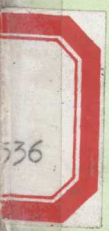
Pharmaceutical Medicine

Edited by D.M. Burley MB BS FRCP

and T.B. Binns FRCP DCH



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With a Foreword by Professor Sir Abraham Goldberg

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Foreword

Before giving an unconditional welcome to a textbook on a new subject, it is a salutary exercise to justify its publication. No one can deny the importance to medical practice of the pharmaceutical industry, which, in its exports, also makes a major contribution to the national economy. In 1983, about £420 million was spent by the industry on research compared with £180 million spent by the Medical Research Council — an unfair comparison perhaps but nevertheless a fact. Pharmaceutical companies have played a major part in drug innovation in the twentieth century, although the seminal role of academic research must not be forgotten, for as Miles Weatherall has put it, 'the fruits of research in the university departments and in laboratories of research councils contain the seeds from which new drugs may be cultivated'.

As the century has advanced, the importance of drug safety has loomed large. The problems associated with thalidomide, practolol, the non-steroidal anti-inflammatory agents and contraceptive medication have created new challenges for the drug regulating authorities and industry. The thalidomide disaster provoked the activity leading to the co-ordination of a number of systems of legislation to form the Committee on Safety of Drugs. That committee showed the way in which government, industry and the medical profession, who have so much to contribute together, could harmonize their efforts, even in a voluntary fashion. Voluntary arrangements were clearly insufficient to cope with the emerging problems, however, and thus there followed the Medicines Act of 1968 which came into force in 1971. This provided the powers to control pharmaceutical manufacturers and introduced the requirement to assess efficacy in addition to safety and quality.

About that time Dr Eric Snell coined the title of 'pharmaceutical physician' for the doctor who stands at the interface between the industry and the many clinical problems which the development and introduction of new drugs entail. Over the intervening 10 years the responsibilities and professional requirements of the pharmaceutical physician have become greater. He must have an appreciation of the essentials of pre-clinical studies and of the many intricacies of clinical trials as well as knowledge of the post-marketing surveillance of a drug after licensing. The introduction of the clinical trial exemption scheme has thrust greater responsibilities on to him. All this, often carried out under the glare of media publicity, has required the emergence of a cadre of highly trained and talented doctors in the new specialty of pharmaceutical medicine.

Landmarks in this development have been the emergence of the

Association of Medical Advisers in the Pharmaceutical Industry (AMAPI); the introduction of a two-year course in pharmacutical medicine now centred in Cardiff and giving tuition in various aspects of the subject to the young pharmaceutical physician; the introduction in 1976 of the Diploma in Pharmaceutical Medicine sponsored by the three Colleges of Physicians in London, Edinburgh and Glasgow and now in its eighth year; and 1984 has seen the emergence of the Journal of Pharmaceutical Medicine. This book on pharmaceutical medicine must be seen in the light of these developments, all of which provide the impressive justification for its publication.

The contents of such a book must reflect the diversity of interests which the discipline entails. The excitement and difficulties of the subject are introduced by Miles Weatherall in dealing with the process of discovering a new drug, which he describes as 'a kind of snakes and ladders game in which the snakes commonly lead back to the starting point and the ladders have been removed because the rungs are unreliable'. The chapters on pre-clinical testing and 'making drugs into medicines', although in the domains of the pharmacologist, biologist and pharmaceutical chemist, form the necessary base for pharmaceutical medicine. Important chapters on clinical trials, statistical considerations, adverse reactions and post-marketing surveillance reflect the essential core of knowledge in this discipline. That pharmaceutical medicine is a subject of an international dimension is emphasized by the separate chapters on the regulations of medicines in the United Kingdom, in Europe and in the United States of America. Chapters on 'education, information and promotion' by Snell, economics by von Grebmer and ethics by Marsh emphasize the intellectual and emotional ramifications of the subject. A final chapter on the work and challenges of the pharmaceutical physician by Burley will provide a very useful guide to the doctor entering this discipline.

It is clear that pharmaceutical medicine is now an important specialty in its own right. It has emerged as a post-graduate topic. Only the future can determine to what extent it may be taught at the undergraduate level. There is intense community interest in the subject of drug safety, and the media have correctly exploited this. Such an interest will play its part, both political and scientific, in the development of pharmaceutical medicine, the high ideal of which must be the provision to the community of safe drugs of quality and efficacy.

1984 A. Goldberg

Preface

The tremendous growth of drug research and the increasing availabilty of new and effective remedies have changed the whole face of medicine in the past thirty years. One consequence has been the development, albeit rather hesitant, of the academic discipline of clinical pharmacology, often described as 'the scientific study of drugs in man'. There is now an abundant literature on this subject with several textbooks and numerous journals.

It is more difficult to define Pharmaceutical Medicine. It has much in common with clinical pharmacology, but it includes the medical aspects of the work of the pharmaceutical industry which discovers and develops almost all of the new drugs. It also includes insight into the social and legal aspects of medicines and particularly the involvement of government through the regulatory authority and through various controls on prices and promotion.

Thus it could be said that pharmaceutical medicine occupies the area of common ground between the medical profession, the pharmaceutical industry and government. Its boundaries are hazy but the principal areas are indicated by the chapter headings of this book which is designed to complement but not compete with those on related disciplines such as clinical pharmacology and statistics. The growing importance of the subject was recognized by the institution in 1976 of the Diploma in Pharmaceutical Medicine jointly by the three Royal Colleges of Physicians in the UK.

We believe that this is the first text book on Pharmaceutical Medicine. It is intended especially for doctors employed in this work by the pharmaceutical industry. In the UK alone the membership of the Association of Medical Advisers in the Pharmaceutical Industry has grown nearly ten-fold in the past twenty-five years. The numbers involved are now comparable with those in other sub-specialties of general medicine. Corresponding numbers of doctors are employed in other developed countries and the problems they face are similar.

Large sections of the book will be of interest to others in the industry, not only to clinical research associates, statisticians, information and regulatory personnel but also to staff in research, marketing and management.

Despite its great contribution to health care over many years, there is still remarkable ignorance about the industry even among people whose work brings them into contact with it. It is hoped that this book will find its way into the libraries of medical and pharmacy schools and postgraduate centres. Not only do most doctors regularly prescribe the industry's products, but an increasing number of doctors and pharmacists are

involved in clinical testing, in teaching and as members of expert committees at local or national level. Finally we hope that the staff of regulatory authorities will find the book useful.

The information it contains could doubtless be found scattered in the literature. It is not otherwise available under a single cover.

No individual can be expected to be expert in so many disparate fields, but many people, especially pharmaceutical physicians, should have sufficient knowledge of them to be able to converse intelligently and constructively with the experts.

We should like to thank the contributors, their secretaries and our secretary, Mrs Julia Wehrle, for their co-operation, hard work and forbearance.

1984

D.M. Burley
T.B. Binns

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1 How are drugs discovered?

M. Weatherall

Over the last fifty years technical advances in medicine have been considerable. A moderately knowledgeable layman might expect drugs for particular diseases to be easy to invent, to be just a matter of design and manufacture. But the knowledge necessary for designing drugs intelligently is still largely unknown. In many industries, a design team usually has a definite purpose in mind for any machine on the drawing board, and expects, sooner or later, to produce a machine which actually achieves that purpose, rather than some handy but unrelated one, or one which even fails to work at all. In pharmaceutical research the position is less simple. Drugs act by interfering with the very complex physical and chemical machinery of living organisms. In spite of the labour of generations of physiologists and biochemists, knowledge of living machinery is still very limited, and the basis for understanding how drugs act, or could act, is often inadequate. Commonly, knowledge develops in the other direction. The discovery that a substance produces a recognizable effect on an animal or a patient can be the starting point of physiological or clinical research, as when Langley used nicotine to discover the location of synapses in the autonomic nervous system,[1] or when β-blockers were found to be effective agents for treating hypertension.[2,3] The possibilities of the reverse process, designing drugs from a basis of physiological knowledge, are more limited. However rationally one may try to design a drug at present, the basic factual and theoretical understanding is often insufficient. The sooner such knowledge is accumulated, the sooner rational design will be possible. Meanwhile, the process of discovering a new drug is a long and tortuous trail of investigation, a kind of snakes and ladders game in which the snakes commonly lead back to the starting point and the ladders have been removed because their rungs are unreliable.

Choice of experimental or test systems; screens

For the first stage of discovering a new drug, two ingredients are essential; a test system (or a battery of tests) and a substance (or stock of substances). The most relevant evidence that a drug works is given by treating appropriate patients. Until about a century ago, therapeutic efficacy was discovered in no other way. It still happens that new uses are discovered for substances already in use when an unexpected activity is observed during clinical application, and the observation is pursued intelligently. When

isoniazid was introduced for the chemotherapy of tuberculosis,[4] a related compound, iproniazid (Marsilid) was also tried and found effective. Among the merits of the new drugs euphoria and improvement of appetite were prominent. The original reports do not clearly distinguish the two compounds in this respect.[5,6] However, about the same time, iproniazid unlike isoniazid, was shown to be a potent inhibitor of monoamine oxidase (MAO).[7]Knowledge of brain chemistry at that time made plausible the concept that depression was associated with depletion of amines from specific sites and suggested that the euphoriant action was not simply a consequence of arrest of the tuberculous infection. On this theoretical basis more extended trials of MAO inhibitors were made in depressed patients.[8,9] Success led to the introduction of a long series of useful drugs. As commonly happens, wider clinical experience revealed toxic effects which limited the value of the drugs. New uses for existing drugs have been found with simpler reasoning: mepacrine was tried successfully for giardiasis 'as it is so energetic in malaria'.[10]

However, this approach is strictly limited to substances aleady in use. The risks involved in giving to man substances with wholly unknown pharmacological properties are not acceptable. It is essential, before trial in man, to have a great deal of evidence from laboratory studies about the likely consequences of administration of a new chemical entity or an unidentified plant or animal extract. The acquisition of this evidence is very expensive, and is likely to be undertaken only if the substance seems really likely to do what is wanted and if the cost of acquiring the evidence can be recovered in some way. The initial test system is therefore extremely important. It must be reliable though often is not so. It is likely to depend on a species other than man (unless cells or tissues obtained from humans can be used *in vitro*) and so has one built-in source of potential error. And, if any number of substances are to be tried, it must be quantitative and relatively simple to operate. Much ingenuity has been spent in devising 'screens' which achieve these ends.[11,12,13]

The success of screening depends on the kind of disease for which a drug is sought, and on how much is known about what causes it. When microbes had been identified as causes of infectious diseases, cultivated *in vitro*, and used to produce disease in experimental animals, test systems or screens were immediately to hand. Use of rabbits infected with *Treponema pallidum* enabled Ehrlich and Hata[14] to test many hundreds of compounds as remedies for syphilis, and led to the introduction of arsphenamine (606, Salvarsan) and later neo-arsphenamine (914, Neo-salvarsan) which were the principal means of therapy until superseded by penicillin. Similarly, sulphonamides, most antibiotics and anti-protozoal agents, as well as anthelminthics, have been discovered by testing substances against the infecting organism, either *in vitro* or *in vivo*.

The choice, between experiments on organisms in culture and in infected animals, is of great importance, though the way it is made depends largely on the temperament and strategy of the investigators. If no methods are known of cultivating the organism *in vitro*, the choice does not arise. So

Ehrlich and Hata's experiments were done *in vivo*, and gave the additional benefit of showing not only the therapeutic action but also the acute toxicity to the host of the compounds tested. Very properly Ehrlich insisted on an adequate margin of safety and on quantitative treatment of results, rejecting any substances where the ratio of 'toxic' to 'therapeutic' dose was less than three. Unfortunately, acute toxicity in rabbits is a very inadequate predictor of clinical hazard. The criterion led to rejection of the compound *m*-amino-*p*-hydroxyphenyl-arsenoxide (oxophenarsine) which is more stable than neo-arsphenamine, easier to administer, and was adopted clinically some 30 years later with considerable advantage[15]. Here the experiment *in vivo* gave misleading information. The opposite may occur. Early in the 1930s a range of azo-dyes were tested against streptococcal septicaemia in mice. One dye, 4'-sulphonamido-2,4-diaminoazobenzene (Prontosil) was highly effective and was promptly shown to be beneficial in patients[16]. This success was extremely important. It overcame beliefs that chemotherapy of bacterial infections was impossible, and presaged the widespread development of the sulphonamides. Without it, the history of chemotherapy might have followed a very different course. Nevertheless, if Domagk had relied on experiments *in vitro*, the discovery would probably not have been made. The azo-dye is relatively inactive *in vitro*, except against or in the presence of organisms possessing enzymes which split the diazo linkage. The compound was therefore liable to have been missed if it had not been tested in whole animals, in which, as was soon shown by Tréfouël *et al.*,[17] it is hydrolyzed to release the active substance sulphanilamide.

Once sulphanilamide was identified as the antibacterial agent, active both *in vitro* and *in vivo*, the discovery of many similar but more potent or more widely active drugs was greatly simplified, because initial *in vitro* testing, which is usually quicker and cheaper, was possible. Experiments *in vitro* also enabled the mode of action of sulphanilamide and other sulphonamides to be established as one of competition with the essential metabolite *p*-aminobenzoic acid.[18,19] This discovery was of fundamental importance for the deliberate design of new drugs, and is discussed later.

In seeking remedies for diseases of known (or partly known) cause, other than an infecting organism (for instance, endocrine deficiencies or excess, cancers, genetic deficiencies of particular enzymes), a chemical and biochemical approach still has considerable scope. The biochemical problems are likely to be even more intricate than those involving the metabolism of micro-organisms, but the principle holds good: given an identified substance which plays a key role in the disease being studied, can it itself or an analogue either replace it or block its activity, and in one or other way be therapeutically useful? Also it is natural to consider drugs already used in treatment: do they throw light on the mechanism of the disease, and can they be modified in any way to produce substances which are more effective or easier to use, or both?

When drugs are sought for diseases of unknown cause, the choice of a suitable screen is more difficult. Shall some cardinal feature of the disease,

such as a high blood pressure in hypertension, or fluid retention in heart failure, be used, and experiments done to look for agents which lower the blood pressure or cause diuresis? Valuable remedies have been found in this way, but they are palliative, not curative. Should experiments be done to elucidate the cause of the disease, with a view to blocking the causal process? This is a very long term strategy, liable to take many years before even a screen can be devised. Shall drugs which are known to be beneficial be tested in animals until a simple procedure is found which gives positive responses with known effective drugs, and negative with those which do not? This is a route to 'me-too' drugs, some of which are a substantial improvement on existing remedies but many of which serve mainly to give the discoverer a share of the market without special benefit to patients. All these and other strategies have been adopted, and have revealed valuable drugs, drugs of dubious merit, and also very many compounds which have fallen by the wayside in subsequent development and testing. Perhaps the worst hazard of screening is in the codification of screening practices, so that they are operated with a high level of efficiency and an absence of continual curiosity. A well ordered laboratory sometimes develops in which chemists labour unceasingly so that the screens are fed, and biologists work unremittingly in order not to fail to evaluate the products of their colleagues. No time is left to appraise the screens themselves, and decide whether the positive results are of genuine value, or the negatives are really useless. Indeed it is very difficult, time-consuming and expensive to establish either set of facts. Such critical enquiry may interfere seriously with the effortless running of the system, and so is unpopular with those who are dedicated to operating it.

Choice of compounds

The second essential ingredient to start the process of drug discovery is a substance, or collection of substances, to be tested. With all the naturally occurring substances in the world plus the millions of new entities which can be synthesized by organic chemists, the choice is embarrassingly large, and some guiding principles are essential.

Perhaps the oldest principle was stated by Ehrlich: *Corpora non agunt nisi fixata.*[14] Substances do not act unless fixed, or, more explicity, drugs act by combining with receptors. Before current biochemical techniques were available, fixation was more easily recognized with coloured compounds, and a considerable proportion of synthetic drugs discovered up to and including Prontosil were coloured. Recognition of the identity of substances with specific physiological or biochemical functions provided a better basis for choosing compounds. Given that an essential metabolite, hormone or transmitter was known, its receptor, by definition, was a substance in the cells or tissues which reacted with it and therefore would react with some at least of its close chemical relatives. The identification of adrenaline as the hormone of the adrenal medulla led to many investigations of related compounds, particularly the classical study of

Barger and Dale.[20] For reasons discussed later, the practical application of these studies was at first very limited. The evolution of useful sympathomimetic and sympathetic blocking agents[21,22] is still perhaps incomplete, but the basis for such search has been established for over 70 years. Again, Dale's account of the properties of acetylcholine[23], and its functions as a transmitter[24] was fundamental to the evolution of muscle relaxants and ganglion blocking agents. Establishment of the structure of oestrogens had more immediate practical application in the development of stilboestrol,[25,26] and a major stimulus to drug development came from the concept of substrate competition. Although *p*-aminobenzoic acid was identified as the normal metabolite after sulphanilamide was established as a useful drug, the argument was easily reversed. Every biochemical advance which revealed a new metabolic pathway suggested a range of analogues potentially valuable for controlling the processes served by the pathway.

This approach was developed with outstanding success by Hitchings,[27] who, in 1944, 'chose to work in the field of nucleic acid biosynthesis. The area was then regarded as somewhat esoteric, and it seemed to us an appropriate quiet backwater where a small group might work relatively undisturbed by the pressures of intensive competition. But there were already signs that the area was important, and, potentially, a worthwhile target for chemotherapy'.[22]Indeed, it was. The organism *Lactobacillus casei* provided a convenient source of anabolic enzymes: the collaborating organic chemists provided a range of purine and pyrimidine analogues; and from this work emerged the anti-malarial pyrimethamine, the anti-neoplastic agent 6-mercaptopurine, the immuno-suppressant azathioprine, allopurinol for gout, the anti-bacterial trimethoprim and the anti-viral agent acyclovir. Seldom if ever has a small group of workers achieved such a wide range of major therapeutic advances by the application of straightforward principles.

Advances in molecular biology now provide much more detailed knowledge of drug receptors[28] than was available when Hitchings' group were achieving their major successes. The practical benefits of this knowledge are not yet evident, nor does it by itself provide a complete basis for useful discoveries. As a long term goal, the pursuit of rational drug design is attractive and desirable, but the complexity of the problems is formidable. Identification of a substance with nearly perfect qualities of affinity for or fit to receptors and appropriate kinetics of combination and release is only a fragment of the objective. To be a useful drug, the substance must also be sufficiently stable to serve in the conditions of medical use; must work when administered either orally or as a sterile injection; must persist *in vivo* for long enough to reach the receptors and cause the desired effect, but not for so long as to cause irreversible blockade or dangers of cumulation with repeated doses; and must not have serious toxic effects or minor but unacceptable properties such as tainting the breath or colouring the skin. The pharmacokinetic properties are particularly important, but all of these requirements are independent of the qualities sought for good receptor fit, and either increase the complexity of