CURRENT MEDICAL TREATMENT

FOURTH EDITION

Edited by C. W. H. Havard

WRIGHT · BRISTOL

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Edited by
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TO MHAIRI

Addenda

Page 437, line 5 from foot. There is now good unpublished evidence that lithium is teratogenic. It should therefore not be taken during the first trimester of pregnancy. Of 160 pregnant women taking lithium during the first trimester 18 babies were born with congenital abnormalities, usually of the heart and great vessels.

Page 473, line 7 from foot. Since the printing of this book the progestational compound megestrol acetate has been withdrawn because continuous administration of this progestogen to beagle bitches is associated with an increased incidence of breast tumours, some of which are malignant. The oral contraceptives which contained megestrol were Volidan 21 and Serial 28.

Preface to the Fourth Edition

Current Medical Treatment was first published in 1965 and a third edition had appeared by 1970. Major therapeutic advances over the past four years demand a fourth edition. The provision of up-to-date information on the treatment of disease continues to be the aim of this book. The format of the book is similar to that of the third edition. We have, however, continued a policy of purposeful renewal of contributors, so that the book may be constantly and fundamentally revised, thereby enabling new editions to be rewarding. The fourth edition is a major revision. Most of the chapters have been rewritten and eight chapters have new authors. Professor Victor Hoffbrand takes over the treatment of diseases of the blood, and J. S. Malpas the management of reticulo-endothelial diseases and leukaemia. John Moorhead assumes responsibility for renal diseases and Anthony Hopkins for diseases of the nervous system. J. T. Scott has taken over the chapter on connective tissue disorders.

The advent of clinical pharmacology as a medical discipline has resulted in an increased understanding of individual differences in the handling of drugs, and this variation in drug response which has important therapeutic repercussions is discussed in the chapter on drug-induced diseases. At the time of the first edition the metric system had become statutory and all doses were quoted in the metric system. We are now in the midst of further changes in the indices of measurement as the SI system is being introduced for measurements of body fluids and electrolytes. We are therefore anticipating this change and quoting the new indices.

1975

C. W. H. HAVARD

Preface to the First Edition

The progress of scientific medicine has been so rapid in recent years that to keep abreast of current advances has become a major challenge. This is particularly true of medical treatment. Nearly one-half of prescriptions today are for drugs which did not exist five years ago, and new remedies continue to appear in increasing number. The advent of the double blind technique of drug evaluation should now make it possible to abandon useless remedies and segregate compounds of real therapeutic value from those whose efficacy depends on the faith of the patient or of the physician. Whilst we fully acknowledge that many of the problems of medical treatment lie beyond the borders of applied science, it is nevertheless desirable that the management of the physical aspects of disease should have a rational foundation. This is especially relevant to the administration of drugs, many of which are potentially dangerous. We feel that there is a place for a new look at medical treatment and that a generation of physicians nurtured on this therapeutic revolution has some contribution to make. Furthermore, there is an increasing trend for practitioners to turn to the pharmaceutical industry for therapeutic information, a recent survey suggesting that 30 per cent of prescriptions from general practitioners are based on data supplied by drug companies. Whilst respecting the integrity of the pharmaceutical industry, we feel that unbiased physicians, whose life and energy are spent in the application and assessment of medical treatment, should provide the better counsel.

It is no longer possible for one man to give authoritative advice on the diverse aspects of therapeutics and the purpose of this book has been to provide up-to-date information on the treatment of disease from a variety of men actively engaged in the practice of medicine and the teaching of medical students. Whilst this book is intended primarily for the student and practitioner, we hope it will provide a practical book of reference for the house officer and a guide for the postgraduate.

In general, more space has been devoted to the commonly occurring conditions and those for which specific treatment is available, but we have tried not to overlook the general aspects in the management of incurable disease which may mean so much to the comfort and well-being of the patient. The introductory chapter is concerned with the principles of treatment and in it past remedies and outmoded customs are critically reviewed. The increase in therapeutic misadventures has indicated a need for a chapter on drug induced diseases. Antibiotics are considered in greater detail than is necessary for the needs of most students and practitioners, and it is hoped that the information presented will help the junior hospital medical staff in the selection of appropriate antimicrobial therapy. Over 12 per cent of prescriptions in this country at present are for antibiotics and the subject is growing in complexity. The treatment of serious infection now requires the assistance of the bacteriologist, but the therapeutic responsibility remains with the physician, so that he must not only be familiar with the value and limitations of the bacteriologists' techniques but also with the antimicrobial range of the various drugs and their applied pharmacology.

Corticosteroid therapy has been given prominence because of the wide therapeutic application of these compounds and their increased and sometimes ill-advised prescription and because of the hazards that are associated with their administration. The borders of clinical pharmacology and medical treatment are ill-defined and no apology is made for the digression into the physiological and pharmacological principles underlying both corticosteroid and diuretic therapy. Upon their appreciation depends the intelligent use of these compounds.

The growing importance of psychiatry with the appreciation of the protean manifestations of psychiatric disease and the increasing number of psychotropic drugs has demanded greater emphasis on the medical treatment of mental illness. Owing to the increasing incidence and variety of domestic poisoning greater attention has also been paid to this aspect of medical treatment. The advent of the jet aeroplane has enhanced the importance of tropical diseases to those who live in more temperate climates, and the treatment and prevention of these conditions has received appropriate attention.

Discrimination in the methods of treatment and choice of drugs is inevitable in the interests of space. Treatments whose efficacy is generally accepted have been expressed dogmatically, but more recent and controversial remedies have been discussed at greater length. To avoid unnecessary interruption of the text the number of cross references has been restricted and efforts have been directed to ensuring a comprehensive index. Selected references for further reading are given at the end of the book. These have been chosen either because they are in the nature of a general review of a therapeutic method or because they are concerned with a recent advance in treatment.

The metric system has been used for dosage throughout, but for drugs with which Apothecary measures have long been associated, the Imperial grain equivalent has been quoted in addition. The trend towards prescribing in metric units has recently received official impetus. The 1963 British Pharmacopoeia has abandoned the grain for expressing doses and the 1964 Weights and Measures Regulations give statutory authority to the metric system. In accordance with international practice the symbol g has been used for gramme, mg for milligramme and μg for microgramme. Attention is drawn to the similarity between the symbols for milligramme and microgramme and, until the metric system has entirely replaced the apothecary measures, confusion may also arise between the symbols for gramme and grain. Every student should familiarize himself with these symbols and beware of the possibility of confusion.

Both approved and proprietary names of drugs are given. In the chapters in which large numbers of drugs are discussed, tables appear at the end of the chapter giving the approved and trade names of the compounds concerned. Whilst it is desirable that the use of the approved names should be encouraged, it would be foolish to ignore the fact that many practitioners are more familiar with proprietary equivalents and that 67 per cent of all prescriptions dispensed in 1962 were for proprietary preparations. The fact that there are now over two hundred alternative names for stilboestrol and over one hundred preparations of hydrocortisone or its derivatives for topical application is sufficient warning of the confusion that will accompany an increase in the trend towards the use of proprietary names. The use of approved names for drugs should be encouraged, not only for the sake of clarity, but also for the sake of economy and to give the

pharmacist a choice of brands available. Occasionally, where the approved name of a drug is long or difficult, the use of the proprietary name may be justified.

Each contributor has sources of assistance and encouragement which he would wish to acknowledge, but in the interests of space they must remain anonymous. I, too, have received help and encouragement from many directions, but I cannot allow myself the privilege I have denied others.

I must, however, acknowledge the help and advice of Dr. I. Schrire, the Medical Consultant to Staples Press. I thank Dr. J. E. Stark for his assistance with proof reading and each contributor for making the book possible.

1964 C. W. H. HAVARD

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Contents

CHAPTER 1

Principles of Treatment

SIR DERRICK DUNLOP

DRUGS

Voltaire defined medical treatment as the art of pouring drugs of which one knew nothing into a patient of whom one knew less. When he uttered this classical cynicism over 200 years ago it was nearly true for he was born only 52 years after the death of Galileo and 37 after that of Harvey who may be regarded respectively as the fathers of modern scientific thought and scientific medicine. Up till their time thought had been largely deductive based on the authority of Hippocrates, Aristotle and Galen.

Not only, therefore, was the scientific method of thought still young in Voltaire's time but for over 150 years afterwards medical scientists were concerned not so much with treatment as with anatomy, physiology, pathology, bacteriology and diagnostic medicine. They had to blaze the trail along which scientific therapeutics could eventually advance; for it is impossible to treat rationally unless one knows how the body is constructed and how it works in health, about the natural history of disease, about the agents of infection and about what is the matter with the patient. Thus, at much the same time as Laennec, the inventor of the stethoscope, was beginning to put diagnostic medicine on a firmer foundation, some 30 million leeches a year were being used by his brother physicians in France in treatment, and doubtless in Edinburgh James Gregory, famous or perhaps notorious for the powder which bears his name, was complacently prescribing 20 gr of calomel—a fearsome dose—to one of the unfortunate lieges; when, about the middle of last century Virchow in Germany was revolutionizing pathology and altering the whole basis of our knowledge of disease, the pharmacopoeias then in use still contained a mass of rubbish, the relics of medieval superstition; when Osler published his classical *Textbook of Medicine* about the turn of the century, therapeutic nihilism was still so rife that less than 10 per cent of the space in the first edition was devoted to treatment and much of this consisted of pious hopes and vague generalities—'arsenic might prove useful', 'vaccines should be tried', 'the general health should receive attention'; and even the Edwardian physician, who often had so much diagnostic skill, had to rely for treatment very largely on bottles of medicine elaborately prescribed, meticulously bottled, elegantly flavoured and exquisitely labelled but, as Oliver Wendell Holmes said, if 80 per cent of them had been poured into the sea only the fishes would have suffered. It was all still faintly reminiscent of the witches in *Macbeth*—'fillet of a fenny snake in a cauldron boil and bake'. Our drugs were then, with very few exceptions, derived from substances which happened to occur in nature, from the quicksilver, the poppy, the foxglove and the cinchona bark. With the exception of quinine they were all symptomatic remedies and the conception that a drug could be curative, in that it could dispel or neutralize the cause of an illness, was still a revolutionary idea.

Young physicians nowadays, armed with the therapeutic thunderbolts of Jove which the synthetic chemist, bacteriologist and biological pharmacologist have put into their—often very ungodlike—hands, can have no idea of the physician's

sense of therapeutic impotence even in the 1920s. And now how different everything is! Since 1930 the mortality from gastro-intestinal infections, one of the chief causes of infantile death, has fallen by over 80 per cent, and that from pulmonary infections by nearly 70 per cent, while tuberculosis, meningococcal infections, mastoiditis and venereal disease all show a similar decline; diphtheria, from which as late as 1940 there were 2500 fatal cases in England and Wales, has disappeared; typhoid, typhus, tetanus, cholera, plague, yellow fever, smallpox, whooping-cough, measles and poliomyelitis can be prevented; many tropical diseases such as malaria have been brought under control; and the lives of patients suffering from diabetes and pernicious anaemia are preserved. The list is far from comprehensive and makes no mention of the relief of suffering which the purely symptomatic use of modern drugs confers.

Doubtless the all-round improvement in living conditions has greatly contributed to these remarkable results which have since 1930 increased the average expectation of life of men and women in this country by over 10 years, but the use of potent new drugs has been an even more important factor. To take tuberculosis alone as an example: the decline in its mortality from 1900 to 1945 was at about 3 per cent per year in Britain and the United States apart from the years of the two world wars when in Britain there was a slight increase. This 3 per cent annual decline was almost entirely due to the improvement in social conditions; after 1948 when effective antituberculous chemotherapy became available the decline in mortality abruptly accelerated to an average of 15 per cent a year in both countries and if this continues—and there are good grounds for expecting it to do so—tuberculosis as a cause of death in this country will virtually disappear in the next decade.

The scientific attitude which has made these great advances possible is still, however, unnatural to man and only employed by a minority of people who themselves confine its employment to a minority of problems. 'Most people', as Samuel Butler said, 'would rather die than use their brains.' The majority of our opinions are mere wish-fulfilments like dreams in the Freudian theory and the mind of the most rational can be compared to a stormy ocean of passionate convictions based upon desire upon which float perilously a few tiny boats carrying their cargo of scientifically tested beliefs. Nor is this entirely to be deplored: life has to be lived and time is too fleeting to test rationally all the beliefs by means of which our conduct is regulated. In regard to drug treatment, however, it is much to be desired that the art should be tempered by a wholesome dose of scientific reason.

Excessive Use of Drugs

Nevertheless, in respect of treatment, scientific reason is just what many patients and some doctors do not seem to want. Like Lot's wife, they are all too prone to look back, longing to return to the past with its ritual and its magic; and when disease arises with its toxic and frightening influences the primitive man creeps out of the cave in which reason has shamefacedly tried to conceal him, whimpering and crying for his witch doctors, his totems and his charms. During recent years there have been several analyses of the prescriptions issued on form EC 10 under the National Health Service whose total drug bill now reaches the formidable figure of over £300 million a year. Such studies stimulate the reflection that if we laugh at the witch doctoring of the past—'the eye of newt and toe of frog'—our smile should be a wry smile and not one of smug self-satisfacton. There are those who say, rather cynically perhaps, 'but the public demands a good bottle of medicine and after all it has a great psychological effect'. Yes, but the public

demands all sorts of mumbo-jumbo and quackery which may also have a great psychological effect. What we condemn in others we should not so complacently condone in ourselves but should attempt more than we do to educate the public in rational therapeutics instead of pandering to its primitive desires, even though the desire to take medicine seems to be the chief thing which differentiates man from the lower animals.

Satirists and enemies of the National Health Service have delighted to depict Britain as a nation of pill swallowers. We are not, however, exceptional in this and we spend rather less on medicines per head of population than most other countries in the Western World and very much less than some. Nevertheless, gross excess elsewhere does not justify overprescribing here.

There are many causes for overprescribing: the insistent demands of patients for medicine which is often matched by the *furor therapeuticus* of some doctors which makes them give a new medicine—often prescribed at spinal reflex level—for every symptom which develops; there are too few doctors for our increasing population so that most are busy and some overworked, and it takes a long time to elicit a careful clinical history, to carry out a thorough physical examination and to give wise advice, but it takes only a moment to write a prescription which is thus apt to become a means of emptying over-crowded surgeries and out-patient clinics; and, lastly, there is the impressive and skilled promotion of drugs by the pharmaceutical industry, some of which is subject to justifiable criticism.

Cost of Drugs

The cost of drugs to the National Health Service has steadily risen from £48 million in 1949–50 to over £300 million in 1975. This has been due not so much to their overall increased price as to the greater number of prescriptions written and to the much greater use of more expensive drugs such as antibiotics which account for about a quarter of the total bill.

The cost has been great but the savings have been much greater: as we have seen there has been a vast saving in mortality which is well documented; but the tremendous savings to the national economy in diminished morbidity—less time from work and decrease in the number and duration of admissions to hospital—is more difficult to estimate; but it has been accurately estimated that the annual saving resulting from the use of anti-tuberculous agents alone is £55 million a year. To put the cost of drugs which have conferred such immense benefits into perspective we should remember our expenditure on alcoholic drinks and on tobacco is respectively over eleven and ten times what we spend on drugs.

Prescribing

The practitioner and student should become familiar with the official or generic name of common drugs. This is the name applied to them in the British Pharmacopoeia (BP), the British Pharmaceutical Codex (BPC) and the British National Formulary (BNF) or, if the drug is not included in these volumes, the approved name given by the British Pharmacopoeia Commission. Lists of such approved names are issued by the Commission periodically and a committee of the World Health Organization tries to ensure that some uniformity of nomenclature is maintained by different countries so that a drug can be universally recognized; cosmopolitan pharmacological and therapeutic literature would otherwise be often unintelligible. Related drugs usually produce similar toxic effects and there is cross sensitization between them. Generic names give some idea of the family to which the drug belongs and some impression of its chemical nature, but the

trade name gives no idea to the prescriber of its possible relationship to the drug which may previously have caused the patient trouble. If drugs were invariably prescribed by their generic names significant economies would be effected for in the majority of cases their cost is less than their proprietary equivalents.

Many drugs are marketed under a variety of trade or branded names as well as the generic one. Their nomenclature has thus for long been a source of confusion and frustration in medical practice, teaching and publication. It has, therefore, been advocated that to bring order to the pharmaceutical Tower of Babel, brand names should be abolished and only generic names used. While the suggestion that each drug should have only one name is most attractive it is difficult to conceive of its practical application quite apart from the disastrous effect which the abolition of brand names would have on the pharmaceutical industry to which modern medicines owes so much.

While the generic name refers only to a basic chemical ingredient, a great many preparations currently prescribed under brand names are—whether we like them or not—compound preparations of two or more drugs. It is hard to imagine how such compound preparations could be given generic names.

Further it must be emphasized that the active constituent of a drug, to which the generic name only refers, does not constitute the sole basis for its effect. This is obvious when the branded drug is, for example, an aerosol or an elegantly flavoured linctus for children; but what may appear to be minor changes in formulation—coating, capsuling, particle size, disintegration time and so forth—may well make all the difference to the active constituent.

Lastly, there has till recently been little effective machinery to enforce the quality control of drugs in the United Kingdom—especially of preparations purporting to comply with British Pharmacopoeia specifications. It is true that such controls did exist if a drug came under the Therapeutic Substances Act, and the Department of Health and Social Security carried out occasional checks on imported drugs for use in hospitals. Till recently, however, there was inadequate official control on the quality of most drugs. This situation has now been considerably remedied by the 1968 Medicines Act which provides for the inspection of pharmaceutical premises and the licensing of medicines. Nevertheless, it is doubtful whether the occasional testing of samples by the Licensing Authority can ever match the scrupulous quality control exercised by a good firm on every batch of each drug it produces, for the brand name by which the product is marketed reflects the reputation of the manufacturer.

Drugs should always be described in English and never in Latin. The dog-Latin in which prescriptions are still often written is simply a survival of the obscurantism and magic which played such a large part in medicine in bygone times and which we should strive to avoid nowadays.

The dosage of drugs should be specified in metric measures. All new drugs are introduced in metric quantities and in 1963 the British Pharmacopoeia entirely abandoned the Imperial system of weights and measures even for the older galenical drugs, thus preceeding general adoption in this country of the more convenient and sensible metric system which is in use throughout much of the rest of the world.

A drug should usually be administered orally unless its parenteral administration is dictated because it is nauseating, inactive when taken by mouth or because a different speed of action is required. Tablets and capsules are more convenient for both pharmacist and patient than fluid preparations: they are a more accurate way of giving drugs and are usually cheaper with a lower dispensing fee, as bottles containing fluid preparations often have to be frequently renewed. Sometimes

of course, drugs cannot be dispensed as solids because of their physical properties, and those intended for infants and children must also be dispensed in a suitably flavoured liquid vehicle.

The administration of drugs to children presents special problems. The infant is not epicurean in his taste which is underdeveloped, and will often readily accept medicines like cod liver oil which are highly distasteful to adults. The best way to give drugs to an infant is to place him in the semi-erect posture with the arms imprisoned by a shawl. The mouth can be opened by gently squeezing the cheeks with the thumb and forefinger of the operator's left hand and the medicine is poured well back into the mouth from a teaspoon held in the right hand. In order to get the infant to swallow, it may be necessary to compress the nostrils for a few seconds. There is no really satisfactory formula by which to calculate suitable dosage of many of the drugs used in paediatric practice. The classic Young's formula was

$$\text{Dose} = \text{Adult dose} \times \frac{\text{age}}{\text{age} + 12}.$$

There is little chance of overdosage when such a formula is used, but children tolerate with advantage many drugs in greater quantity than the formula would indicate, including chloral hydrate which is an ideal sedative for them: on the other hand, young children are extremely intolerant to many others—the opiates, for example—owing to the immaturity of their hepatic enzyme systems, particularly glucuronyl transferase. Indeed, the recent progress in discovering inborn deficiencies in enzyme activity which decrease the rate of metabolism of drugs explains many adverse reactions to them previously vaguely attributed to intolerance or idiosyncracy. Young's formula takes no account of the child's weight which is really of more importance than its age; the same applies to adults, for it is manifest that the dose which should be given to a small thin woman may be quite different to that required by a large powerful man. Thus, the conventional dose given in most books is usually that for a 70-kg adult, and considerable variations from this size should always be considered. Similarly, the dosage of most potent modern drugs given to young children is expressed in terms of mg per kg of body weight.

Relative overdosage may result from defective renal function, such, for example, as the alarmingly high levels of streptomycin which may occur in the blood from ordinary doses given to some elderly people. The same thing may result from the slow metabolism of hypothyroidism; on the other hand, hyperthyroid people often tolerate very large doses of a drug like digitalis without experiencing adverse effects. Interference with metabolism leading to relative overdosage may also result from the concomitant or recent administration of agents which inhibit enzyme activity, and this activity is usually reduced in old people. When monoamine oxidase inhibitors were introduced for the treatment of depression they were found to potentiate the effect of other drugs whose metabolism depended on the blocked enzyme, such as sympathomimetic amines, depressants and antidepressants of the central nervous system and certain foodstuffs like cheese.

Many other examples of one drug potentiating the effect of another can be given: for example, the pharmacological activity of a drug usually depends on the concentration of its fraction which is free to diffuse and is not bound to plasma protein, and a relative overdose may result if the level of the unbound drug is increased by the administration of another with a greater affinity for the binding protein; thus, haemorrhage may occur if a patient is given phenylbutazone while receiving the anticoagulant, warfarin.