1 What is Pharmacology?

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1.1 Introduction

Pharmacology is the study of the action of drugs on living systems – neatly paraphrased as the chemical control of physiology and pathology. It lies at the interface of chemistry and biology. *Drugs*, in this context, are chemicals of known structure that are administered as external agents – whether deliberately or accidentally – to the organism, and produce an observable effect on its function. Living organisms are, of course, complex chemical machines, which produce and use many of their own chemicals as a means of controlling their own functions. Not surprisingly, exposure to other chemicals (*i.e.* drugs) from the outside world is liable to confuse and subvert the internal signals, and that in essence is what pharmacology is all about. An understanding of pharmacology plays an essential role in the discovery and application of drugs as therapeutic agents, where the aim is to provide benefit to individuals by the alleviation of symptoms and disabilities, improved prognosis, prolongation of life, or disease prevention. A drug that does none of these things, even though it has been exquisitely engineered to interrupt what was thought to be a key step in the pathogenesis of the disorder, is of no use as therapy, though it may prove to be a valuable research tool.

Pharmacology comprises two main components, namely *pharmacodynamics*, which is concerned with the effects that drugs

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produce on living systems (*i.e.* what the drug does to the body), and *pharmacokinetics*, which describes the mechanisms by which the drug is absorbed, distributed, metabolised and excreted (*i.e.* what the body does to the drug). To explain fully the effects of a drug in an intact organism, both need to be understood.

Given the extreme chemical complexity of living organisms, and the delicately balanced regulatory mechanisms that have evolved over millions of years to allow organisms to survive environmental threats, it is not surprising that the intrusion of a foreign chemical is, in general, more likely to do harm than good.[†] The aim of drug discovery research is to find those few compounds that – against all odds – can deliver benefit to individuals affected by disease. Therapeutic benefit depends not only on choosing the right compound, but delivering it in the right dose, to the right patient, by the best route, at the right time and under the right circumstances. These important aspects are the concern of the subdiscipline of clinical pharmacology.

When developed as therapeutic agents, drugs are incorporated into *medicines*, which normally include other substances to enable them to be administered as pills, solutions for injection, skin patches, aerosols or other dosage forms (Box 1.1).

1.2 Origins and Antecedents

The word ''pharmakon'' in ancient Greek, could mean a medicine or a poison; in the ancient world there was little distinction. Attempts to heal the sick by the use of ''medicines'' – largely herbal and mineral in origin, and based on spiritualist dogma rather than science – was in the hands of spiritual healers, and the tradition survives to the present day, carried on by ''medicine men'' and ''witch doctors'', whose stock-in-trade is not only to heal the sick, but also to inflict harm on enemies. Compilations of such remedies go back thousands of years and it was the task of healers to produce them according to closely guarded recipes. Such traditional practices, based on dogma rather than science, remain popular to this day, despite the fact that evidence that they deliver benefit is generally weak or nonexistent. Prior to the 19th century, even though ''medicines'' based on traditional dogma had been catalogued and used for thousands of years,

[†]We do not expect to correct a fault in, say, the navigation system of an aircraft by spraying a chemical into the works, so it may seem remarkable that physiological malfunction can sometimes be put right by a circulating drug. What makes it possible is that living systems, unlike electronic ones, deploy chemical signalling to control their function, providing points of attack for chemical interventions.

Box 1.1 Some definitions

Pharmacology. The study of the action of drugs on living systems. **Clinical pharmacology** is a branch of pharmacology concerned with the action of drugs used clinically to treat patients.

Drug. A substance of known chemical structure that produces a functional effect when added exogenously to a living system. Many endogenous chemical mediators that regulate normal physiological functions in higher animals can also be administered as drugs, but most drugs are synthetic chemicals or natural products not found in higher animals.

Medicine. A preparation containing one or more drugs, designed for therapeutic use. Medicines usually contain additional materials to improve their suitability for clinical use, for example as an injectable solution, a pill to be swallowed, or an ointment for topical application.

Therapeutic efficacy. The disease-related benefit to humans that a medicine produces. The benefit may be:

- relief of symptoms or disabilities associated with disease;
- improved prognosis, *i.e.* slowing or reversal of the progress of the disease;
- prolongation of life;
- prevention of disease.

the understanding of drug action in terms of scientific principles – in other words, the emergence of pharmacology – was impossible. Chemistry had not yet advanced to the point of defining compounds in terms of their structure; physiology and pathology could not yet describe the functioning and malfunctioning of the body; traditional teaching emphasised the importance of esoteric procedures for concocting herbal preparations as a prerequisite for their clinical use. There were, however, a few earlier breaks with tradition – discoveries that found application in modern medicine. For example, Thomas Sydenham (1624–89) described in 1666 the use of opium (containing morphine) to control pain and ''Jesuit's bark'' (containing quinine) to control ''intermittent fever'' (*i.e.* malaria); William Withering (1741–99) described the use of foxglove (digitalis) to treat ''dropsy'' (heart failure) in 1785. But until the nineteenth century these preparations were generally assumed to owe their properties to the vital forces possessed by ''organic'' substances. Chemistry did not come into it, nor did any understanding of biological mechanism.

Materia medica – the description of natural products and their medicinal uses, based on beliefs passed from generation to

generation down the ages – began to be commercialised in the mid-17th century by the apothecary's trade, the forerunner of the modern pharmaceutical industry, its aim being to satisfy the demand for medicines containing ingredients that were difficult to obtain, and prepared in an approved manner. At the same time, the ''Age of Enlightenment'', a gradual shift from dogma to science in the practice of medicine began to grow, when luminaries such as Robert Boyle (in chemistry) and William Harvey (in physiology) started to use evidence based on careful observation and experiment, as opposed to received wisdom, as a basis for understanding the natural world. The idea of living organisms as machines governed by the same physical laws as everything else in the material world, and of chemistry as the underlying basis of every substance and structure, slowly took root over the next two centuries, and dogmatic beliefs began to be challenged by discoveries based on empirical observations, many of which have stood the test of time.

1.3 The Emergence of Pharmacology as a Science

Pharmacology as a distinct biomedical discipline began in 1847, when Buchheim (1820–1879) established the first university department with that name in Dorpat. His was a bold vision, for at that time the medicines in use were mainly plant extracts of unknown composition and a few, mostly poisonous, inorganic compounds, such as salts of mercury and arsenic. Complicated mixtures were recommended, prepared and administered in accordance with elaborate rituals. Vomiting, sweating, diarrhoea and fever commonly resulted, and were regarded as evidence of the treatment's effectiveness in ridding the body of harmful ''toxins''. **A famous quotation from an eminent contemporary physician, Oliver Wendell Holmes in 1860 dismissed them thus: ''If all the materia medica, as currently used, could be thrown into the sea, it would be the better for mankind, and the worse for the fishes''.**[1] It is certainly true that the ''remedies'' in use at that time were not based on any understanding of how they produced their effects, or of the underlying pathological dysfunction that needed to be corrected (beyond the ''toxins'' notion mentioned above), and the idea of testing their therapeutic efficacy rarely surfaced. Nevertheless, Buchheim saw that the challenge, then as now, was to understand better the mechanisms by which they produced their effects in order to put their medicinal uses on a rational, and hopefully effective, basis. Even though organic chemistry had hardly

come into being, he had the vision to see that physiology, pathology and chemistry were all advancing rapidly in the very fertile scientific environment of the mid-nineteenth century, to a point where a new interdisciplinary science could emerge.

1.3.1 Chemistry Makes its Entry

One of the essential foundations of pharmacology – the use of structural formulae to define chemical compounds – did not exist until the middle of the nineteenth century. A key figure was August Kekule, a German chemist who described both the tetravalent nature of carbon and the aromatic ring structure of benzene, two essential principles that allowed accurate structural formulae of organic molecules to be produced for the first time. The idea that the biological effects of plant extracts was likely to result from their chemical constituents rather than mysterious vital forces was implicit in the work of Buchheim and other pharmacological pioneers in the nineteenth century, but it was not until 1905 that a German pharmacist, Serturner, isolated crystals of morphine from opium poppies, tested it on himself and nearly died – the first irrefutable evidence that opium worked by chemistry, not by magic. Serturner's achievement was followed quickly by others who similarly extracted and purified chemical compounds from medicinal plants and showed them to possess distinctive pharmacological properties. Studying how such plant-derived substances as nicotine, atropine, curare, strychnine and ergot alkaloids, produce their effects, and relating them to the emerging knowledge of physiology and pathology, gave pharmacology the scientific foundations that it needed. But still, at this time, synthetic compounds, as opposed to natural products, played only a very minor part.

1.3.2 Pathology and Physiology Lay Important Foundations

The other essential foundations of pharmacology, namely physiology and pathology, also flourished in the nineteenth century. Some key milestones are worth noting. The cell theory, proposed by the German pathologist Rudolf Virchow (1821–1902), identified the cell as the fundamental unit of all living organisms, and proposed that cellular dysfunction – cells dying, dividing, migrating, or otherwise functioning incorrectly – was the basic cause of disease. Louis Pasteur (1822–1896), a French chemist, proposed the germ theory of infection in 1878, having famously demonstrated the role of air-borne

micro-organisms in fermentation. He showed that cholera could be transferred from chicken to chicken by inoculation with fresh, but not ''stale'' material. In fact, inoculation with stale material actually protected against future infection, so Pasteur inadvertently discovered the phenomenon of immunisation.

The first physiological studies aimed at pinning down the site of action of poisons were performed by Francois Magendie (1783–1855) in Paris, who showed that the convulsant action of strychnine was due to its action on the spinal cord, rather than elsewhere in the brain, nerves or muscles. His pupil, Claude Bernard (1813–1878) used a similar anatomical approach to pinpoint the paralysing effect of the arrow-poison curare to the junction between motor nerve and muscle fibre.

1.3.3 The Receptor Concept is Established

The realisation that drugs act very specifically at precise anatomical sites led in later years to the search for cellular components and actual molecules involved. A particularly important stage in the development of modern pharmacology was the emergence of the receptor concept, pharmacology's Big Idea (reviewed by Rang, 2006[2]) of a ''lock and key'' mechanism by which drug molecules act on specific cellular molecules to produce their effects. This idea had been expressed, in a philosophical way, centuries earlier: **''Did we but know the mechanical affections of the particles of rhubarb, hemlock, opium and a man. . . . . .we should be able to tell beforehand that rhubarb will purge, hemlock kill and opium make a man sleep. . . . . .''**[3] **(John Locke, 1690, Essay concerning human understanding).** These ''mechanical affections'', which we would today call chemical interactions, are what pharmacology is all about. The Cambridge physiologist, J. N. Langley (1852–1925), first used the term ''receptive substance'' in 1878 to describe the hypothetical endogenous substance in salivary glands with which pilocarpine (which causes salivary secretion) and atropine (which blocks pilocarpine's action) combine and compete with each other for binding. A. V. Hill (1886–1977), a student in Langley's laboratory, applied the Law of Mass Action to describe quantitatively the interaction of drug and receptor molecules, and this quantitative approach was further developed by later pharmacologists. We now know that specific receptors exist in all cells and tissues, and are key players in the numerous chemical signalling pathways used by all living organisms to control their physiological functions. The subversion of these signalling pathways by introducing

alien chemicals is the basis is modern pharmacology. Understanding pharmacology in this mechanistic way, underpinned now through the application of molecular biological approaches and by detailed knowledge of the structure and function of receptor molecules, has become crucial for the discovery of new therapeutic drugs.

Receptors form one important class of targets for therapeutic drugs. Enzymes, transporter molecules, ion channels, *etc*. are other types of target, described elsewhere in this book. Identifying such drug targets, and explaining how drugs are able to act on them to influence the function of the cells and tissues that express them, is a central theme in modern pharmacology, and an important starting point for drug discovery and therapeutic innovation.

1.3.4 Many Chemical Mediators are Identified

The idea that internal secretions – chemical substances liberated into the bloodstream by organs such as the thyroid gland, testis and liver – play an important physiological role, emerged in the 17th century, and slowly gained ground over the next 200 years. The term ''hormone'' was coined in 1905 by Bayliss and Starling, who showed that the duodenum, in response to gastric acid production, produced a substance ''secretin'' that caused the pancreas to release digestive enzymes. Around the same time, many physiologists described the effects of removing individual glands – adrenal, thyroid, pituitary, pancreas, *etc.* – and of injecting various gland extracts, on different physiological functions, though chemical techniques for isolating and identifying the mediators involved were not yet available. The realisation that the release of chemical transmitters is the mechanism by which nerve cells communicate with each other, and with other cells and tissues came initially from work by Dale and Loewi, who identified acetylcholine as the transmitter released by parasympathetic nerve endings (winning the Nobel Prize in 1936), and the identification of other chemical mediators became – and remains – a major focus of pharmacology. Many large families of mediators are now recognised. These include:

- low molecular weight amines, such as acetylcholine, noradrenaline, histamine, dopamine, 5-hydroxytryptamine;
- peptides, such as insulin, oxytocin and angiotensin;
- protein mediators, such as growth hormone, interferon and a wide variety of cytokines;
- lipid mediators, such as prostaglandins and leukotrienes;

- steroids, such as oestrogens and adrenocortical hormones;
- amino acids, such as glutamate, glycine and γ-amino butyric acid (GABA);
- purines, such as adenosine, ADP and ATP;
- small molecules such as nitric oxide, carbon monoxide and hydrogen sulfide.

New members of each of these groups of mediators are still being discovered, particularly in the protein group, where modern techniques in molecular biology, cell biology and genomics have made a big impact in recent years.

1.4 Receptors and Drug Targets

From a pharmacological perspective, this profusion of mediators gives rise to many potential drug targets. Each mediator acts by binding to a specific recognition site located on a protein – the receptor – through which it produces its physiological effects. The four main types of receptor are:

- G-protein coupled receptors (GPCRs);
- ligand-gated ion channels;
- kinase-linked receptors;
- nuclear receptors.

Apart from nuclear receptors, most receptors are proteins that span cell membranes, accessible to mediators acting on the extracellular surface, and controlling events within the cell.

Most mediators act on more than one receptor, producing different effects on different cells. GPCRs are a particularly large and important type; approximately 350 GPCRs for endogenous mediators have been identified in the human genome, and roughly half the drugs in clinical use target GPCRs. Ligand-gated ion channels, activated by transmitters such as acetylcholine and glutamate, are important mainly in mediating fast synaptic neurotransmission. Kinase-linked receptors, located on the cell surface, respond to mediators such as growth factors, cytokines and insulin. Activation of the intracellular kinase moiety of the receptor protein initiates a cascade of protein phosphorylation reactions within the cell, culminating in the functional response. Nuclear receptors are intracellular proteins, responding to mediators such as steroids and thyroid hormones that are able to

enter the cell; these receptors act by controlling gene expression in the nucleus.

Drug targets are the endogenous molecules (mostly proteins) to which drug molecules bind as the first step in producing their pharmacological effects. The various type of receptors for endogenous mediators, described above, constitute one important class of drug targets, but other types of functional protein, and also DNA, are also important.

1.5 Pharmacology in Drug Discovery

The pathologist, Paul Ehrlich (1854–1915), was impressed by the ability of chemical dyes to stain biological specimens in a very specific way, and argued that this selective binding to particular cell types might be used as a basis for finding drugs that would bind to and kill pathogenic organisms. Arsenic, in various forms, had been used as a poison and a medicine for thousands of years, so Ehrlich, working with an organic chemist, embarked on the first systematic attempt at drug discovery by chemical synthesis. They made and tested hundreds of organic arsenic compounds, based on aniline dyes (the constituents of many of the biological stains that had engaged Ehrlich's attention) as possible treatments for trypanosomiasis (sleeping sickness, a common and serious infectious tropical disease). From this came, in 1907, Compound 606, named Salvarsan, the first effective drug for this disorder, and the beginning of the era of anti-microbial chemotherapy – arguably the biggest therapeutic success story to date.

Synthetic chemistry had given rise to clinically useful drugs before this, though by serendipity rather than design. Diethyl ether was discovered in the 16th century (known then as ''sweet oil of vitriol'' because it was made from alcohol and sulfuric acid) and gained notoriety in the 19th century as a party drug (''ether frolics''). Nitrous oxide (laughing gas) had similar origins, and the ability of both of these agents to produce reversible insensibility led in the mid-19th century to their introduction as surgical anaesthetic agents – a vital breakthrough that allowed surgery to develop from agonising butchery to humane intervention. It was in the late 18th century that chemistry began to take over from alchemy, and the production and purification novel compounds of known structure became possible. But understanding and determination of chemical structure, and synthetic methods were still very limited, and it was not until the end

of the 19th century that synthetic chemistry really took off, and some of the products were discovered to have medical uses. Among the earliest drugs that came from this were the local anaesthetic, procaine (1905), and the sedative, barbital (1907), both forerunners of important classes of clinically used drugs.

Chemistry-led drug discovery grew rapidly in the 20th century, and quickly became the leading source of new therapeutic agents, and, as a byproduct, new research tools that proved valuable in the study of physiological and pathological processes. Intervening in metabolic pathways, by synthesising ''antimetabolites'' – analogues of endogenous metabolites – was an approach followed for many years by the highly successful drug discovery team led by Hitchings (1905–98) and Elion (1918–99), working at Burroughs Wellcome in the USA. Earlier, Domagk (1895–1964) in Germany had developed sulfonamides, the first effective antibacterial drugs, which were later shown to work by inhibiting the synthesis of folic acid, a metabolite essential for bacterial growth. Hitchings and Elion sought other inhibitors by making and testing a range of purine and pyrimidine analogues, which acted as inhibitors of the enzyme dihydrofolate reductase. Their antimetabolite approach, begun in 1944, generated not only antibacterial drugs, but also a range of other chemotherapeutic agents, active against protozoa and human cancers. The same sulfonamide-based chemical lineage later gave rise to novel diuretics (acetazolamide, chlorothiazide), antidiabetic drugs (sulfonylureas) and antihypertensive drugs (diazoxide) – an extraordinary example of chemical inventiveness leading to important new therapeutic drug classes. Domagk was awarded the Nobel Prize in 1939, Hitchings and Elion in 1988.

Analytical chemistry later also played an important role in providing tools for identifying the signalling molecules – hormones, neurotransmitters, inflammatory mediators, *etc.* – that play such a major role in physiological regulation, and whose dysfunction commonly leads to disease. Chemists became very successful at inventing new drugs by synthesising analogues and derivatives of known structures. An intuitive sense – hard to pin down – possessed by successful medicinal chemists, guiding them to the kind of structures likely to yield clinically useful drugs, was an important driver of these inventions. The compounds would be handed over to biologists for testing on animals, and anything that looked interesting could be further tested and developed as a medicine. This compound-led strategy sustained a successful drug industry for many years. Nevertheless, natural products continue to be a fruitful source of new useful

drugs, most notably in the discovery of penicillin, relying on the inventiveness of evolution rather than of human chemists.

From the mid-20th century ''target-led'' drug discovery began to rival the compound-led approach. The coming together of chemistry, physiology and pathology under the banner of pharmacology drew attention to the importance of ''drug targets'', namely the endogenous molecules – in most cases proteins – to which drugs bind in order to produce their effects. Such protein targets are of many kinds, including enzymes, receptors for endogenous mediators, transporter molecules, *etc*. and new ones are constantly being identified. James Black (1924–2010), a British pharmacologist working in industry, was a leader in this new target-led approach. Selecting the recently identified β-adrenoceptor as a promising target for treating cardiovascular disease, he and his team developed the first β-adrenoceptor antagonist, pronethalol, to be approved for clinical use (1965). Pronethalol was quickly withdrawn owing to adverse effects, to be followed by practolol (which had even more severe toxicity), and finally by propranolol (1973), which proved to be a valuable treatment for a range of cardiovascular and other disorders, and is still widely used. Black's team went on following this approach with another major success, the first H_2-histamine receptor antagonist, cimetidine (1975) used to treat gastric and duodenal ulcers. For this work he won the Nobel Prize in 1988. The example set by these early target-led drug discovery projects was quickly followed by pharmaceutical companies worldwide, and became the main source of new therapeutic drugs up to the late 1990s – a particularly fruitful period for drug discovery. Target-led drug discovery began with no knowledge of the molecular nature of the targets in question, the chemistry being led mainly by knowledge of the chemical nature of the relevant physiological mediators. From the 1980s, when receptors and other drug targets began to be isolated as proteins, sequenced and cloned, these new molecular approaches gave a big boost to drug discovery, both by identifying and characterising the many subtypes of receptors, transporters, enzymes and other targets, and also by providing a range of much faster and more powerful methods by which chemical leads could be screened and tested. The subdiscipline of molecular pharmacology, which emerged at this time, grew rapidly in importance, and gained a powerful boost when the human genome sequence was published in 2003. The use of genomic techniques to identify and characterise human drug targets is now a necessary part of most drug discovery projects (covered in later chapters).

1.6 Pharmacology Today

As we have seen, pharmacology arose through the convergence of medicine, chemistry, pathology and physiology, its purpose being to throw light on how medicines and poisons produce their effects. Biochemistry and molecular and cell biology joined the party as these newer disciplines emerged in the 20th century. One important spin-off from molecular biology was the emergence of *biopharmaceuticals* in the form of protein-based therapeutic agents, such as insulin, growth hormone and a variety of monoclonal antibodies, produced by genetically engineered bacteria or eukaryotic cells as an alternative to drugs made by synthetic chemistry. Biopharmaceuticals now constitute about one-third of newly approved therapeutic agents. Since the sequencing on the human genome in 2003 genomics has had a major impact on pharmacology and drug discovery, mainly by providing abundant new information about potential new disease-relevant human drug targets, and also paving the way for ''personalised'' therapeutics that aims to take into account an individual's genetic make-up as a guide to maximising the efficacy and reducing drug side effects. The multidisciplinary nature of pharmacology, present throughout its history, remains its abiding characteristic, and has grown in complexity as biomedical science has progressed. Pharmacology, you could say, is sustained by hybrid vigour, rather than intellectual purity.

As well as being a key driver of drug discovery and development, pharmacology figures in many other aspects of modern life. A few examples follow:

- Drugs prescribed by clinicians are often ineffective in a significant proportion of patients, and commonly cause adverse effects.[4,5] Selecting the right drug, the right dose, and where possible in the right patient, which can significantly diminish these problems, is the domain of clinical pharmacologists. The emergence of genomics-based personalised medicine is a likely to provide powerful new tools for clinical pharmacologists.
- Pharmacological knowledge is essential in the design and conduct of clinical trials of new medicines, which have to be conducted according to strict protocols governing standards of ethics, experimental design and statistical analysis in order to pass scrutiny by regulatory authorities as a condition of approval of the new drug for clinical use.

- Widely consumed ''social'' drugs, including alcohol, nicotine and caffeine have been subjected to extensive pharmacological research, the results of which provide the basis for official advice regarding their possible health risks.
- Drug abuse and addiction are serious problems in many countries, and present difficult challenges for prevention, remediation, legislation and policing; understanding the pharmacological properties of abused substances, including the mechanisms by which they produce psychological reward, as well as dependence and harm, is essential in planning rational control measures. The continuing emergence of new synthetic ''street drugs'' is a particular problem for pharmacologists and legislators.
- Drugs in sport present problems of a different kind, mainly concerned with detection, where understanding of the routes of metabolism and excretion of banned compounds, coupled with sensitive analytical methods, is the basis of most of the control measures that are used.

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