TEXTBOOK OF ADVERSE DRUG REACTIONS

EDITED BY

D. M. DAVIES, FRCP

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Editor of the *Adverse Drug Reaction Bulletin*

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Preface

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.

Drugs can affect the results of laboratory tests either indirectly, by altering the function of organs; or directly, by interfering *in vitro* with the chemical or physical processes employed in the laboratory. Effects of the first type are discussed in several chapters in this book; and effects of the second type are given attention in Appendix 1.

Only official or approved names of drugs are used in the text, but, for the benefit of those who find trade names helpful, a selection of British, North American, and Australasian proprietary equivalents are listed in Appendix 2. Some of the drug names used in the text refer to chemical, pharmacological, or therapeutic groupings; and examples of individual members of these groups are given in Appendix 3. Appendix 4 lists the sex hormones referred to in the text and their principal actions.

The contributors are most grateful to the medical secretaries who assisted them with the preparation of their chapters; and a very special vote of thanks is due to Miss Jean Hill, Editorial Secretary of the *Adverse Drug Reaction Bulletin*, for the immense help she has given the Editor and many of the contributors at every stage in the evolution of this book.

August 1976 D.M.D.

Foreword

by 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 salutory, 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 postgraduate, 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 enthusiams 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 review-in 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, especially 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.

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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 B.C., 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 B.C.), who said of drugs that there were 'many excellent when mingled, and many fatal' (*Odyssey*, IV). Hippocrates (460–570 B.C.) 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 the 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 'Colomel considered as a poison' (Mitchell, 1844), 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 Oettingen 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 U.S. 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

dyscrasias. A little while later, the first reports 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. 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. 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

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 respresentative of all hospital medical wards.

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.

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; Flood 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 Mediterranean Jews. Compared with fast acetylators, slow acetylators are more likely to develop peripheral neuropathy due to izoniazid and lupus erythematosus associated with treatment with this drug or with hydrallazine (Rawlins, 1975); but, interestingly, fast acetylators may be more susceptible than slow acetylators to the type of lupus erythematosus associated with procainamide therapy (Davies *et al.*, 1975). Acetylator status also appears to influence susceptibility to phenytoin toxicity, for though this drug is metabolized by oxidation, rather than acetylation, its metabolism is impaired and its toxic effects become more likely when it is given at the same time as isoniazid to slow acetylators (Kutt *et al.*, 1970; Brennan *et al.*, 1970).

Glucose 6-phosphate dehydrogenase (G6PD) deficiency, which predisposes to haemolytic anaemia caused by certain drugs (see Chapters 2 and 22) is much commoner among Africans, Kurdish and Iraqui Jews, some Mediterranean peoples, and Filipinos than among other races.

It has been demonstrated (Jick *et al.*, 1969) that a woman's blood group significantly influences her chances of developing thromboembolic disease should she use the contraceptive pill; and since the frequencies with which the various blood groups occur in a population differ widely throughout the world, it follows that the incidence of thromboembolism complicating oral contraceptive therapy might be expected to be influenced by race, other things being equal. The same can be expected of digitalis toxicity, for it has been shown that there is a relationship between blood groups and susceptibility to digoxin-induced cardiac arrhythmias (Miller, 1974a).

There may be racial differences in the incidence of haemolytic anaemia induced by methyldopa; for while a positive direct antiglobulin test is found in 15 per cent of Caucasian patients under treatment with this drug, no positive tests were found in 73 Indians and Africans who had been taking methyldopa for at least 3 months (Seedat and Vawda, 1968), or in 58 Chinese patients who had received the drug for at least 9 months (Burns-Cox, 1970; Chen and Ooi, 1971).

Women in Scandinavia and Chile appear to be particularly susceptible to the cholestatic jaundice induced by oral contraceptives (Sherlock, 1972).

Some of the types of porphyria that are aggravated by drugs (see Chapter 2) vary in incidence between different races. For instance, acute intermittent porphyria is more frequent in people of Scandinavian,

Anglo-Saxon, or German origin than among other ethnic groups, while the disease is very rare in Negroes (Schmid, 1971).

Other Genetic Influences

Some individuals have a genetically determined deficiency or abnormality of plasma pseudocholinesterase which makes them liable to unusually prolonged muscular paralysis and apnoea when they are given the muscle relaxant suxamethonium during a surgical operation. Another genetically determined abnormality of importance in relation to anaesthesia is malignant hyperpyrexia, which may develop in susceptible subjects when they are given a general anaesthetic (usually halothane) together with a muscle relaxant (suxamethonium).

An inherited resistance to coumarin anticoagulants has been described (O'Reilly *et al.*, 1964; O'Reilly, 1970); such an abnormality could result in a disastrous delay in achieving a therapeutic anticoagulant effect.

There are several inherited biochemical abnormalities of red blood cells which make affected patients more vulnerable than usual to methaemoglobinaemia induced by oxidant drugs (Rawlins, 1975).

Sex

Experiments in animals have shown that sex influences susceptibility to the toxic effects of some drugs. When normal male mice were exposed to low concentrations of chloroform they developed renal damage, but castrated males were not affected in this way, and males treated with oestrogens became partially resistant to this toxic effect. Normal females were immune, but became partially susceptible following oöphorectomy, and fully susceptible after treatment with androgens (Hurst, 1958). Female rats slept a longer time than male rats when given the same dose (per kg body weight) of a barbiturate (Hurst, 1958).

Several studies have shown that women are more likely than men to suffer adverse reactions to drugs (Seidl *et al.*, 1965; Hurwitz, 1969b; Davies *et al.*, 1976; Caranasos *et al.*, 1974; Miller 1974a). Women also appear to be more susceptible to the toxic effects of digoxin (Hurwitz and Wade, 1969) and to haemorrhage induced by heparin (Miller, 1974a). Agranulocytosis caused by phenylbutazone or chloramphenicol is about three times commoner in women than in men (D'Arcy and Griffin, 1972), and aplastic anaemia due to chloramphenicol twice as common (Yunis and Bloomberg, 1964). Drug associated lupus erythematosus more often affects women than men, as does the spontaneous disease (Lee and Siegel, 1968).

Age

The Elderly

Hurwitz (1969b) found that patients over 60 years of age were more liable to suffer adverse drug reactions than those under this age. Miller (1974a) concluded that patients in the 66–75 age group were 'slightly' more prone to adverse drug reactions than those in other categories, and Caranasos and others (1974) found that in the 71–80 age group there was a significantly greater number of admissions due to adverse drug reactions; but Davies and his colleagues (1976) could not demonstrate a difference in the incidence of adverse drug reactions among those over 65 compared with those younger than this.

Digoxin Toxicity. It has been shown that a single dose of digoxin produces a higher plasma concentration and a longer plasma half-life of the drug than is found when the same dose is given to younger people (Ewy *et al.*, 1969) and this may partly explain the high incidence of digitalis toxicity found in older patients (MacDonald and MacKay, 1964; Ogilvie and Ruedy, 1967; Hurwitz and Wade, 1969), though potassium depletion induced by powerful modern diuretics in patients taking a poor diet may play a part, and renal tubular excretory and secretory factors may also be involved (Hall, 1972).

Anticoagulant Haemorrhage. Elderly patients are more likely to bleed during heparin treatment than are younger patients (Miller, 1974a), the reaction rates being 50 per cent for women over 60, 19 per cent for men over 60, 14 per cent for women under 60, and 10 per cent for men under 60. Experiments in man have shown that the anticoagulant effect of a single dose of warfarin is greater in the old than in the young (Hewich *et al.*, 1975), a finding in keeping with clinical experience.

Reactions to Analgesics and Hypnotics. It has long been accepted that elderly patients are more sensitive to the effects of powerful analgesics than younger patients; and that they are apt to become confused and disturbed by barbiturates. Possible explanations for these clinical impressions are provided by experiments which show that after a standard single intravenous dose of pethidine, the plasma concentration is higher and the half-life of the drug is

longer in the old than in the younger subjects (Chan *et al.*, 1975); and that the rate of hydroxylation of amylobarbitone is reduced in the elderly (Irvine *et al.*, 1974). Geriatric patients are particularly prone to cerebral dysfunction when they take nitrazepam in the usual adult dose (Evans and Jarvis, 1972).

Experimental studies also suggest that the old may be at greater risk of suffering adverse reactions to phenylbutazone (O'Malley *et al.*, 1971) and propranolol (Castleden *et al.*, 1975). The elderly are more liable than the young to develop potassium depletion from diuretic therapy, postural hypotension caused by antihypertensive drugs and phenothiazines, urinary retention from anticholinergics and antiparkinsonian drugs, and spontaneous hypothermia associated with treatment with sedatives and tranquillizers (Hall, 1972).

The Young

In the neonate, especially when premature, some of the enzymes involved in drug metabolism and elimination are poorly developed, and consequently the risk of adverse reactions to some drugs is increased. The most hazardous drugs in this respect are chloramphenicol, sulphonamides, novobiocin, barbiturates, morphine and its derivatives, and vitamin K and its analogues. In the very young child, chloramphenicol may induce the Grey Syndrome, characterized by abdominal distension, vomiting, peripheral cyanosis, profound shock, respiratory failure, and death. Sulphonamides, novobiocin, and vitamin K analogues may induce or aggravate kernicterus, and barbiturates and morphine, and other narcotics, may cause severe respiratory depression.

Some ototoxic antibiotics (e.g., streptomycin) are cleared by the kidney more slowly in the young child than in the adult, and toxic effects may occur unless the dose is suitably adjusted. The increased sensitivity to digoxin in the first two weeks of life may be explained by a similar mechanism (Robinson and Williams, 1970).

The increased sensitivity of the newborn to morphine and its derivatives has been attributed to a poorly developed glucuronidation process (Holzel, 1965), 'imbalance' of cholinergic and adrenergic regulation (Gädeke, 1972), and the inefficiency of the immature blood–brain barrier (Done and Jung, 1970).

Poorly developed oxidation reactions and/or inadequate renal function may also account for the poor tolerance of the newborn to some barbiturates (Gädeke, 1972).

Other Factors

Allergic Disorders. It has been found that patients with a history of allergic disorders are more likely than others to develop adverse reactions, including those which are not allergic in character (Hurwitz, 1969b; Davies *et al.*, 1976).

Previous Adverse Reactions. Patients who have previously suffered a drug reaction appear to be more susceptible than others to adverse reactions in general (Hurwitz, 1969b; Davies *et al.*, 1976).

Renal and Hepatic Disease. Impaired renal function predisposes to adverse reactions to those drugs wholly or mainly excreted unchanged in the urine, while hepatic dysfunction has a similar effect in relation to drugs that are detoxicated in the liver. The influence of these and other disease states on susceptibility to adverse drug reactions are described in the relevant chapters of this book.

Plasma Protein Binding. The pharmacological actions and toxicity of certain drugs are influenced by the degree to which they are bound to plasma proteins (mainly albumin), and a decrease in plasma albumin due to age, malnutrition, or disease may modify both the pharmacological activity and metabolism of drugs that are highly protein-bound (Trounce, 1975).

Formulation of Drugs. On rare occasions 'epidemics' of a particular adverse reaction have occurred because of a toxic vehicle or a change in formulation. The sulphanilamide disaster of 1937 has already been described. In the 1960s came reports of a Fanconi-like syndrome in patients who had been treated with outdated, degraded tetracyclines (Gross, 1963; Frimpter *et al.*, 1963; Sulkowski and Haserick, 1964). The chemical change responsible for the toxic effects had been initiated by the buffering agent citric acid, no longer used in tetracycline formulations. In Australia, in 1968, pharmaceutical manufacturers changed the excipient present in some capsules of phenytoin from calcium sulphate dihydrate to lactose, and many patients taking the new preparation developed symptoms and signs of phenytoin toxicity (Tyrer *et al.*, 1970). These and other problems presented by components of drug vehicles have been reviewed by Rogers and Barrett (1974).

CONCLUSIONS

Opinions differ on the conclusions to be drawn from the evidence given above. Some commentators take a gloomy, almost horrific, view: 'economic con-

sequences are staggering, one seventh of all hospital days are devoted to the care of drug toxicity at an estimated cost of $3,000,000,000' (Melmon, 1971). 'It is now known that billions of wasted dollars, hundreds of thousands of unnecessary hospitalizations for adverse drug reactions, and thousands of lives needlessly lost is the price society pays for the promotional excesses of the drug industry' (statement at a Congressional hearing—quoted by Jick, 1974). Others see things in a different perspective. Jick (1974), while accepting that in the U.S.A. adverse drug reactions 'yearly afflict millions of people, causing hundreds of thousands of hospitalizations, and deaths numbering tens of thousands', concludes, from data collected for the Boston Collaborative Drug Surveillance Program, that drugs 'are remarkably non-toxic, as benign as one could reasonably expect'. He points out that rates and severity of adverse reactions to individual drugs are remarkably low in view of their pharmacological properties; and that the large amount of illness and large number of deaths caused by adverse drug reactions reflect the extensive use of drugs rather than the intrinsic toxic potential of particular drugs. Most adverse reactions, he claims, are self-limiting and of little consequence to the clinical course of the patient's illness. Serious reactions are uncommon, tend to occur in patients who are quite ill, and are mainly caused by a relatively small number of drugs which by their nature are known to be quite hazardous. Death caused by a drug is quite rare and occurs usually in patients who are already severely ill. The majority of deaths are attributed to a small number of drugs. From the nature of these drugs one may safely assume that the number of deaths caused by them is quite small in relation to the number of lives they save. He believes that only in fluid and electrolyte therapy are individual adverse drug reactions preventable to any significant degree.

This view is reassuring, but it implies an overall care and competence in treatment which is not always apparent to experienced clinicians with open eyes and an interest in therapeutics, who are convinced that many powerful and potentially dangerous drugs are used with insufficient thought and caution and continue to be given when they might be withdrawn without detriment and, indeed, with benefit to the patient's condition. They would point out that many illnesses are short-lasting and do not require the drug that is often given; that simple and innocuous remedies can provide greater and quicker relief than the more complex remedies usually employed; that the safest drug is not always used when there is a choice; that where one drug would have sufficed, more have often been given; and that a doctor has sometimes prescribed a drug without knowing what other drugs the patient is taking, or used a mixture not knowing precisely what it contained and the pharmacological actions of its ingredients.

'There can be little doubt that much modern medicinal treatment is unnecessary. Patients have come to believe that the mildest of symptoms, even the ordinary trials and tribulations of everyday life, must be matched by a drug. Sir Derrick Dunlop (1970) has calculated that in the U.K. in 1968 enough phenothiazine tranquillizers were prescribed to give a month's treatment with one of these drugs to every tenth patient, and enough hypnotics to ensure that every tenth night's sleep was drug-induced. He comments that when one examines prescribing figures it is difficult 'to avoid the suspicion that the overworked medical profession in this country may be unduly concerned with satisfying the public's "wants" rather than what we think are its "needs", and that the extent to which their demands are acceded to by our profession are disturbing features of modern medicine'.

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