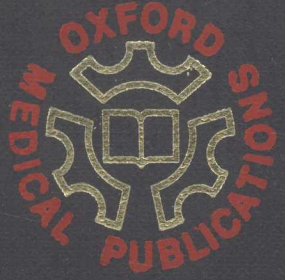

TEXTBOOK OF ADVERSE DRUG REACTIONS

Second Edition

EDITED BY D. M. DAVIES

TEXTBOOK OF ADVERSE DRUG REACTIONS

SECOND EDITION

EDITED BY

D. M. DAVIES, FRCP

Consultant Physician; Editor of the *Adverse Drug Reaction Bulletin*

OXFORD
OXFORD UNIVERSITY PRESS · 1981
NEW YORK TORONTO

Oxford University Press, Walton Street, Oxford OX2 6DP
OXFORD LONDON GLASGOW NEW YORK
TORONTO MELBOURNE WELLINGTON
NAIROBI DAR ES SALAAM CAPE TOWN
KUALA LUMPUR SINGAPORE HONG KONG TOKYO
DELHI BOMBAY CALCUTTA MADRAS KARACHI

First edition 1977
Second edition 1981

British Library Cataloguing in Publication Data
Textbook of adverse drug reactions.
2nd ed.—(Oxford Medical publications).
1. Drugs—Side effects
I. Davies, D.M.
615'.704 RM302.5 80-41982
ISBN 0-19-261270-0

PRINTED IN GREAT BRITAIN BY
THOMSON LITHO LTD., EAST KILBRIDE, SCOTLAND

OXFORD MEDICAL PUBLICATIONS

TEXTBOOK OF ADVERSE DRUG REACTIONS

Dedicated to the memory of
FRANCIS T. ROBERTS of the
United States of America and
LEOPOLD MEYLER of the Netherlands
who did so much to remind doctors
of the hazards of drug therapy.

Foreword

by the late SIR DERRICK DUNLOP MD, FRCP

This considerable volume—a tribute principally to the Newcastle Medical School which supplies 22 of its 32 contributors—is the most comprehensive account published of adverse reactions to drugs, and also supplies a very complete bibliography on the subject. Its unsensational but unavoidably somewhat horrific contents might well give the average reader an aversion to drugs in general, but this would be unjustified. Although modern drugs are formidable agents, if prescribed and used with skill, wisdom, and propriety their benefits far exceed their occasional adverse effects. It is appropriate, therefore, that a foreword to a book on the dangers of drugs should be prefaced by a reminder of the great blessings they have conferred upon society.

Since the beginning of this century the average expectation of life at birth in this and most other European countries has increased by about 25 years. In the early part of the century this improving expectation of longevity was largely the result of better hygiene, housing, and nutrition but during the last 30 or 40 years it has been mostly due to modern medicines (a term taken to include bacteriological products and hormones). Quite apart from their favourable effect on mortality statistics, the relief from suffering resulting from their purely symptomatic use, and the saving to national economies in diminished morbidity—less time lost from work, fewer and shorter admissions to hospital—is vast but more difficult to compute. It is becoming hard for older physicians to remember and it must be difficult for young ones to imagine what it was like to practise medicine when there was no insulin, vitamin B_{12}, sulphonamides, antibiotics, specifics for tropical diseases, hypotensives, anticoagulants and potent hormones, diuretics and anticonvulsants. Further, few of us would be callous enough to practise medicine without anaesthetics, narcotics, hypnotics, and analgesics.

No revolution, however, no matter how salutary, ever occurs without being harmful to some and the revolution in medicinal therapeutics of the last 50 years is no exception to this rule. Just as the old horse and buggy, though very slow, caused few fatal accidents whereas the modern automobile, though very fast, is a lethal instrument, so the old-fashioned bottle of medicine, elaborately compounded, meticulously bottled, elegantly flavoured, and exquisitely labelled, though relatively ineffective, was also comparatively innocuous whereas modern drugs, like atomic energy, are powerful for good but also for evil. The ill health that may result from their use—'iatrogenic illness' as it is called or, more optimistically, if a little ironically, 'illness due to medical progress'—has become a new dimension in the aetiology of disease: perhaps up to 10 per cent of patients suffer to a greater or lesser extent from efforts to treat them. Our powers over Nature in this as in other respects have advanced so far that Nature seems to have become retaliatory and to be exacting a massive retribution. A drug that can modify or repress biological processes is invaluable in treatment but if it has this capacity it is bound also to cause adverse effects from time to time. Those who say that nothing but the complete safety of drugs will suffice demand the impossible: a drug without any side-effects is probably an ineffective one. The public who require progress must be prepared for some risk: it has always accepted the not inconsiderable risks of surgery to which some modern drugs are equivalent in efficacy. While shuddering at a death rate of, say, one in 40 000 patients dying as the result of taking a usually valuable remedy (and which surgeon, incidentally, would not be enchanted with such statistics for the most minor operation?) we are much more complacent about the far greater dangers of cigarette smoking, alcoholism, or road accidents. Yet were all drugs invariably prescribed and used properly, and sensible governmental controls were enforced, the dangers would be small, for the majority of their adverse reactions—though by no means all—are due to their well-recognized and predictable side-effects.

The medical profession has not been entirely guiltless in their use of drugs. We must confess that there has been a good deal of excessive, and occasionally ignorant and irresponsible prescribing for which there are many reasons.

Firstly, there are too few doctors in most countries for their increasing populations, so that most are busy and some overworked. Although it

takes a long time to elucidate an accurate clinical history, to carry out a careful, physical examination, and to give wise advice, it only takes a moment to write a prescription which often satisfies both patient and doctor that some positive action has been taken. Most excessive prescribing is 'placebo' prescribing for which there is a limited justification—the patient expects some treatment or the doctor wants to give his patient hope. When genuine placebos are prescribed they should be cheap, innocuous, and pharmacologically largely inactive. The old 'tonics' we used to prescribe fulfilled these criteria, but the modern psychotropic drugs do not. The latter have of course changed the whole atmosphere and length of stay in our mental hospitals, have done much to prevent anguish of mind and suicide, and have brought the merciful dispensation of sleep to many in need of it. Nevertheless, they are overprescribed: all the anxieties, frustrations, and disappointments in life do not necessarily demand drug treatment. A good doctor should be a placebo in himself.

Secondly, ignorant prescribing may often be due to inadequate instruction about drugs. In most medical schools pharmacology has traditionally been taught as a pre-clinical subject—a valuable scientific academic discipline, using drugs to illustrate physiological problems—an 'acetylcholine' type of pharmacology, so to speak; but it is impossible at this stage in an undergraduate's career to teach the therapeutic use of drugs: the student is not familiar with pathology, bacteriology, or patients. Fortunately, the relatively new discipline of clinical pharmacology has now been introduced into most medical schools and plays an important part in the undergraduate curriculum and in the continuing education of the post-graduate, instructing them in the therapeutic use of the powerful tools of their trade.

Thirdly, excessive prescribing may be encouraged by the insistent and skilful promotion of drugs by the pharmaceutical industry, some of which, in the past at any rate, has been subject to justifiable criticism. The pharmaceutical industry seems to possess most of the conventional commercial virtues: a high rate of investment; satisfactory labour relations; good quality control; an admirable record of supplying customers during epidemics or individual emergency; generous benefactions to charities and to medical, dental, veterinary, and agricultural research; and a brilliant record of commercial success which in 1975 contributed over £300 million to our export drive. It is therefore a little surprising that few other industries have been subjected to so much adverse criticism, jealous political antagonism, or stringent bureaucratic controls. It must be confessed that in the creation of this atmosphere the industry itself has not been entirely blameless: in its period of most rapid development from the 1940s till the early 1960s it sometimes got carried away by its success and salesmanship occasionally took precedence over what was best for medicine. It would be idle to deny that commercialism sometimes dictated the marketing of a product before it had been completely investigated or that research workers in industry were occasionally subjected to commercial pressures. Of course, equally, academic research workers are sometimes carried away by their enthusiasms and the medical profession—or any other for that matter—have not always had their actions dictated by motives of pure altruism. In some future Utopia non-profit-making motivations may achieve the same brilliant results without side-effects. Till then we must take the world as we find it and remember that since the October Revolution the state-owned industries in the USSR and its satellites have hardly produced a single new product of real therapeutic importance.

In the old days medicines did not greatly influence the natural history of disease and it was not sufficiently stressed that an account of what drugs a patient had recently been taking should be an invariable and important part of any clinical history. Neglect of drug history taking often persists even in this chemotherapeutic era. Many adverse reactions to drugs exquisitely simulate the signs and symptoms of naturally occurring disorders. Thus complicated, often disagreeable, and expensive investigations are frequently undertaken when a few simple questions about the patient's recent consumption of drugs would have rendered these attempts to elucidate obscure symptoms unnecessary. Further, it is undesirable to anaesthetize or operate on a patient taking certain drugs—corticosteroids for example—without taking precautions; and the danger of giving unsuitable drugs to patients already being given, particularly, monoamine oxidase inhibitors, anticoagulants, or oral hypoglycaemic agents is considerable. When the taking of a drug history has become a routine part of a clinical history a significant advance will have been made in the prevention of adverse reactions to drugs.

Though science does not always lend itself to legislative or regulatory manipulation, modern drugs are such potent weapons that there is a general consensus that the sole responsibility for their production and use can no longer be left entirely to the manufacturer and prescriber. Yet it is difficult to know how far Government should attempt to control their production and prescription without undue interference with the advance of scientific therapeutics, the well-being of the pharmaceutical industry, and the cherished freedom of the doctor, dentist, or veterinary surgeon to prescribe as he thinks best. Inadequate regulation may prejudice public safety but excessive regulation can also be prejudicial in stultifying innovation and delaying the introduction of valuable remedies. The thoughtful legislator must direct his efforts between these two extremes and protect the public from inadequately tested and dangerous drugs, but at the same time permit an orderly progress of research, development, and marketing by the pharmaceutical industry. The operation of controls must be efficient, economical, and expeditious for otherwise the public are denied new and useful drugs. Finally, labelling, while excluding exaggerated and dangerous claims must be sufficiently elastic to permit the physician to exercise his judgement in the use of drugs. Very restrictive or directive types of labelling might result in a so-called learned profession being reduced to signing forms entitling their patients to receive such drugs for such purposes as the regulatory agencies permit.

One of the most urgent tasks confronting us today is to place adverse drug reactions on a sound epidemiological basis. No matter how meticulous the preparatory work of the pharmacologist and clinician may have been before a drug is marketed or how careful a licensing authority may have been in reviewing its protocols, nothing can replace experience of its use in practice over many years. Thus, the computerized collection, tabulation, and analysis of suspected adverse reactions on a national and ultimately on an international scale is of paramount importance and in recent years many countries, including Britain as a pioneer, have established monitoring systems of this nature. Their success depends on the co-operation of the medical profession in reporting suspected adverse reactions, expecially to new drugs. It took many decades before the deleterious effects of aspirin on the alimentary canal became apparent and almost as long before it was recognized that the protracted abuse of phenacetin could produce renal papillary necrosis; 35 years elapsed before it became clear that amidopyrine could cause agranulocytosis; and several years before the association of phocomelia with thalidomide became obvious. Had a register of adverse reactions then existed these effects would have become apparent much earlier than was the case. The frequency of even major adverse reactions to drugs is not as yet really well known nor is their cause invariably well understood. A proper understanding of the dangers involved is the first step to their intelligent prevention. This book admirably supplies such an understanding.

Preface to the Second Edition

This book has been well received; the first edition, which appeared in 1977, has been reprinted twice, and some translations have been completed, and others are in progress. Reviewers have been generous in their appraisal. Almost all criticism has been constructive, and we have acted upon it when it has been possible to do so without altering our chosen approach to the subject. Thus, the new classification of adverse reactions as proposed in Chapter 2 is now used in the other chapters, a chapter on drug-induced disorders of temperature regulation has been added, and a new appendix lists and briefly describes the drug interactions discussed in more detail elsewhere in the text. However, we have not felt it necessary to provide separate chapters on adverse reactions in the elderly or on drug hazards in anaesthesia, because we feel that these aspects are already dealt with adequately in existing chapters; and while we admit that the way in which we have arranged the material makes it something of an effort to track down all the reactions that may be caused by a particular drug or group of drugs, we hope that the task will be made easier by our very detailed index, and we believe that our method of arrangement has its own merits.

All contributors have taken pains to bring their chapters up to date, and where there is a paucity of recent references this will usually be due to neglect of the subject in the literature rather than to lack of effort by the contributor. And, of course, even Herculean efforts by editor and publisher can never produce results likely to satisfy readers eager for the very latest information.

The contributors are again very grateful to the medical secretaries and the librarians who helped with the preparation of their chapters; and the Editor is particularly indebted to Miss Jean Hill, Assistant Editor of the *Adverse Drug Reaction Bulletin*, for invaluable assistance at all stages in the production of this book and its index; to Mrs. Jennifer Fatkin, Medical Secretary of the Northern Regional Clinical Pharmacology Unit, for much help with the text, references, appendixes, and index, and to Miss Felicity Davies, B.A., Barrister-at-Law, for detecting and eliminating a number of blemishes.

April 1980 DMD

From the Preface to the First Edition

In recent years a vast amount has been written about adverse reactions to drugs in a multitude of medical books and journals; yet, paradoxically, this surfeit of information has made it more difficult for the clinician to obtain prompt and unambiguous answers to his questions. He now requires help to find his way through the jungle of toxicological fact and theory, and it seemed to us that there was a need for a 'map' arranged in the style of the orthodox textbook of medicine and written by doctors able to view the problems posed by adverse reactions in perspective against the background of their own experience.

Our desire to be comprehensive has been tempered by our wish to produce a book of reasonable size, and we hope that our compromise will satisfy our readers. In a book with so many contributors it is not easy to ensure that each topic is given as much attention as it warrants, but no more than it deserves. We have tried very hard to achieve such a balance, and where a section seems disproportionately long it will usually be found that it deals with matters of fundamental importance or with subjects that have been particularly well studied.

August 1976 DMD

List of Contributors

J. Anderson, M.B., B.S., F.R.C.P., Honorary Consultant Physician, Newcastle Area Hospitals; Academic Sub-Dean of the Medical School and Senior Lecturer in Medicine, University of Newcastle upon Tyne.

G. Ansell, M.D., F.R.C.P., F.R.C.R., Consultant Radiologist in Charge, Whiston Hospital, Merseyside; Lecturer in Radiodiagnosis, University of Liverpool.

C. Heather Ashton, M.A., D.M., F.R.C.P., Honorary Consultant in Clinical Pharmacology, Newcastle Area Hospitals; Senior Lecturer in Pharmacology, University of Newcastle upon Tyne.

E.-S. K. Assem, M.B., B.Ch., Ph.D., Dip. Med. (Cairo), F.R.C.P. (Ed.), M.R.C.P., M.R.C.P. (Glas.), M.R.C.Path., D.C.H. (Cairo), Honorary Consultant Physician (Allergy and Clinical Pharmacology), University College Hospital, London; Senior Research Fellow, Department of Pharmacology, University College, London.

P. J. Balson, M.Sc., lately Scientific Officer, Department of Human Genetics, University of Newcastle upon Tyne.

D. N. Bateman, B.Sc., M.D., M.R.C.P. (U.K.), Senior Registrar in Clinical Pharmacology, Newcastle Area Hospitals.

Margaret Beedie, M.B., Ch.B., M.R.C.P. (U.K.), M.R.C.Psych., lately Research Fellow, Shotley Bridge General Hospital, Co. Durham; Registrar, Burton Road Hospital, Dudley, W. Midlands.

R. A. L. Brewis, M.D., F.R.C.P., Consultant Physician, Newcastle Area Hospitals; Senior Lecturer in Medicine, University of Newcastle upon Tyne.

F. Clark, M.B., B.S., F.R.C.P., Consultant Physician, Newcastle Area Hospitals; Senior Lecturer in Medicine and Clinical Tutor in Postgraduate Medicine, University of Newcastle upon Tyne.

W. I. Cranston, M.A., M.D., F.R.C.P., Honorary Consultant Physician, St. Thomas's Hospital, London; Professor of Medicine, University of London; Chairman of the Subcommittee on Adverse Reactions, Committee on Safety of Medicines.

A. L. Crombie, M.B., Ch.B., F.R.C.S. (Ed.), Consultant Ophthalmologist, Newcastle Area Hospitals; Professor of Ophthalmology, University of Newcastle upon Tyne.

D. M. Davies, F.R.C.P., Consultant Physician, Newcastle Area Hospitals and Shotley Bridge General Hospital; Director, Northern Regional Clinical Pharmacology Unit; Senior Lecturer in Clinical Toxicology and Clinical Tutor in Postgraduate Medicine, University of Newcastle upon Tyne; Member of the Subcommittee on Adverse Reactions, Committee on Safety of Medicines; Editor, *Adverse Drug Reaction Bulletin*.

M. Davis, M.D., M.R.C.P. (U.K.), Senior Lecturer in Medicine and Honorary Consultant Physician, Liver Unit, King's College Hospital, London.

C. Diamond, M.B., Ch.B., F.R.C.S. (Glas.), Consultant Ear, Nose, and Throat Surgeon, Newcastle Area Hospitals; Clinical Lecturer in Ear, Nose, and Throat Studies and Clinical Tutor in Postgraduate Medicine, University of Newcastle upon Tyne.

A. P. Douglas, B.Sc., M.D., M.R.C.P., M.R.C.P. (Ed.), Chief of Gastroenterology, University of Southern California School of Medicine, Los Angeles, California, U.S.A.

J. F. Dunne, B.Sc., M.B., B.S., Ph.D., Senior Medical Officer, Pharmaceuticals, World Health Organization, Geneva.

D. C. Evered, B.Sc., M.D., F.R.C.P., Director, Ciba Foundation, London.

R. H. Felix, M.A., M.B., B.Chir., M.R.C.P. (U.K.), Consultant Dermatologist, Frimley Park Hospital, Surrey.

J. B. Foster, M.D., F.R.C.P., Consultant Neurologist, Newcastle Area Hospitals; Reader in Neurology, University of Newcastle upon Tyne.

R. G. Gold, M.B., B.S., F.R.C.P., F.R.A.C.P., Consultant Cardiologist, Regional Cardiothoracic Centre, Freeman Hospital, Newcastle upon Tyne; Clinical Lecturer in Cardiology, University of Newcastle upon Tyne.

A. R. Horler, M.D., F.R.C.P., Consultant Physician, Newcastle Area Hospitals; Clinical Lecturer in Medicine, University of Newcastle upon Tyne.

W. H. W. Inman, M.A., M.B., B.Chir., M.R.C.P., F.F.C.M., Director, Drug Surveillance Research Unit, Faculty of Medicine, University of Southampton; formerly Principal Medical Officer, Committee on Safety of Medicines.

D. N. S. Kerr, M.Sc., M.B., Ch.B., F.R.C.P., F.R.C.P. (Ed.), Honorary Consultant Physician, Newcastle Area Hospitals; Professor of Medicine, University of Newcastle upon Tyne.

H. A. McClelland, M.B., B.S., F.R.C.P., F.R.C.Psych., D.P.M., D.C.H., Consultant Psychiatrist, Newcastle Area Hospitals; Clinical Lecturer in Psychological Medicine, University of Newcastle upon Tyne.

M. D. RAWLINS, B.Sc., M.D., F.R.C.P., Honorary Consultant Physician, Newcastle Area Hospitals; Professor of Clinical Pharmacology, Department of Pharmacological Sciences, University of Newcastle upon Tyne; Member of the Committee on Safety of Medicines.

D. F. ROBERTS, Sc.D., Professor of Human Genetics, University of Newcastle upon Tyne.

W. M. ROSS, T.D., D.L., M.D., F.R.C.S., F.R.C.R., Consultant Radiotherapist, Regional Radiotherapy Centre and Newcastle Area Hospitals; Honorary Lecturer in Radiotherapy, University of Newcastle upon Tyne.

C. J. STEVENSON, M.D., F.R.C.P., Consultant Dermatologist, Newcastle Area Hospitals; Honorary Lecturer, Department of Dermatology and Honorary Lecturer, Department of Occupational Health and Hygiene, University of Newcastle upon Tyne.

E. G. STEWART-WYNNE, M.B., Ch.B., M.R.C.P., F.C.P. (S.A.), Consultant Neurologist, Royal Perth Hospital, Perth, Australia.

J. LEAHY TAYLOR, M.B., B.S., M.R.C.G.P., D.M.J., Secretary, Medical Protection Society, London.

J. W. THOMPSON, M.B., B.S., Ph.D., M.R.C.P., Consultant Clinical Pharmacologist, Newcastle Area Hospitals; Professor of Pharmacology, Department of Pharmacological Sciences, University of Newcastle upon Tyne; Advisory Editor, *Adverse Drug Reaction Bulletin*.

Y. TOWNSEND, B.Sc., Research Assistant, Department of Medicine, St. Thomas's Hospital, London.

W. M. G. TUNBRIDGE, M.A., M.D., F.R.C.P., D.T.M. & H., Consultant Physician, Newcastle Area Hospitals; Clinical Lecturer in Medicine, University of Newcastle upon Tyne.

J. G. WALTON, B.D.S., Honorary Consultant Dental Surgeon, Newcastle Area Hospitals; Senior Lecturer in Operative Dental Surgery and Lecturer in Dental Pharmacology, University of Newcastle upon Tyne.

M. K. WARD, M.B., B.S., M.R.C.P. (U.K.), Consultant Physician, Newcastle Area Hospitals.

ROGER WILLIAMS, M.D., F.R.C.P., Consultant Physician and Director of the Liver Unit, King's College Hospital, London.

Contents

1. History and Epidemiology

HISTORY

Adverse reactions to drugs are as old as Medicine. Some of the earliest writings bear witness to the potential dangers of contemporary medical treatment, and the punishments prescribed for incompetent practitioners. The Babylonian *Code of Hammurabi*, of 2200 BC, ordained that a physician who caused a patient's death should lose his hands, and the *Hermetic Books of Thoth* outlined therapeutic paths from which the physician strayed only at his peril.

In the course of medical history many laymen and doctors were to advise caution in therapeutics and to criticize the materia medica and those who used it. Among the first was Homer (*c.* 950 BC), who said of drugs that there were 'many excellent when mingled, and many fatal' (*Odyssey*, IV). Hippocrates (460–570 BC) pleaded 'Do not harm'; Galen (131–201) warned against the dangers of badly written and obscure prescriptions; and Rhazes (860–932) advised 'if simple remedies are effective do not prescribe compound remedies'.

Most of the drugs then in use were of plant or animal origin, but mercury, arsenic, and antimony were also used. The toxic effects of arsenic were well recognized from its deliberate use as a poison, and the dangers of mercurial inunction were also familiar, but toxic properties of antimony attracted less attention.

As time passed, the questionable purity of remedies began to exercise the minds of both civil and professional authorities. In 1224 the Hohenstaufen Emperor, Frederick II, ordered the regular inspection of the drugs and mixtures prepared by apothecaries, and pronounced that the life of a purveyor of a poison, a magic elixir, or a love potion would be forfeit if a consumer died. For many years after the foundation of the Royal College of Physicians, in 1518, its Fellows concerned themselves with the quality control of drugs; and the authors of the first London *Pharmacopoeia* (1618) spoke harshly in their preface of 'the very noxious fraud and deceit of those people who are allowed to sell the most filthy concoctions ... under the name and title of medicaments ...'. Ironically, they themselves were content to include worms, dried vipers, and fox lung in their catalogue of acceptable remedies.

In the seventeenth century, for the first time, a named drug was proscribed because of its toxicity: members of the Paris Faculty of Physicians were forbidden to use antimony. But the ban could not be maintained after the drug was credited with the cure of an attack of typhoid suffered by Louis XIV in 1657.

Not until 1745, when Sir William Heberden published his *Antitheriaca, Essay on Mithridatium and Theriaca*, was the value of compound remedies and animal extracts seriously questioned. Even so, physicians were very slow in improving their standards of treatment and they long continued to deserve Voltaire's stricture that they 'poured drugs of which they knew little into bodies of which they knew less'.

Perhaps the most elegant and definitive of descriptions of an adverse drug reaction was William Withering's account of digitalis toxicity in 1785: 'The Foxglove, when given in very large and quickly repeated doses, occasions sickness, vomiting, purging, giddiness, confused vision, objects appearing green or yellow, increased secretion of urine with frequent motions to part with it, and sometimes inability to retain it; slow pulse, even as low as 35 in a minute, cold sweats, convulsions, syncope and death.'

At about this time, epidemics of yellow fever in some American states brought to mercury both fame and notoriety. Believing that in this disease 'the gastrointestinal tract was filled with putrid and fermenting biliary substances' and that their expulsion was the key to cure, some physicians advocated large doses of calomel (mercurous chloride) often mixed with other purgatives (Risse, 1973). Many patients were apparently unharmed by this heroic therapy, possibly because the vomiting caused by the infection drastically reduced the systemic absorption of the mercury. Others were less fortunate and developed classical mercurialism with intense salivation; loosening of the teeth; and ulceration, even gangrene, of the mouth and cheeks, and osteomyelitis of the mandible (Risse, 1973).

Nevertheless, by the next century calomel had become a 'cure-all' in febrile illness, the 'Sampson of the Materia Medica'. But if most doctors had come to view the drug through rose-coloured spectacles, some laymen regarded it (and its prescribers) in a different light:

> Since calomel's become their boast,
> How many patients have they lost,
> How many thousands they make ill,
> Of poison with their calomel.

Some physicians now added their protests. One wrote of 'Calomel considered as a poison' (Mitchell, 1844–5), and another, with calomel in mind, commented: 'if the whole materia medica, as it is now used, could be sunk to the bottom of the sea, it would be all the better for mankind—and all the worse for the fishes' (Holmes, 1861). Despite such broadsides, calomel remained in favour among physicians for years to come and is believed to have paved the way for such unorthodox (but, at the time, gentler) systems of healing as homeopathy, osteopathy, chiropractic, Thompsonianism, and Grahamism.

The nineteenth century saw the appearance in several countries of important new pharmacopoeias which for the first time laid down standards of drug purity. In 1848, the first statute was passed to control the quality of drugs in America after quinine imported for the Army was found to have been adulterated.

In the closing years of the nineteenth century and the early years of the twentieth came other innovations. There were the formal enquiries into suspected adverse reactions to drugs; the first concerned with sudden deaths during chloroform anaesthesia (McKendrick *et al.*, 1880), and the second with jaundice following arsenical treatment of syphilis (Medical Research Council, 1922). Then the American Medical Association established the Council on Pharmacy and Chemistry and its publication *New and Nonofficial Remedies* 'a mighty service for American medicine' (Leake, 1929). Next, the American Food, Drug and Insecticide Administration (later the Food and Drug Administration) was established. But much remained to be done: in 1929 Leake drew attention to the inadequacy of existing testing procedures for new drugs: 'many drug firms make the mistake of believing that their chemists can furnish trustworthy pharmacologic opinion. Indeed some eminent chemists impatient with careful pharmacologic technic have ventured to estimate for themselves the clinical possibilities of their own synthetics .... There is no short cut from the chemical laboratory to the clinic except one that passes too close to the morgue.' His words were prophetic: in 1937, 107 people died as a result of poisoning by an elixir of sulphanilamide containing as a solvent diethylene glycol (Department of Health, Education and Welfare, 1972; Geiling and Cannon, 1938). The manufacturers had not troubled to enquire whether the solvent was safe for its purpose; yet the toxic effects of diethylene glycol and closely related compounds were already documented (Von Óettingen and Jirouch, 1931; Barber 1934). In the wake of the disaster came a Federal act which forbade the marketing of new drugs until they had been cleared for safety by the Food and Drug Administration.

In France, a disaster of similar magnitude occurred in 1954 when 100 people died from poisoning by Stalinon, an organic compound of tin used in the treatment of boils (Wade, 1970).

Major catastrophies of this kind focused attention on the problem of drug toxicity, but awareness and concern were only transient. The profession's threshold of stimulation remained too high and its latent period before reaction too long. It had taken some 47 years to discover that amidopyrine was a potent marrow poison (Wade, 1970). Fifteen years had passed before it was appreciated that cincophen caused jaundice (Worster-Drought, 1923) and 11 years more before this fact gained recognition (Wade, 1970). Aspirin had been in use for 39 years before it was incriminated as a cause of gastric haemorrhage (Douthwaite 1938) and for another 20 before the news spread adequately (Alvarez and Summerskill, 1958). The dangers of chloramphenicol were first appreciated in the early 1950s, yet some two decades later the Chairman of a US Senate Subcommittee had good cause to complain that warnings of these dangers had gone unheeded (*Journal of the American Medical Association*, 1968). Until the 1950s textbooks of medicine devoted comparatively little space to adverse drug reactions, and that only to the ill-effects of one or two drugs. Few medical teachers had much to say on the subject. Epidemiological studies of adverse drug reactions were almost unknown.

Then the climate began to change. In 1952 appeared the first book to concern itself entirely with adverse drug reactions (Meyler, 1952). In the same year the Council on Pharmacy and Chemistry of the American Medical Association set up an organization to monitor drug-induced blood dyscr-

asias. A little while later, the first report of epidemiological studies of adverse drug reactions were published; and in 1960 the Food and Drug Administration began to collect reports of adverse reactions and sponsored new hospital drug-monitoring programmes.

In the winter of 1961 came news of the thalidomide disaster—a sudden upsurge in the number of babies born with the deformities of phocomelia or micromelia. Thalidomide had been prescribed as a 'safe' hypnotic. It had not been tested in animals for teratogenicity, but thousands of babies born to mothers who had taken the drug during pregnancy provided the missing data.

As a result of this horrifying epidemic, many countries established agencies concerned with drug safety such as our own Committee on Safety of Drugs: and later the World Health Organization set up an international bureau to collect and collate information from national drug-monitoring organizations. Such agencies have done much to identify and prevent illness caused by drugs; but they provide no absolute guarantee against outbreaks of novel and quite unpredictable reactions such as those produced by practolol (see Chapter 4).

In Great Britain the Medicines Act of 1968 provided new and comprehensive safeguards covering most aspects of drug development, production, and use. The beneficial effects of these measures on drug safety have been supplemented in recent years by the wealth of information on rational therapeutics and drug toxicity provided by general and specialized medical journals and books and by teachers of clinical pharmacology and toxicology.

Governments, editors, and teachers have done a great deal—perhaps as much as they can ever do. It remains for the prescribing doctor to match their efforts.

M. A. Beedie and D. M. Davies

EPIDEMIOLOGY

INCIDENCE OF ADVERSE DRUG REACTIONS

Reactions during Hospital Admission

The reported incidence of adverse drug reactions varies from 1 per cent or less (Barr, 1955; MacDonald and MacKay, 1964; Schimmel, 1964; Reidenberg, 1968) to 28 per cent (Miller, 1974a), but in most studies the figure has been between 10 and 20 per cent (Seidl *et al.*, 1965; Smith *et al.*, 1966; Ogilvie and Ruedy, 1967; Hoddinott *et al.*, 1967; Simmons *et al.*, 1968; Hurwitz and Wade, 1969; Gardner and Watson, 1970; Davies *et al.*, 1976). This disparity reflects differences in the methods used to detect and report adverse reactions: when investigators have relied on other people to notify them of adverse reactions the yields have been low (MacDonald and MacKay, 1964; Reidenberg 1968), but when they have undertaken both detection and recording for themselves (Hurwitz and Wade, 1969; Davies *et al.*, 1976) yields have been much higher. Both types of survey are open to criticism: records dependent on information from a number of sources are unlikely to be complete; on the other hand, direct questioning of patients by an 'adverse reactions officer' may generate spurious reactions by suggestion. All surveys are bedevilled by the problem of differentiating between symptoms or signs due to natural disease and those due to its treatment.

The formidable difficulty in deciding whether a disorder was or was not drug-induced is well illustrated by an investigation described by Koch-Weser (1977). As part of a drug monitoring programme, doctors writing case summaries following the discharge of patients from hospital reported and briefly described any clinical event they suspected to have been an adverse drug reaction. Five hundred of these reports were then evaluated by three clinical pharmacologists, all using 'the same explicit and tried definitions' of adverse drug reactions. They decided that in only about a fifth of the cases were the reporting doctors undoubtedly correct in their diagnosis of an adverse drug reaction. Furthermore, the clinical pharmacologists disagreed with each other surprisingly often, not only on the question of whether a disease was definitely, probably, possibly, or not an adverse reaction, but also on the drugs most likely to have been responsible for individual reactions. Even when untreated patients have been used as controls there has been some possibility of bias because the assessors have not been 'blind' (Hurwitz and Wade, 1969). And control observation of symptoms and signs before the administration of drugs is not usually practicable in surveys of this kind. A detailed analysis and criticism of the surveys reported up to the present time has been published by Karch and Lasagna (1975), and it is clear that the data at present available provide at best only a very rough guide to the incidence of adverse drug reactions.

Reactions as a Cause of Admission to Hospital

Reported estimates of the incidence of adverse reactions as the only or main reason for a patient's admission to hospital fall within the fairly narrow range of 2.9–5.1 per cent (Hurwitz, 1969a; Caranasos *et al.*, 1974; Miller, 1974b; Seidl *et al.*, 1965; Gardner and Watson, 1970).

Fatalities

The deaths reported to the Committee on Safety of Medicines as possibly caused by drugs (taken in therapeutic doses) during the period June 1964 to October 1971 have been reviewed by Girdwood (1974), but the difficulty in interpreting the data in the face of incomplete reporting (Inman, 1970) and inadequate knowledge of drug usage was stressed by this author.

After carefully analysing the data obtained from a number of published surveys, Karch and Lasagna (1975) have concluded that 'the range of prevalence of fatal drug reactions' is 0–0.31 per cent of hospital medical inpatients, but they point out that all of these studies were carried out in university teaching hospital services which may not be representative of all hospital medical wards. Surveys published since the Karch and Lasagna analysis put the figure for deaths mainly or wholly due to treatment at 0.01 per cent for surgical inpatients (Armstrong *et al.*, 1976) and about 0.1 per cent for medical inpatients (Caranasos *et al.*, 1976; Porter and Jick, 1977).

Day of Onset of Adverse Drug Reactions

The period during which most patients are likely to suffer an adverse reaction was identified by Seidl and his colleagues (1965) as the first day, by Miller (1974a) as the second day, by Hurwitz and Wade (1969) as the first 2 days. The reactions recorded by Ogilvie and Ruedy (1967) were divided almost equally between the first 9 days. In all series almost all the reactions occurred by the eleventh day.

Types of Reaction

In the patients studied by Hurwitz and Wade (1969) the type of reaction which occurred most frequently was the unwanted pharmacological action of a drug; next most common was an excessive effect of the required pharmacological action of a normal dose of the drug; and the third was an allergic reaction. In the series reported by Caranasos and others (1974) the bulk (82.4 per cent) of the reactions responsible for the patient's admission to hospital were considered to have a pharmacological mechanism, and the remainder (17.6 per cent) were allergic in character. In the survey of Ogilvie and Ruedy (1967), 81 per cent of the reactions were thought to have a pharmacological basis.

Drugs Causing Reactions

In the series of Caranasos and others (1974) one-third of all reactions were attributed to eight types of drug, the first five of which were aspirin, antimicrobials, digoxin, anticoagulants, and diuretics. Ogilvie and Ruedy (1967) found that 90 per cent of reactions were caused by digitalis, antimicrobials, insulin, and diuretics. Miller (1974b) reported that the drugs most commonly causing or strongly influencing admission to hospital were digoxin, aspirin, prednisone, warfarin, and guanethidine; and that heparin, prednisone, spironolactone, hydrochlorothiazide, and digoxin had the highest reaction rates.

In an analysis of cases reported to the Committee on Safety of Medicines, Girdwood (1974) found that the drugs suspected to have caused over 50 deaths in the period under review were oral contraceptives (332 deaths), phenylbutazone (217), chlorpromazine (102), adrenal corticosteroids (94), isoprenaline (84), phenacetin (77), aspirin (72), oxyphenbutazone (69), indomethacin (68), halothane (57), and amitriptyline (50).

Differences in Prescribing Habits

The incidence of adverse drug reactions may vary from place to place within the same country because of differences in prescribing habits. For example, in Northern Ireland the use of an oral antidiabetic drug and the prescribing of amphetamines differed greatly in different areas (Wade, 1968; Hood and Wade, 1968). Others have shown a wide variation in the prescribing of antibiotics in different European countries (Engels and Siderius, 1968).

PREDISPOSING FACTORS

Race

Some investigators (Miller, 1974a) have observed that adverse drug reactions of all types are commoner in white than in dark races, but others (Seidl *et al.*, 1965; Caranasos *et al.*, 1974) have found no such difference.

The rate at which drugs are acetylated varies considerably between individuals and ethnic groups. Rapid acetylators predominate among Eskimos and Japanese, and slow acetylators among Mediter-