pharmaceutical Industry, London
Formerly Professional Head of the Medicines Division, DOH, London (now MHRA)

6TH EDITION

WILEY-BLACKWELL
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From 1976 to 1984 John P. Griffin served on the Joint Formulary Committee of the British National Formulary, during which period the first eight issues of the current format were produced.

John P. Griffin was the director of the Association of the British Pharmaceutical Industry from 1984 to 1994. During this time he was a member of the Executive Board of the European Federation of the Pharmaceutical Industries' Associations and IFPMA. He chaired the ICH Safety Working Group from 1988 to 1994 and presented papers at ICH1 and ICH2 in the plenary sessions.

Since June 1994, John P. Griffin has run his own independent consultancy company, which has provided independent and impartial advice to governments on the development of a pharmaceutical policy, and to national trade associations and individual companies. John P. Griffin was Visiting Professor in Pharmaceutical Medicine at the University of Surrey, for 6 years and was also Honorary Consultant Clinical Pharmacologist at the Lister Hospital in Hertfordshire, UK.

Professor Griffin was on the Board of the Faculty of Pharmaceutical Medicine for 12 years, was Chairman of the Board of Examiners of the Faculty of Pharmaceutical Medicine of the Royal College of Physicians for 7 years, and was Academic Registrar and served on the Task Force on Specialist Medical Training in Pharmaceutical Medicine. He has served on a number of Royal College of Physicians, London Working Parties including that on the 'Development of Clinical Pharmacology and Therapeutics in a Changing World'.

Professor Griffin is the author and co-author of over 250 publications on adverse drug reactions and iatrogenic disease, aspects of neurophysiology and clinical pharmacology and toxicology and drug regulation. Notable among his publications are the following four standard texts:

- *Iatrogenic Diseases.* Oxford University Press, 1st edn 1972, 3rd edn 1986; jointly with Professor PF D'Arcy.
- *A Manual of Adverse. Drug Interactions.* John Wright, Bristol, 1st edn 1975; Elsevier Press, Amsterdam, 5th edn. 1997; jointly with Professor PF D'Arcy.
- *The Textbook of Pharmaceutical Medicine.* The Queen's University of Belfast Press, 1st edn 1993, 2nd edn 1994, 3rd edn 1998, 4th edn 2002 published by the BMJ Publishing Group in 2002, 5th edn. 2006 Blackwell.
- *Medicines, Research, Regulation and Risk.* The Queen's University of Belfast Press, 1st edn 1989, 2nd edn 1992.

From 1991 to 2003 he served as Editor in Chief of *Adverse Drug Reactions and Toxicological Reviews*, a peer-reviewed journal produced quarterly by Oxford University Press.

In 2005 he was awarded the Faculty of Pharmaceutical Medicines Commemorative Medal for outstanding services to the Faculty.

John Griffin
London
2009

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Preface: the development of pharmaceutical medicine as a specialty in the UK

The UK is at the forefront in the recognition of pharmaceutical medicine as a fulfilling career for physicians, enabling them to make a major contribution to patient and public welfare, both in terms of bringing new medicines to market and of ensuring their safe and effective use. The Faculty of Pharmaceutical Medicine has been instrumental in supporting pharmaceutical physicians and in achieving specialty recognition in the UK in order to achieve and ensure the practice of the highest standards for the benefit of patients. As with all other recognised medical specialties in the UK, achievement of specialist registration confers a comparable standard of professional competence. As such, speciality training in pharmaceutical medicine will continue to evolve in line with other UK specialties.

Compared with the history of many other medical and surgical specialties, pharmaceutical medicine is a relative newcomer. Despite having only a relatively short history it has made major strides and, in the UK, has overtaken certain other medical specialties in terms of trainee numbers and viability.

Pharmaceutical medicine is a medical specialty concerned with the discovery, evaluation, licensing and monitoring of medicines and the medical aspects of their marketing. Physicians practising in pharmaceutical medicine have, in the past, mainly worked for pharmaceutical companies although more recently there has been a shift towards a greater number working in the regulatory agencies, contract research organisations and, now, a substantial proportion being independent contractors. The pharmaceutical industry itself has a rather longer history. Its formal beginnings were in 1891 when the Drug Club was set up. The members were not companies as would be recognised today but were certainly the forerunners. The members of the Drug Club had to be principals of wholesale druggists and at the time of the first meeting in February 1892 there were 50 members. In 1929 the Wholesale Drug Trade Association was formed and the Drug Club was wound up. This organisation was renamed the Association of the British Pharmaceutical Industry (ABPI) in 1948. It was probably around this time that physicians started to provide advice to pharmaceutical companies on medical matters although there were few who did so and for those who did it was usually in addition to their other medical work rather than as a full-time employee of a company. It may have been lucrative but it would certainly not have been considered prestigious.

However, the 1950s saw the introduction of a large number of therapeutic agents and in parallel there was a need for informed medical advice to the pharmaceutical companies. As a consequence, there was a rapid expansion of doctors employed by those companies to advise on drug development and medico-marketing. Inevitably, these doctors were breaking new ground and the need for peer support and a forum in which to share issues and ideas resulted in the formation, in October 1957, of the first pharmaceutical physicians' association, the Association of Medical Advisers in the Pharmaceutical Industry (AMAPI). AMAPI also provided some training.

The term 'pharmaceutical physician' came into use in the mid-1970s and, in 1986, AMAPI changed its name to BrAPP – British Association of Pharmaceutical Physicians – to reflect this new nomenclature.

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AMAPI grew rapidly from its original 20 or so members to about 700 in the mid-1980s of whom around one-quarter were from overseas. An enlightened group of physicians from within this fraternity realised that if pharmaceutical physicians were to develop further their chosen career paths within medicine, they needed to establish an organisation alongside the medical Royal Colleges which would set and continually develop high ethical and professional standards in the practice of pharmaceutical medicine. The primary aim of this charitable organisation would be to promote the science of, and knowledge in, the field of pharmaceutical medicine for the benefit of patients and the public – a different remit from that of the AMAPI.

Thus, with very considerable support and advice from the Royal College of Physicians of London, the Royal College of Physicians of Edinburgh and the Royal College of Physicians and Surgeons of Glasgow, the Faculty of Pharmaceutical Medicine was established in 1989 as a Faculty of all three colleges and as a registered charity. The Faculty now has a membership of over 1300 pharmaceutical physicians with almost 40% working overseas in nearly 40 countries. The membership is primarily physicians who work within the pharmaceutical industry, contract research organisations and regulatory agencies or who are self-employed.

Back in the mid-1970s, AMAPI and ABPI, in collaboration with the University of Wales Institute of Science and Technology (later Cardiff University), set up a 2-year modular postgraduate course to prepare physicians for the examination in pharmaceutical medicine – the Diploma in Pharmaceutical Medicine. Originally, the responsibility for the examination rested with the three parent medical Royal Colleges. With the establishment of the Faculty as the standard setting body, it was entirely appropriate that in 1994 responsibility for the setting, conduct and adjudication of the examination, together with awarding the Diploma, passed to the Faculty. The syllabus has been updated regularly and has acted as a template for other diplomas in pharmaceutical medicine in other countries. The format of the examination has evolved such that it now includes a multichoice question paper but, as from the outset, comprises written and oral components. A Board of Examiners, comprised of over 40 of the Faculty membership and around 10 external medical and scientific colleagues, are responsible for all aspects of the examination, including question setting, conduct of the examination and marking. The pass rate is comparable to that of the Membership examination for the Royal College of Physicians.

Some 10 years after the formation of the Faculty, towards the end of the century, the Trustee Board of the Faculty took the decision to work to establish pharmaceutical medicine as a recognised speciality. In the late 1990s, in conformance with the European Specialist Medical Qualifications Order 1995, the UK introduced specialist medical training for clinical specialties leading to the granting of a Certificate of Completion of Specialist Training (CCST). The introduction of specialist training afforded pharmaceutical medicine, through the Faculty, the opportunity to seek equivalent recognition as a listed specialty and for pharmaceutical physicians to gain a CCST-UK and then apply to be listed on the General Medical Council (GMC) Specialist Register. If the Faculty could put in place all the requisite processes and documentation to achieve this, pharmaceutical physicians would be able to undertake Higher Medical Training (HMT) in this specialty as with other medical specialties in order to be recognised for entry onto the GMC Specialist Register. [The CCST became the CCT (Certificate of Completion of Training) in 2005.]

There was a very considerable amount of work for the Faculty to do to prepare the requisite documents and define its procedures in compliance with the requirements of the Specialist Training Authority (STA) of the medical Royal Colleges in order to apply to become a recognised specialty. A curriculum had to be prepared for approval and a system had to be set up to ensure each trainee had a Senior Specialty Adviser (SSA) as well as an Educational Supervisor (ES) – all of whom would have to be trained by the Faculty. The SSA is a joint appointment by the Faculty and the Lead Dean for Pharmaceutical Medicine who is also a Dean of Postgraduate Medical and Dental Education. The Lead Dean is responsible for quality managing the training programme across the UK. The role of the SSA is to oversee the delivery of the training programme in a specified number of approved training sites – usually determined geographically or, for the larger ones, by company or institution. It is a role of considerable responsibility as the Specialty Advisory Committee (SAC) of the Joint Royal Colleges of Physicians Training Board (JRCPTB) on Pharmaceutical Medicine relies very heavily on these committed individuals, who are usually Fellows of the Faculty, to assure ongoing quality of the training sites. The Educational Supervisor role also carries considerable responsibility. It is a mandatory requirement that the ES must be a registered doctor and an experienced

pharmaceutical physician, normally a Member or Fellow of the Faculty, and must be familiar with the trainee's work and able to oversee the medical work of the trainee. The ES is normally the trainee's medical manager working in the same organisation. The ES carries overall responsibility for the supervision of training for the trainee including the conduct of educational and performance appraisals, assessments of performance and competency and ensuring availability of and access to the components of the curriculum.

It was also a requirement that the Faculty establish a process for reviewing progress throughout the period of HMT in Pharmaceutical Medicine in the form of the annual Review of In-Training Assessments (RITAs). This process was set up in line with that established for clinical trainees within NHS bodies except that evidence of experience would be documented in the context of work-related modules rather than clinical ward-based practice.

Hard work and patience were eventually rewarded and in 2002 the Secretary of State signed his agreement to pharmaceutical medicine becoming a recognised specialty. The first National Training Numbers (NTNs) were issued in March 2003, and 73 pharmaceutical physicians had started their specialist training by the end of that year. No doubt these first trainees entered the programme with some trepidation as they were stepping into unchartered waters. This recognition of pharmaceutical medicine as a specialty was a major milestone for pharmaceutical physicians. No longer could they be considered outside of mainstream medicine. Their training programme and standards achieved had been externally validated and recognised to be at least equal to that of any other medical or surgical specialty. Pharmaceutical medicine was truly born even if it did still have some further steps to take to achieve complete independence. Between 2002 and 2007 pharmaceutical medicine existed as a specialty under the umbrella of Clinical Pharmacology and Therapeutics, but as the specialty rapidly expanded it became clear that it needed its own separate identity in line with all the other medical specialties that constituted the Joint Committee of Higher Medical Training (JCHMT) and its successor, the JRCPTB. This independence was achieved in 2007 with the establishment of the Specialty Advisory Committee on Pharmaceutical Medicine of the JRCPTB and pharmaceutical medicine 'became of age'.

The regulatory work of the STA was transferred to the newly formed Postgraduate Medical Education and Training Board (PMETB) in 2005. One of the roles of this body is responsibility for approving both the training site and the individualised (*ad personam*) training programme. At about this time, agreement was gained for the training to be approved across a group of company sites, such approval remaining appropriate for whatever individual might be in post (if they were registered for training). This change in arrangements allows trainees to move more easily within a company within the UK, or even across Europe and beyond, provided that the company's programme is approved for training, that the curriculum can be delivered in its entirety and that appropriate named supervisors are available. The Faculty of Pharmaceutical Medicine, in conjunction with the Lead Postgraduate Dean for the specialty, monitors the training programmes approved within companies, and it provides, on an annual basis, the regulatory body with evidence gathered from trainees, trainers and from on-site visits, evidence of appropriate quality management.

The growth in trainee numbers is a major success story reflecting the commitment of those entering pharmaceutical medicine to their chosen specialty and to working to achieve the highest standard of professional competence for the benefit of both patients and the public. Around 40 new trainees enter the training programme each year. As of mid-2009, there are approximately 195 pharmaceutical physicians who have NTNs and are actively undertaking specialty training and 90 who have completed their training and are on the GMC Specialist Register as a consequence of undertaking specialty training in pharmaceutical medicine.

Structured training in pharmaceutical medicine, whether through the old curriculum of basic and higher specialist training, or the new (from 2007) Pharmaceutical Medicine Specialty Training (PMST) programme, requires commitment, enthusiasm and application. In preparation for training, doctors must have completed 4 years of clinical medicine following qualification (or 3 years for those qualifying prior to August 2005).

The revised (2007) curriculum for PMST sets out six specialty specific modules: Medicines Regulation, Clinical Pharmacology, Statistics and Data Management, Clinical Development, Healthcare Marketplace and Drug Safety Surveillance. Each module comprises up to 10 items and the trainee must attain a specified level of competence for each item. In addition, there is a generic module, in line with all UK specialty training programmes, encompassing Interpersonal and Management Skills and, for pharmaceutical medicine,

the tenets of Good Pharmaceutical Medical Practice as approved by the GMC. Trainees are required to produce a portfolio of validated documented evidence to demonstrate that this level of competence has been achieved and each item has to be authenticated and signed off by the ES trained and approved by the Faculty. The trainee must identify a minimum of at least two modules which must be undertaken in their entirety in the workplace in addition to the generic module. The other modules can be undertaken in their entirety by attendance and completion of assignments at Faculty approved courses or can be achieved by a mixture of work-based assessments and attendance at other courses. The majority of trainees complete considerably more than the required minimum number of courses through in-house experience.

To facilitate appropriate and adequate collection of information as evidence of satisfactory achievement of competencies, trainees require the self-discipline and rigour of integrating their programme with their day-to-day work and it is this evidence that is reviewed by a panel of assessors at the Annual Review of Competence Progression (ARCP), formerly the RITA process. As a guide, the volume of documentation required is likely to be a full Lever Arch File for each module although frequently a piece of work can be used to fulfil the requirements for items within two or more different modules. All evidence within a Training Record can be appropriately anonymised with respect to confidential matters but it has to be clear that the work submitted is that of the trainee personally, whether by their name appearing on, for example, the front sheet of the protocol or by authentication as such by the ES. In future, it is likely that such authentication will be supported by a related entry of 'reflective learning' which will summarise what the trainee will have learnt from that particular experience. Original records may be archived within company records but they must be available for inspection in the event of an audit by the PMETB. In line with the requirements of the PMETB, the specialty is developing a set of tools to support workplace-based assessments. These will be validated tools which will align with the curricular requirements and they will enable the ES to document the trainees' progress through their daily work. In addition to satisfactory completion of all the modules of the programme, success in the Diploma of Pharmaceutical Medicine is an absolute requirement prior to the issue of a CCT.

For UK pharmaceutical physicians, revalidation, involving relicensing as a physician, and recertification for those who are on the specialist register, will be mandatory within the next few years if those physicians want to remain licensed to practise with the GMC. It will be the responsibility of the Faculty to put in place for its physicians a system for recertification whose processes and standards are acceptable to the GMC. The Faculty will also be working with the GMC to enable all pharmaceutical physicians to relicense and remain on the general medical register.

Pharmaceutical medicine has come a long way and would not be recognisable, in terms of its acceptance as a specialty and the consequent high standards it demands, to those physicians who gave advice to drug wholesalers and companies while undertaking their main medical practice some 60 years ago. But it still has a long way to go. It is recognised as a specialty in only a very few countries other than the UK (Mexico, Switzerland, Eire) and few countries hold examinations of an equivalent standard to the UK Diploma of Pharmaceutical Medicine. Yet it is a global specialty and, in the interests of patient and public safety and benefit, there needs to be an extension of the standards set by the Faculty of Pharmaceutical Medicine in the UK and similar bodies elsewhere, so that pharmaceutical medicine becomes recognised as a medical specialty in all countries where it is practised.

Susan Bews and Huw Jones
2009

The contributions provided by the authors and any opinions or views expressed therein are their personal views and do not necessarily reflect the views or opinions of the companies for which they work or their employees.

Part I Research and development

1 Discovery of new medicines

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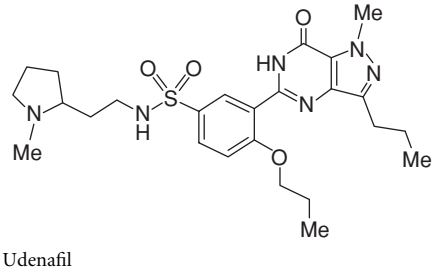
1.1 Introduction

Ancient civilisations, like modern society, had a keen interest in the health of man and other animals. Continuation of this interest over a period of time led to the discovery of a large number of therapeutic agents primarily from the natural sources; many of the natural sources are still being used as lead structures for the discovery of new drugs. In more recent times (~50 years), with the involvement of a large number of pharmaceutical companies and many academic institutions, progress in the understanding of the disease processes and mechanisms to control or eliminate the disease has accelerated. Similarly, despite the advances and achievements of the last 50 years, the need to discover treatments for existing and evolving diseases has also increased. This is primarily because of the inadequacies of current medicines. In many cases treatment only leads to symptom relief or cure is associated with undesirable side effects. In infectious diseases such as tuberculosis, malaria and HIV, resistance or tolerance may develop to existing treatments, thus making them ineffective against the infecting bacteria, parasite or virus.[1–3] New infectious agents such as severe acute respiratory syndrome (SARS), hepatitis C, human herpes virus-6, -7 and -8 and bird flu (H5N1 virus) are also appearing.[4] In addition, with changing environmental factors, lifestyle and increasing lifespan, more pathological abnormalities that require new treatments are being identified. Obesity and a number of cardiovascular diseases have their origins in altered (more prosperous?) lifestyle habits including environmental and psychosocial factors and diet. Prevalence of obesity is rising worldwide and there are few drugs currently available for treatment. Obesity appears to be a risk factor for other diseases such as cardiovascular disease, diabetes, some forms of cancer and severe asthma.[5,6] Changing social attitudes are also creating markets for the so-called 'lifestyle' drugs. Although the term 'lifestyle' drug is applied currently to drugs such as sildenafil for erectile dysfunction[7] and minoxidil or finasteride for baldness, the precise definition of 'lifestyle' drugs is a subject of debate.[8] Designer steroids also have the potential to produce various agents that can be useful as lifestyle drugs and drugs of abuse.[9] Treatment of erectile dysfunction is currently based on oral phosphodiesterase-5 inhibitors (e.g. sildenafil, vardenafil, udenafil (**1**) and tadalafil). Increasing use of drugs for illicit purposes (substance abuse), such as opiates, cannabis, cocaine and amphetamines, is creating a need for additional treatments to manage and treat drug addiction and mental disorders associated with many of the illicit drugs.[10,11] Addiction is broadly defined as a chronic brain disease that involves complex interactions between repeated exposure to drugs along with biological (i.e. genetic and developmental) and environmental (i.e. drug availability, social and economic variables) factors. Although some agents such as methadone, buprenorphine (Subutex) and naloxone are available to control opiate addiction, treatments



1 Udenafil

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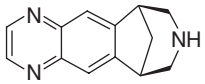


2 Varenicline

for addictive substances are generally lacking.[12] In addition to these illicit drugs, treatments are also required for tobacco and alcohol addiction.[13,14] Nicotine patches are available as nicotine replacement therapy for tobacco addiction and recently a nicotinic $\alpha_4\beta_2$ partial agonist varenicline (Champix) (**2**) has been launched as a non-nicotine therapy. Varenicline partially activates the nicotinic receptors and reduces the severity of craving for nicotine as well as withdrawal symptoms. Approved medicines for the treatment of alcohol abuse include the aldehyde dehydrogenase blocker disulfiram, the opioid antagonist naltrexone, the functional glutamate antagonist acamprosate and topiramate.[15]

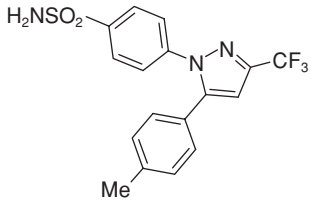
Increasing knowledge about the underlying causes of diseases is enabling the discovery of more selective and less toxic drugs. Progress in molecular biology (e.g. sequencing of the human genome, proteomics, pharmacogenomics and protein engineering) is creating new avenues for understanding precise disease mechanisms (biochemical pathways) and the discovery of new targets based on new disease pathways. Advances in the field are expected to lead to highly selective and efficacious medicines. Recombinant technologies are now enabling the synthesis of larger biologically active proteins in sufficient quantities. Proteins and monoclonal antibodies are therefore becoming more important and common as therapeutic agents. More vaccines are being developed against infectious diseases.

Equally important is the progress being made in the fields of combinatorial chemistry, enabling the synthesis of millions of compounds. High-throughput screening technologies and other automation techniques are facilitating more rapid drug discovery. In the longer term, a combination of all these new developments is likely to generate safer and more effective medicines, not only for the existing diseases, but also for the diseases of the future which may become more important as a consequence of lifestyle changes and increasing age.

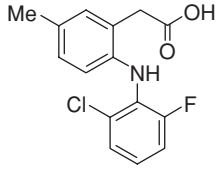
Malaria (caused in humans by single-celled *Plasmodium* protozoa parasites), tuberculosis (caused by *Mycobacterium tuberculosis*) and leprosy (caused by *Mycobacterium leprae*) can be considered examples of 'older' diseases still in need of more effective and cheaper treatments. Each year, 300–500 million people contract malaria and about 2–3 million die. A number of medicines, including chloroquine, 4-aminoquinolines, atovaquone, malarone, halofantrine, mefloquine, proguanil and artemisinin derivatives, are available for treatment.[16,17] Three main types of vaccines, based on the three major phases of the parasite life cycle, are being developed: antisporozoite vaccines designed to prevent infection (pre-erythrocytic vaccines); anti-asexual blood stage vaccines (anti-invasion and anticomplication) designed to reduce severe and complicated manifestations of the disease; and transmission-blocking vaccines aimed at arresting the development of the parasite in the mosquito itself.[18] A number of vaccines are in phase I and II clinical trials. Monoclonal antibodies against specific malarial antigens are being explored for diagnostic and potential therapeutic purposes. In addition, efforts are beginning to be made to shed light on the origin of the development of resistance in specific cases. Discovery of complete genome sequences of the human malaria parasite *Plasmodium falciparum* and the malaria-transmitting mosquito *Anopheles gambiae* is likely to enhance the discovery of antimalarial drug candidates.

Like malaria, tuberculosis and leprosy are more common in less developed countries. Tuberculosis is the second leading cause of death worldwide, killing nearly 2 million people each year. Multidrug-resistant tuberculosis continues to be a serious problem, particularly among some countries of Eastern Europe, China and Iran. Currently available drugs for tuberculosis include isoniazid, rifampicin, pyrazinamide and ethambutol. Further work is ongoing to discover new tuberculosis targets and drugs.[19–22] Several vaccines, including subunit vaccines and live vaccines such as recombinant bacille Calmette–Guérin (BCG) and other attenuated live vaccines, are currently in development for the prevention and treatment of tuberculosis.[23] The goal is to obtain a new generation of vaccines (superior to BCG), effective against more transmissible forms of tuberculosis. The first-line drugs against leprosy are rifampicin, clofazimine and dapsone. Other drugs such as minocycline, the macrolide clarithromycin and the fluoroquinolones pefloxacin and ofloxacin are all highly active against *M. leprae* but because of their cost are rarely used in field programmes.

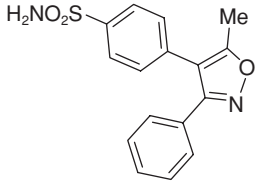
Bone disorders such as arthritis, osteoporosis and Paget's disease are examples of diseases that are becoming increasingly important with the ageing population.[24,25] Anti-inflammatory glucocorticoids such as prednisolone and methylprednisolone, and



3 Celecoxib



4 Lumiracoxib



5 Valdecoxib

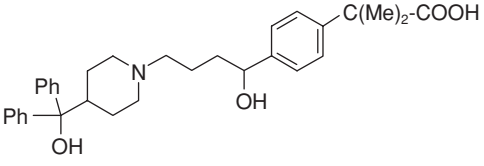
immunosuppressants such as ciclosporin and dexamethasone are used for treatment. Although the treatment options have increased recently, most of these therapies focus on addressing the symptoms rather than the underlying causes of the disease. For example, cyclo-oxygenase-2 (COX-2) inhibitors such as celecoxib (**3**), lumiracoxib (**4**), etoricoxib,[26] valdecoxib[27] (**5**) and parecoxib (prodrug of valdecoxib) are being marketed as safer non-steroidal anti-inflammatory drugs (NSAIDs).[28,29] Although the older NSAIDs are highly effective as analgesic, antipyretic and anti-inflammatory agents, long-term ingestion causes gastric lesions. The discovery that the COX enzyme, which catalyses the conversion of arachidonic acid to prostaglandin H_2 (common biosynthetic precursor to prostaglandins and thromboxane – mediators of physiological and pathological processes, including pain, fever and inflammation),[30] exists in two isoforms, with COX-2 being the primary isoform at sites of inflammation, led to a suggestion that inhibition of this isoform accounts for the therapeutic benefit of NSAIDs whereas inhibition of COX-1 results in adverse effects. The newer COX-2 selective agents appear to have a superior gastrointestinal safety profile. COX-2 inhibitors are also being investigated for the prevention and treatment of colorectal cancer. In addition to COX-2 inhibitors, inhibitors of matrix metalloproteinases (MMPs) are emerging for the treatment of many diseases including arthritis. Enzymes that degrade the extracellular matrix are normally controlled by a set of tissue inhibitors that, if disrupted, will allow the enzymes to work unchecked, degrading the matrix and promoting not only arthritis but also tumour growth and metastasis. Another treatment option is inhibition of tumour necrosis factor α (TNFα), an inflammation-promoting cytokine associated with multiple inflammatory events, including arthritis. Anti-TNFα therapies are already on the market.

Recently, the process of drug discovery has been expanded to cover a range of molecular biology, biotechnology and medicinal chemistry (including combinatorial chemistry) techniques. The newer disciplines such as genome analysis, proteomics and bioinformatics are likely to lead to many new targets (e.g. receptors, enzymes) and therapeutically important proteins. Techniques such as combinatorial chemistry and high-throughput screening are expected to identify hits/leads against various therapeutically important receptors and enzymes. Depending upon the knowledge available on the receptor or the enzyme of interest, the hits/leads can then be modified in a random, semi-rational or rational manner to generate drug candidates. From the commercial point of view, this progress is essential as the discovery process becomes more expensive and more generic drugs become available.[31] Some of the best-selling drugs of today that have either come off patent recently or are near the end of their patent-protected life include alendronate, cetirizine, interferon β-1b, risperidone, lansoprazole, atorvastatin, docetaxel, donepezil, pioglitazone, clopidogrel, enoxaparin and sildenafil.

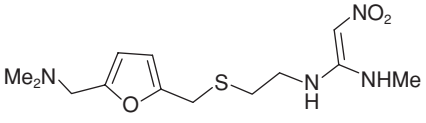
As in earlier chapters in the 4th and 5th Editions of the book,[32] this chapter includes a short account of the historical aspects[33] and a short introduction to some of the newer disciplines. The main objective of the chapter is to give an idea about the changing disease patterns which may be reflected in the discovery process, examples of receptor agonists and antagonists, enzyme inhibitors (including signal transduction inhibitors) and inhibitors of protein–protein interaction that have been discovered by random and 'semi-rational/rational' approaches, antibody, vaccine and protein therapeutics and currently available drugs for more widespread diseases. This enables one to understand actual drug discovery procedures and the science that has led to many drugs currently on the market and also gives an idea about the currently

available drugs for the treatment/prevention of various diseases. Examples of some of the commonly used drugs to treat various diseases (acting by different mechanisms) include:

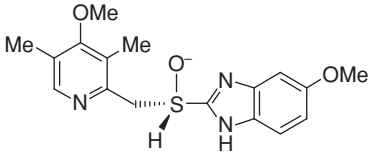
- COX inhibitors (**3**–**5**);
- Angiotensin-converting enzyme (ACE) inhibitors (antihypertensives such as captopril and lisinopril);
- Histamine H_1 receptor antagonists [anti-allergic compounds such as fexofenadine (**6**)];
- Histamine H_2 receptor antagonists [acid secretion inhibitors such as cimetidine and ranitidine (**7**)];
- Proton pump inhibitors [acid secretion inhibitors such as omeprazole and esomeprazole (**8**);[34]
- Nuclear peroxisome proliferator activated receptor-γ activators such as pioglitazone (**9**) and troglitazone (type 2 diabetes mellitus treatments);
- Lipid-lowering agents such as atorvastatin (**10**) and rosuvastatin and cholesterol absorption inhibitor ezetimibe (**11**);[35]
- Anti-influenza treatments such as zanamivir (**12**);[36]
- Acetylcholinesterase inhibitors such as donepezil (**13**) for the treatment of Alzheimer's disease;



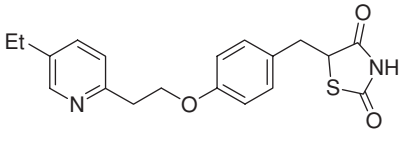
6 Fexofenadine



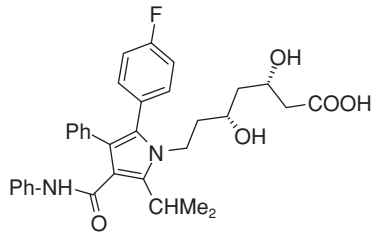
7 Ranitidine



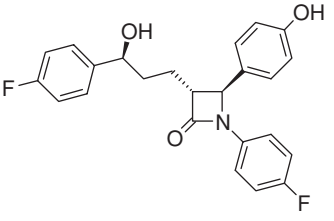
8 Esomeprazole



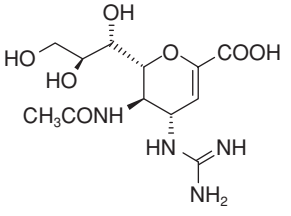
9 Pioglitazone



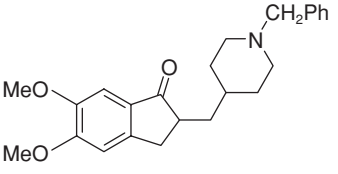
10 Atorvastatin



11 Ezetimibe



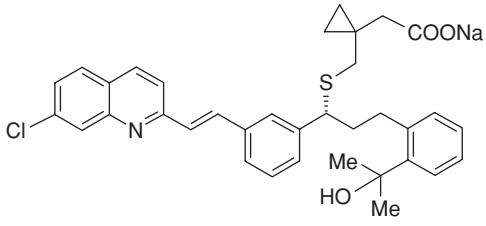
12 Zanamivir



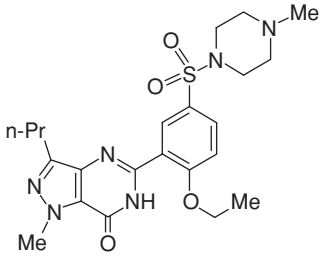
13 Donepezil

- Selective and competitive inhibitor of the cysteinyl leukotrienes (LTC_4, LTD_4 and LTE_4) such as zafirlukast and montelukast (**14**) for the treatment of asthma;
- Sildenafil (**15**) and udenafil (**1**) (inhibitors of phosphodiesterase type 5 used for erectile dysfunction);
- Antiobesity drugs such as orlistat (**16**);
- Atypical antipsychotic agents such as quetiapine (**17**) and olanzapine (**18**); and
- Immunosuppressant drugs such as tacrolimus (FK506) (**19**), ciclosporin (calcineurin inhibitors)[37] and everolimus.[38]

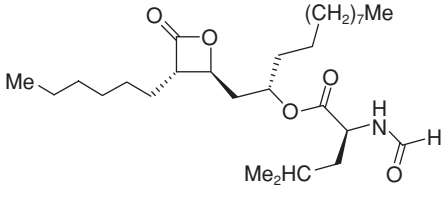
It may be useful to mention at this stage that many of the highly successful drugs launched in the last



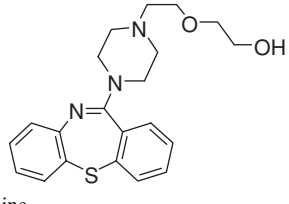
14 Montelukast



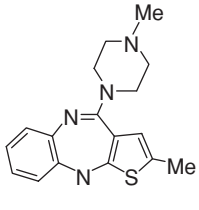
15 Sildenafil



16 Orlistat

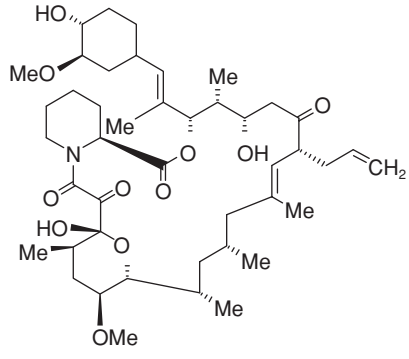


17 Quetiapine



18 Olanzapine

25 years were discovered in the pre-genomic era and the real contribution of all the new technologies mentioned above remains to be proven. In some cases the drug was initially investigated for different indications. For example, sildenafil was being investigated



19 Tacrolimus

in the clinic as an anti-anginal drug when its beneficial effects in improving erectile function were observed.

1.2 Market needs and changing disease patterns

From the point of view of the discovery of new medicines, it is important to project changing disease patterns and markets so that the new drugs may become available early. Currently, the industrialised world accounts for 11–12% of the global burden from all causes of death and disability but >90% of health expenditure; most of the remainder is spent in the form of public health aid. The Global Burden of Disease Study initiated in 1992 by the World Bank in collaboration with the World Health Organization (WHO) has sought to quantify mortality, life expectancy and risk factors for different regions of the world, and to project trends in mortality and disability in 2020. Of the 10 leading causes of death and disability in 1990 (Table 1.1), those from ischaemic heart disease, cerebrovascular disease, cancer and lower respiratory infections are in the established market economies, whereas most deaths brought about by diarrhoea, communicable diseases, maternal and perinatal conditions and nutritional deficiencies are in the developing world. Overall, in the industrialised regions, only 6.1% deaths were brought about by communicable (infectious and parasitic diseases), maternal, perinatal and nutritional conditions, and deaths from non-communicable diseases (e.g. cardiovascular, cancer) and injuries accounted for 86.2% and 7.6%, respectively. Considering disability alone in the industrialised regions, the leading causes in 1990 were unipolar major depression, iron deficiency anaemia, falls, alcohol abuse, chronic obstructive pulmonary disease,

Table 1.1 Leading causes of death and disability worldwide (1990–2020)

Rank	1990	2020
1	Ischaemic heart disease	Ischaemic heart disease
2	Cerebrovascular disease	Unipolar major depression
3	Lower respiratory infections	Road traffic accidents
4	Diarrhoeal diseases	Cerebrovascular disease
5	Perinatal disorders	Chronic obstructive pulmonary disease
6	Chronic obstructive pulmonary disease	Lower respiratory infections
7	Tuberculosis (HIV excluded)	Tuberculosis
8	Measles	War injuries
9	Road traffic accidents	Diarrhoeal diseases
10	Lung, tracheal and bronchial cancer	HIV

In 1990, just over 50 million died worldwide (53% males); 10.912 million in the industrialised world and 39.554 million in the developing regions.

bipolar disorder, congenital anomalies, osteoarthritis, schizophrenia and obsessive-compulsive disorder. Absence of cancer from the top 10 killers of 2020 reflects use of a disability-adjusted measure used in the study rather than discovery of a magical cure, although new medicines and regimens have increased survival rates in cancer patients. Indeed, the fact that the analysis of gastrointestinal cancer is organ-based while cancers affecting the respiratory system are lumped together also distorts the above analysis. Thus, deaths from all cancers affecting the respiratory system (lung, trachea and bronchi) have been aggregated to make this the tenth leading cause of mortality. Aggregating all the data for the bowel (oesophageal, stomach and colorectal tumours) would elevate gastrointestinal cancer to eighth place. Similarly, liver disease (cirrhosis plus cancer) at 1.38 million would rank as the ninth leading cause of death.

Health trends over the next 20 years will be largely determined by ageing of the world's (female) population, a 40% fall in developing world deaths from communicable, perinatal and nutritional causes, and a 77% increase in non-communicable diseases, including a 180% increase in tobacco-attributable mortality. The potential for so-called 'lifestyle' drugs (e.g. anti-smoking treatments) is also apparent. While the drug industry may not be quite so aware of opportunities in relation to trauma, it has recognized the threats posed both by psychotic illness and AIDS. The prediction that depression will rank second in terms of disability-adjusted life-years creates opportunity for drugs directed at peripheral as well as central sites such as those targeting the brain–gut axis.

1.3 Medicines marketed in the years 2004–2007

The issue of productivity in drug discovery using all the new technologies is currently being debated.[39–41] Looking at the drugs marketed during 2004–2007 (approximately 250 in total) it is clear that very few are medicines with a new mechanism of action (first-in-the-class) and the remaining are follow-up compounds based on the initial discovery, new formulations of existing drugs, new indications for existing medicines or combination products incorporating existing medicines.[42–44] In fact, over the last 30 years (1997–2006) only about 70 first-in-class drugs were launched.[45] The best-known examples of these include cimetidine (1977), captopril (1980), lovastatin (1987), omeprazole (1987), enoxaparin (1987), ondansetron (1990), losartan (1994), saquinavir (1995), clopidogrel (1997), celecoxib (1998), trastuzumab (1998), ezetimibe (2002), enfuvirtide (2003), natalizumab (2004), rimonabant (2006) and sitagliptin (2006). Many of the new formulations (Table 1.2) were transdermal formulations (ease of administration) or depot formulations allowing the drug to be released over an extended period of time. In some cases, such as albumin-bound paclitaxel (Abraxane), the new formulation was designed to increase solubility and to increase drug delivery to tumour cells.[46] Drugs marketed for new indications (Table 1.3) included many drugs such as aripiprazole, quetiapine, risperidone, duloxetine and pregabalin, initially licensed for neurological diseases such as schizophrenia, depression and epilepsy and then expanded

Table 1.2 Examples of new drug formulations

Drug	Constituent	New formulation, indication
Veramyst	Fluticasone furoate	Nasal spray, seasonal and year round allergy symptoms
Omnaris	Ciclesonide	Nasal spray formulation, allergic rhinitis symptoms
AzaSite	Azithromycin	DuraSite drug delivery vehicle – synthetic polymer-based formulation (ophthalmic solution), bacterial conjunctivitis
Relestat	Epinastine HCl	Ophthalmic solution formulation – prevention of itching associated with allergic conjunctivitis
Retisert	Fluocinolone acetonide	Drug reservoir to deliver sustained levels of the drug for 30 months (intravitreal implant), chronic non-infectious uveitis affecting the posterior segment of the eye
Daytrana	Methylphenidate	Transdermal patch (adhesive-based matrix), once daily, attention deficit hyperactivity disorder
Emsam	Selegiline	Transdermal patch, major depressive disorder
Exelon	Rivastigmine	Transdermal patch, Alzheimer's disease
Reclast, Aclasta	Zoledronic acid	Once-yearly formulation (15-minute intravenous infusion) – reducing the risk of fractures (hip, spine and non-spine)
Synera	Lidocaine and tetracaine	Topical local anaesthetic patch, used to numb the skin before various medical procedures
Zingo	Lidocaine HCl monohydrate	Powder form incorporated in an intradermal delivery system – reduction of pain associated with venous access procedures
DepoDur	Morphine sulfate	Injectable depot formulation using lipid-based drug delivery technology (epidural injection) – 48 h of pain control in patients undergoing surgical procedures (e.g. hip and knee replacement, and lower abdominal surgery)
Abraxane	Paclitaxel	Protein-bound particles for injectable suspension (using nanoparticle albumin-bound technology), breast cancer
Lialda	Mesalamine	Oral once-daily formulation – active, mild to moderate ulcerative colitis
Roliflo OD	Tamsulosin HCl and tolterodine tartarate	Extended-release capsule formulation (once daily) – management of bladder outlet obstruction (men with benign prostatic hyperplasia, with concomitant over-active bladder)
Climara Pro	Tradiol/levonorgestrel	Transdermal patch (once-a-week) – moderate to severe symptoms of menopause such as hot flushes and night sweats
Estrasorb	Oestradiol	Topical emulsion (soya-based oil formulation) – moderate to severe symptoms in menopausal women
Menostar	Oestradiol	Transdermal patch (once-a-week), oestrogen therapy for post-menopausal osteoporosis
Intrinsa	Testosterone	Transdermal patch (twice a week) – low sexual desire in women who have experienced an early menopause
Tostrex	Testosterone	Transdermal gel (metered dose delivery system) – treatment of male hypogonadism
Nebido	Testosterone undecanoate	Depot injection formulation (four times a year) – testosterone replacement therapy for men with hypogonadism

Table 1.3 Existing drugs marketed for new indications

Drug	Old indication	New indication
Abilify (aripiprazole)	Schizophrenia	Acute manic and mixed episodes associated with bipolar disorder
Seroquel (quetiapine)	Schizophrenia	Bipolar disorder in patients experiencing acute mania (in combination with mood stabilisers)
Risperdal (risperidone)	Acute and chronic schizophrenia	Irritability associated with autistic disorder, including symptoms of aggression, deliberate self-injury, temper tantrums and quickly changing moods, in children and adolescents
Cymbalta (duloxetine)	Major depressive disorder, urinary incontinence	Pain associated with diabetic peripheral neuropathy, generalised anxiety disorder
Lyrica (pregabalin)	Epilepsy and neuropathic pain	Fibromyalgia syndrome, generalised anxiety disorder
CellCept (mycophenolate mofetil)	Immunosuppression (with ciclosporin and corticosteroids)	Induction and maintenance treatment of lupus nephritis, when used concomitantly with corticosteroids
Prograf (tacrolimus)	Prophylaxis of rejection (bone marrow and organ transplant), generalised myasthenia gravis	Treatment of lupus nephritis, rheumatoid arthritis in patients who respond insufficiently to current therapies
Tracleer, Actelion (bosenthan)	Treatment of PAH	Reduction of new digital ulcers in patients with systemic sclerosis and ongoing digital ulcer disease
Taxotere (docetaxel)	Breast and lung cancers	Hormone-refractory metastatic prostate cancer (in combination with prednisone)
Evista (raloxifene HCl)	Prevention and treatment of osteoporosis in postmenopausal women	Reducing the risk of invasive breast cancer in postmenopausal women with osteoporosis or at high risk for invasive breast cancer
Sigmart (nicorandil)	Unstable angina pectoris	Acute heart failure, including acute decompensation of chronic heart failure
Aceon (perindopril erbumine)	Hypertension	Treatment of patients with stable coronary disease to reduce the risk of cardiovascular mortality or non-fatal myocardial infarction
Yaz (drospirenone/ethinyl estradiol)	Oral contraceptive, emotional and physical symptoms of premenstrual dysphoric disorder	Treatment of moderate acne in women, oral contraceptive for birth control
EvaMist (estradiol)	Treatment of hot flushes in women	Treatment for vasomotor symptoms associated with menopause
Dinagest (dienogest)	Component in oral contraceptive and hormone replacement therapy agents	Endometriosis
Osonase (ciclesonide)	Asthma	Seasonal and perennial allergic rhinitis in adults and adolescents

PAH, pulmonary arterial hypertension.

to cover other neurological conditions. The combination products (Table 1.4) launched were primarily for cardiovascular and respiratory disorders and type 2 diabetes. Combinations of calcium-channel blockers such as amlodipine and lercanidipine, ACE inhibitors such as ramipril and enalapril, and angiotensin II receptor antagonists such as valsartan and olmesartan were launched for the treatment of hypertension.

Table 1.4 Drugs marketed as combination products

Drug	Components	Indication
Caduet	Amlodipine besylate and atorvastatin calcium	Simultaneous treatment of hypertension and high cholesterol
Exforge	Amlodipine besylate and valsartan	Hypertension
Azor	Amlodipine besylate and olmesartan medoxomil	Hypertension
Zanipress, Zaneril and Carmen ACE	Lercanidpine and enalapril	Hypertension
CVpill	Atorvastatin, ramipril, enteric-coated aspirin and metoprolol succinate (extended release)	Cardiovascular disease in patients with multiple risk factors (LDL cholesterol, hypertension, serum homocysteine and platelet function)
Vytorin, Zintrepid	Ezetimibe and simvastatin	Treatment of hypercholesterolaemia
BiDil	Hydralazine and isosorbide nitrate	Heart failure (black patients)
Pylera	Metronidazole, tetracycline and bismuth biskalcitrate	Eradication of *H. pylori*, gastric acid secretion
Janumet	Sitagliptin phosphate monohydrate and metformin	Type 2 diabetes – not adequately controlled on metformin or sitagliptin alone
Avandaryl	Rosiglitazone maleate and glimepiride	Type 2 diabetes in patients not adequately controlled on a sulphonylurea alone
Duetact	Pioglitazone and glimepiride	Type 2 diabetes
ACTOplus Met	Pioglitazone and metformin	Type-2 diabetes not adequately controlled with metformin or pioglitazone alone
Fosamax Plus D	Alendronatc sodium and cholecalciferol	Osteoporosis in postmenopausal women
GEM-21S	Recombinant human platelet-derived growth factor and β-tricalcium phosphate	Periodontal bone defects and associated gingival recession
Symbyax	Olanzapine and fluoxetine	Depressive episodes associated with bipolar disorder
Ganfort	Bimatoprost and timolol maleate	Open-angle glaucoma and ocular hypertension
DuoTrav	Travoprost and timolol maleate	Open-angle glaucoma or ocular hypertension
Zylet	Loteprednol etabonate and tobramycin	Steroid-responsive inflammatory ocular conditions with superficial bacterial ocular infection or a risk of infection
Osovair	Ciclesonide and formoterol fumarate (dry powder inhaler)	Treatment of asthma
Avessa	Formoterol fumarate and fluticasone propionate	Treatment of asthma
Foster	Formoterol fumarate and beclometasone dipropionate	Treatment of asthma
Clarinex-D	Desloratadine and pseudoephedrine sulphate, extended release (24 h) tablet	Relief of the nasal and non-nasal symptoms of seasonal allergic rhinitis, including nasal congestion

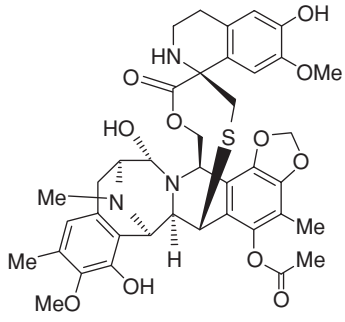
ACE, angiotensin converting enzyme; LDL, low density lipoprotein.

A combination of amlodipine and atorvastatin was marketed for simultaneous treatment of hypertension and high cholesterol. Atorvastatin and ezetimibe were combined to reduce low-density lipoprotein (LDL) cholesterol in patients with high levels of cholesterol. In one case (CVpill), four drugs [atorvastatin, ramipril, enteric-coated aspirin and metoprolol succinate (extended release)] were combined to cover all major cardiovascular risk factors. Combination products for respiratory diseases such as asthma included established therapies with steroids (ciclesonide, fluticasone, beclometasone) and β-stimulants (formoterol). A new approach to design multi-target drugs, in place of combination drugs, has been suggested to be better against complex diseases.[47]

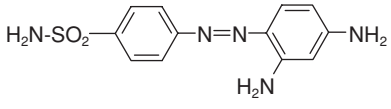
1.4 Historical aspects

1.4.1 Early discoveries

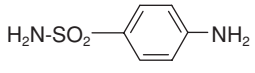
A number of early medicines, including morphine, atropine, salicylic acid and quinine, were isolated from plants. Over the years the search for therapeutic agents was widened to isolate compounds from natural products[48] including living agents such as bacteria, fungi,[49] sea animals and even humans. The important discoveries from this research not only include anti-infective agents such as penicillin and tetracyclin, but many other hormones and transmitters. Ivermectin (a drug used to treat tropical filariosis), amphotericin B, lovastatin (HMG-CoA reductase inhibitor), insulin, heparin (anticoagulant), paclitaxel (anticancer), artemisinin (antimalarial), ciclosporin, mycophenolate mofetil, tacrolimus and FK506 (immunosuppressants) and Xenical (anti-obesity) are other examples either originating from natural sources or modified versions of the natural products. One of the more recent examples of a natural product-derived medicine reaching the market is trabectedin (Yondelis) (**20**). This marine-derived antitumour compound, a DNA minor groove-binding agent, was approved for marketing for the treatment of advanced soft tissue sarcoma. Many of the biologically active peptides such as oxytocin, vasopressin, adrenocorticotrophic hormone, insulin, calcitonin, luteinising hormone releasing hormone, growth hormone and erythropoietin are important examples of compounds isolated from humans and other animals that have led to medicines currently used in clinical practice. In addition, discoveries of many other agents such as adrenaline, histamine, tyramine, tryptamine and γ-aminobutyric acid their receptors have led to extremely important medicines.



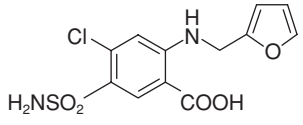
20 Trabectedin



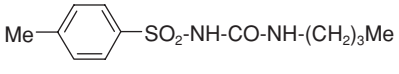
21 Prontosil



22 Sulfanilamide



23 Furosemide



24 Tolbutamide

Many other early discoveries were primarily based on low-throughput random screening approaches. The mechanism of action was later rationalised when additional biochemical and pharmacological information became available. Examples of early drugs include sulfa drugs which led to the discoveries of several other classes of drugs.[33] For example, the active metabolite of the sulfonamide prontosil (**21**), inhibits the enzyme carbonic anhydrase, leading to an increase in natriuresis and the excretion of water. Sulfanilamide (**22**) gave rise to better carbonic anhydrase inhibitors such as acetazolamide and later led to more effective diuretics such as hydrochlorothiazide and furosemide (**23**). Further chemistry in the field led to the development of sulfonylureas such as tolbutamide (**24**), used in the treatment of type 2 diabetes.