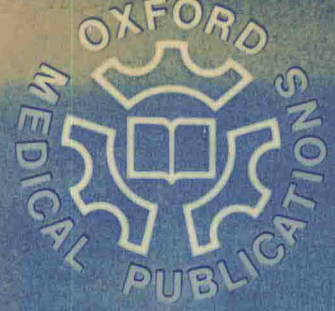

Iatrogenic Diseases

SECOND EDITION

FOREWORD BY SIR DOUGLAS BLACK

P. F. D'Arcy and J. P. Griffin

Iatrogenic diseases

Second edition

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Foreword

by Professor Sir Douglas Black, MD, PRCP
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'Iatrogenic Disease' is by now a convenient and accepted term, used to cover the formidable array of adverse reactions which are, let us face it, an inescapable consequence of the potency of modern therapeutic agents. Traditional remedies on the whole were innocent both of effect and of side-effect; but the Pandora's box of modern drug therapy, while affording previously unattainable prospects of alleviation and of cure, likewise contains the potential of effects which are commonly troublesome, and at times frankly dangerous.

Although by now widely accepted, the term 'iatrogenic disease' is not beyond criticism. Linguistically, by analogy with 'carcinogenic', it might be thought to denote a disease which produces doctors. More seriously, since this confusion is unlikely to arise, it attaches by implication blame for these troubles to the doctor, whereas the actual generation of side-effects is a much more complex affair, arising as it does from a network of interactions between drug and disease on the one hand, and patient and doctor on the other.

Although logically the concept of iatrogenic disease should include the adverse effects of investigation and other medical procedures, the spotlight of public attention, especially after thalidomide and practolol, is understandably focused on the adverse effects of pharmaceutical agents, and more recently biological agents such as vaccines. There is certainly insufficient public awareness that there is no such thing as a drug which is both therapeutically potent, and at the same time absolutely safe under all circumstances. The effectiveness and the specificity of modern drugs greatly increase the responsibility of the doctor first of all to make an accurate diagnosis, and then to devise a scheme of treatment which will bring the disease under control with as little risk to the patient as possible. It is in this latter context that the book to which I am glad to have been asked to contribute this foreword, is particularly helpful. Systematic knowledge of the effects of modern drugs on the various systems of the body is here made available, together with information on the mechanisms of drug interaction. This important corpus of background knowledge, combined with constant vigilance towards the possibilities inherent in the taking of any powerful agent, are the safeguards of specific therapy.

Even so, it is not possible to avoid entirely the adverse effects of treatment. When a patient is struggling with mortal disease, as with the chemotherapy of neoplasm, adverse effects may have to be accepted at a level which would not be reasonable in the treatment of less severe disease. In an emergency situation, drugs may have to be administered, say to a comatose patient, without the possibility of enquiring into previous allergies, or a constitutional deficiency of acetylating enzymes. In long-standing treatment, say with monoamine oxidase inhibitors for depression, no list of foods to be avoided, however comprehensive, will entirely eliminate the risk of the patient taking some exotic delicacy, rich in amines; or taking a 'common cold cure' containing ephedrine.

Nevertheless, we have a collective responsibility to devise a strategy for lessening as far as possible the frequency and severity of drug reactions. The knowledge set out so plainly in this book is an important component of such a strategy, and provides a sound theoretical basis for counselling of the patient on possible side-effects, of which he should be aware. Such an explanation builds up trust between patient and doctor; and it cannot be substituted for by merely passing on the manufacturer's data sheets to a patient, who may lack the background for their comprehension. There is, of course, a place for printed summaries of advice in particular situations; but these supplement, and do not replace, direct verbal explanation by the doctor.

Preface to the second edition

Since the appearance of the first edition of *Iatrogenic diseases* in 1972 there has been a considerable increase in awareness on the part of both the medical and pharmaceutical professions and the general public that therapeutic substances must be judged by a consideration of the benefits and risks. It has also become more generally recognized that the use of any therapeutic agent is inevitably attended by a small risk that the patient may react adversely to the prescribed agent.

The major causes of adverse reactions to drugs are categorized in the Preface to the first edition and in general have not altered. However, awareness of another major factor in the interaction between patient and drug is becoming increasingly recognized and that is the contribution of the disease state in the manifestation of certain adverse reactions. The best known example of this is the characteristic ampicillin-induced rash in the patient with glandular fever. A more recently recognized example is the greater likelihood that patients with Hodgkins disease may develop peripheral neuropathy during vincristine treatment than patients being treated with the drug at comparable doses for other malignancies. In the coming years it is hoped that more emphasis will be placed on the identification of particular patient and disease factors that may influence the reaction to therapeutic substances than to the over hasty but popular and newsworthy condemnation of products that have produced adverse effects in a small number of patients. It is becoming increasingly necessary to determine under what circumstances an adverse event associated with exposure to a product occurred as opposed to the more simple identification of association of an adverse reaction with a particular drug. It is also becoming increasingly necessary to ensure that post-marketing surveillance schemes are established which are capable of identifying low incidence adverse effects.

In the years since our first edition was published the literature on adverse reactions to drugs has grown enormously and it has therefore been necessary for us to share the task of preparing this book with colleagues who have expert knowledge in their own fields and have contributed guest chapters.

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November, 1978

Preface to the first edition

The use of any therapeutic agent is inevitably attended by a small risk that the patient may react adversely to the prescribed agent. Adverse reactions can be caused by several different factors. In correlating the data for this book, it has been apparent that two factors are the major contribution to the manifestation of iatrogenic disease. These are the abnormal patient reaction to a drug, and the development of unexpected toxicity when several drugs are given in combination.

Predictable toxicity is the manifestation of secondary pharmacological actions; this is a hazard that can be well elucidated in the battery of tests to which the drug is subjected during its development stage. In such instances, assuming that the drug has a worthwhile place in therapy, the ratio of dosage of drug to produce the major effect, to dosage to produce a secondary (toxic) effect is the real factor which should be considered and not the 'built in' potentiality to the side-effect itself. Nevertheless, certain groups of patients exist who may be at risk from these predictable manifestations of toxicity. These patients are at peculiar risk because of a genetically determined defect of metabolism, or because their metabolism has been impaired by concomitant hepatic disease, or because their excretory function has been reduced by either liver or renal malfunction. In these instances, the drug or its metabolites may rapidly build up to toxic levels in the body, even at normal accepted therapeutic doses.

Intolerance is a lowered threshold to the normal pharmacological action of drugs. Individuals may vary widely from the well established norm in their reaction to drugs. The very old and the very young are liable to be more sensitive to drugs possibly because the metabolic and excretory mechanisms essential for the disposal of the drug are less efficient than in the adult. In addition, the reactions of the old or the young may also differ qualitatively from those of the adult.

Adverse reactions may follow the use of a drug, and these reactions may be unexpected, in that they are completely unrelated to the known toxicity of the drug. These reactions include hypersensitivity to the agent, in which the patient develops antibodies to the drug. The antigenic factor is usually a combination of drug with body protein. Skin rashes and eruptions are the most common symptoms of this type of allergic reaction, although haemolytic anaemia is not infrequent.

Idiosyncrasy involves a qualitatively abnormal response on the part of the patient to the drug; an example of this is drug-induced porphyria, in which a qualitatively abnormal response of porphyrin metabolism is induced by barbiturates in susceptible subjects. Similarly, mepacrine-induced haemolytic anaemia in glucose-6-phosphate dehydrogenase deficient subjects is an idiosyncratic reaction.

The role of polypharmacy in iatrogenic disease is not insignificant, since toxicities not shown by either drug singly may develop when used in combination. This ill-begotten offspring of medicine and pharmacy has been nurtured through the ages and William Withering wrote in 1785 that 'the ingenuity of man has ever been fond of exerting itself to varied forms and combinations of medicines'. This is equally true today and one objective of this book is to emphasize that the risk of untoward reaction bears a direct relation to the number of drugs prescribed at any one time.

The practice of treating trivial complaints by the simultaneous administration of a wide variety of drugs has been satirized by Moat (1969) in his article 'Life without Leeches' in the *Daily Telegraph Supplement* (255). He humorously described the treatment taken by a guest at his home:

> The other day a friend from the big world came to stay, and when I took him his breakfast I found him swallowing pills. He'd been depressed recently, which was why he took the yellow pills, antidepressants. The white pills were tranquillizers, and he took those because the yellow pills were inclined to agitate him. The mixture of white and yellow made him itch unbearably and affected his vision – hence the blue pills. He found this particular dosage of pills constipating, and for that he took a strong aperient. 'And just look at these', he said excitedly, waving at me a bottle of large multi-coloured pills. 'And what are those?' I asked. 'I don't know', he said, 'but I like to keep them till last'.
>
> I then asked him how he was feeling. He said he felt fine, except that the pills made him feel lethargic, which he personally found depressing.

Laurence, writing in the latest edition of his *Clinical Pharmacology*, expressed similar views when he said that

'habitual polypharmacy is sure to blur the outline of rational thought which should precede the use of any drug'. Unfortunately the danger of polypharmacy is somewhat concealed from the physician, since a patient, blissfully unaware of the hazards of drug interaction, may indulge in self-medication. For example, a prescribed monoamine oxidase inhibitor is taken together with a self-prescribed proprietary common cold remedy containing ephedrine, phenylephrine or other sympathomimetic amine. A life threatening hypertensive crisis may ensue.

In presenting the data in this book, it was felt that classification of drug-induced reactions into a systematic pathological approach would result in the most readable and useful presentation for the prescribing physician, for the student of medicine, for the pharmacist and the pharmacologist. We have attempted in this volume to produce an adjunct for the study of therapeutics and at the same time provide a reference book on the clinical aspects of drug toxicity.

Where we have referred to specific iatrogenic effects of drugs we have used the approved name rather than suggest that the reaction had been exhibited by any particular brand of drug. Nevertheless, to increase the usefulness of the book, we have given, in an appendix, the British, American and continental proprietary names of each drug, together with the approved name.

In conclusion, let all of us who contribute to the ultimate treatment of patients reflect on the prayer of Sir Robert Hutchinson which hangs on the wall of the Children's Ward at The London Hospital:

From inability to let well alone:
from too much zeal for the new
and contempt for what is old:
from putting knowledge before wisdom,
science before art, and cleverness before
common sense,
from treating patients as cases, and from
making the cure of the disease more
grievous than the endurance of the same,
Good Lord, deliver us.

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January 1971

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Contents

1 Monitoring

P.F.D'ARCY

'Our community is reluctant to accept that occasional risks are bound to accompany the benefits obtained from drugs.' This sentence taken from the report of Vere's lecture 'Risks of Everyday Life – Drugs' (1976) clearly sets the scene into which drug monitoring must enter.

It is well accepted that clinical trials do not comprise enough subjects to be reliable sources of drug-risk information (Vere, 1976); indeed huge numbers of subjects are sometimes needed to provide reliable estimates of incidence. Drug risks cannot be anticipated fully before marketing, particularly the delayed immune reactions of the types seen with methyldopa and practolol, nor can teratogenesis or mutagenesis be studied adequately at present (Vere, 1976). Even when an apparent association is found between drug and injury it is still difficult to ascertain whether this is or is not causal. Hill (1965) listed criteria for suspecting a causal relationship, but they are seldom attained with reports on adverse drug reactions; notable exceptions to this, however, are the graded relationship to oestrogen dose reported for thrombophlebitis and oral contraceptives (Inman *et al.*, 1970), and the 'method of successive differences' (Hogben and Sim, 1953) applied to the problem of post-anaesthetic jaundice (Inman and Mushin, 1974). Such analyses can, however, only be regarded as 'early-warning systems'; they alert the community to suspected dangers and indicate the need for, and the direction towards, more illustrative research.

Early methods of detection

Adverse reactions to drug therapy have been recognized for many years and the early medical literature contains numerous reports of such occurrences. For example, the fact that intravenous injections of aqueous solutions might give rise to a pyrogenic reaction has been recognized since the middle of the nineteenth century. The introduction of arsphenamine into clinical practice (Ehrlich and Hata, 1910), apart from being the first step in the effective treatment of syphilis, focused attention on the frequency with which fever followed the intravenous injection of this agent.

As it became more customary to inject drugs intravenously, other types of fever were reported. For example Hort and Penfold (1911, 1912*a*, *b*) showed that the fevers caused by the intravenous injection of drugs in therapeutic use at that time were all due to the contamination of water used in preparing the injections. However, even after large epidemics such as one in which over 90 persons were known to die after ingesting a sulphonamide preparation containing ethylene glycol (Geiling and Cannon, 1938) attempts to organize routine procedures for the early warning of undesired effects of drugs were few and far between. Even during the immediate post-war years when new drugs were rapidly emerging, it seemed adequate to leave the problem of recognizing unwanted drug effects in the hands of the industrial pharmacologists and toxicologists and the physicians who used the new drugs in clinical practice. Gradually, however, it came to be realized that this system was inefficient. In particular, it was appreciated that some drug reactions were so rare that individual clinicians might never see more than one or two examples. It was also recognized that, unless steps were taken to collate experience, important reactions – in the sense that they had serious consequences for the individual – might be missed (Doll, 1969).

It was not until reports of an association between chloramphenicol and bone-marrow depression had appeared (Lewis *et al.*, 1952; Welch *et al.*, 1954) that a Registry of Blood Dyscrasias was set up by the American Medical Association. Physicians were invited to report cases on a special form, and tabulations of the results were distributed twice a year to medical schools and interested organizations in the United States and abroad. Later a systematic review of the world literature was begun, and published reports were added. Subsequently the work of the Registry confirmed the original suspicions of the relationship between chloramphenicol and aplastic anaemia (Best, 1967).

However, this Registry had a restricted aim and did little to promote, or indeed facilitate, notification of information on non-haematological effects of drugs. In such instances information depended upon the practitioner who recognized the effect communicating his evidence to the medical journals or to the manufacturer of the drug in question. Nevertheless, by May 1961, the

results of the Registry had proved so useful that the Association expanded it to include the collection of reports on adverse reactions of all types.

The thalidomide disaster

Just six months after the American Registry expanded its function, Dr. Lenz, of Hamburg, read a paper to a meeting of paediatricians in which he expressed concern at the large increase in the number of children referred to his clinic with phocomelia and other mesodermal deformities. The thalidomide epidemic had arrived, and with this advent the prevention of unwanted drug effects had become a matter of public concern throughout the world.

In retrospect, it is evident that the epidemic began in West Germany in 1959, three years after thalidomide was first marketed. Occasional cases of phocomelia had occurred previously, but the malformation was rare, and most West German paediatric clinics saw none at all during the 10 preceding years. Then 17 cases were seen in 10 clinics in 1959, 126 in 1960, and 477 in 1961. Many factors were considered as possible causes, but when Lenz investigated his patients retrospectively with a questionnaire, at least 20 per cent of the mothers were found to have taken thalidomide in early pregnancy; a figure that was raised to 50 per cent on more intensive interrogation. In contrast, none of the 300 women who had given birth to normal infants were found to have taken the drug in the same period (Lenz, 1962).

Thalidomide was not used to the same extent in the United Kingdom and the total number of affected children recorded in the national survey at the end of 1962 was about 300; less than a tenth of the estimated numbers in West Germany. As a result, in the United Kingdom, the numbers seen in any one clinic were extremely small, and Speirs (1962) and Kohler *et al.* (1962) were the only clinicians to recognize a local epidemic before the cause was discovered. Clear evidence was obtained, however, by examining the registers of congenital malformations that were kept for research purposes in Birmingham and Liverpool. These showed that an epidemic had occurred with a temporal distribution that corresponded with the supply of thalidomide to drug-wholesalers after an interval of nine months (Smithells, 1963). Further evidence was also provided by the fact that both the consumption of thalidomide and the incidence of the characteristic malformations were appreciably greater in Liverpool than in Birmingham. Further discussion on thalidomide and other drug-induced teratogenicity is given in Chapter 25.

Drug regulation bodies

Partly as a result of the thalidomide disaster many countries set up agencies to collect and process data on suspected adverse drug reactions. Included in such agencies were a branch of the American Food and Drug Administration, and a branch of the World Health Organization. At that time, no national machinery existed for the early detection of adverse drug effects in Britain. Existing legislation concerning drugs and poisons was complex and multidirectional and although comprehensive, in so far as sale or supply was concerned, it was not directly orientated towards the safety of medication, except in relation to specific products of biological origin where the Therapeutic Substances Act controlled manufacture and purity. Such legislative machinery seemed to work well in Britain and had done so for decades, but no great problem of drug safety had yet arisen to test its efficacy and suitability.

The need for further and consolidated legislation on medicines had already been considered by the Government Departments concerned when the revelation of the devastating effects of thalidomide focused public attention to the inadequacy of the existing legislation on drugs. A joint sub-committee of the English and Scottish Standing Medical Advisory Committees considered this situation and recommended the establishment of an expert committee to review the evidence as to new drugs and to offer advice on their toxicity; thus in June 1963, The Committee on Safety of Drugs ('The Dunlop Committee') was formed. The Committee had no legal powers, but worked with the voluntary agreement of the Association of the British Pharmaceutical Industry and the Proprietary Association of Great Britain. These two pharmaceutical organizations promised that none of their members would put on clinical trial or release for marketing any new drug against the advice of the Committee, whose advice they would always seek.

In October 1968, The Medicines Act was passed and came into force in September 1971 in the United Kingdom; it replaced most of the previous legislation on the control of medicines. Amongst the new provisions introduced by the Act was The Committee on Safety of Medicines. This was in effect a continuation of the former Committee on Safety of Drugs but with statutory authority to advise the Health Ministers (the Licensing Authority) on questions of safety, efficacy, and quality of medicines. The Committee was also given the responsibility of collecting and investigating reports on adverse reactions to medicines. Government had thus entered into a drug-monitoring role.

Reporting of adverse reactions

The primary mechanism of the British system of monitoring adverse reactions to drugs is based on a voluntary and spontaneous reporting system using a simple, reply-paid, 'yellow card' whereby doctors and dentists are encouraged to report 'all reactions of a serious, uncommon, or unusual nature', and all reactions with new drugs 'no matter how trivial' to the Committee on Safety of Medicines.

The number of reports of suspected adverse reactions to drugs in Britain still, however, remains a disappointingly low proportion of the envisaged total and thus the true incidence of even major drug-induced reactions is as yet not well documented. In 1969, Sir Derrick Dunlop wrote: 'The fraction reported to the Committee just constitutes the tip of the iceberg most of which remains submerged beneath the surface of our awareness'; this situation has not changed.

When in doubt, report!

The reasons for under-reporting by doctors are many; the most obvious are that many doctors seem uncertain what to report, and, in spite of the publicity given to the yellow-card system, some doctors are still uncertain how to report. The situation may be complicated in the hospital when a patient is referred by a general practitioner and is seen by a houseman, a registrar, and a consultant; there is confusion as to who reports – and frequently no report is made by default. There is also the common misapprehension that the Committee on Safety of Medicines expects the doctor to be *certain* that a particular drug has been responsible for a reaction before a report is made. This is not so, indeed it is rarely possible to be *certain* in an individual patient that a particular drug has caused a reaction. The patient may be receiving several drugs simultaneously and many reactions are themselves the signs or symptoms of a disease which can occur independently of drug treatment. Although the degree of suspicion aroused by a single report may be small, a collective assessment of a number of similar cases by the Committee on Safety of Medicines may greatly strengthen this suspicion and lead to the identification of a new hazard. For these reasons the Committee on Safety of Medicines has always asked doctors to report their suspicions and not to restrict their report to reactions which they believe have *definitely* been caused by a drug.

The seven deadly sins

In 1976, Inman described as 'the seven deadly sins' some of the many reasons why reporting by general practitioners is so incomplete. These are well worth repetition in this context since the problem still remains. These comprise:

1. *Complacency*, the result of a mistaken belief that only safe drugs are allowed on to the market;
2. *Fear* of involvement in litigation or of an investigation of prescribing costs;
3. *Guilty feelings* about damage which may have been caused to patients;
4. *Ambition* to collect and publish a personal series of cases;
5. *Ignorance* about what should be reported;
6. *Diffidence* in reporting mere suspicion; and
7. *Indifference* to the responsibility that an individual doctor has to contribute to the general body of knowledge about the effects of drug treatment.

The American scene

In the United States there may be a further complication in collecting accurate statistics on adverse drug reactions from the general practice doctor. The Food and Drugs Administration report of 1966 suggested that physicians were becoming increasingly fearful of reporting reactions and deaths because of the fear of legal reprisals (Inman's sin number two). Certainly this fear may have some firm basis since a conservative estimate among some medical authorities who have studied the problem of faulty prescriptions and preventable adverse drug reactions is that 30000 Americans die each year as a direct result of taking the medicines their doctors have prescribed for them. In January 1976, the *New York Times* published a five-part series on 'Medical incompetency' in the United States and said that, in addition to the 30000 fatalities 'perhaps ten times as many patients suffer life-threatening and sometimes permanent side-effects such as kidney failure, mental depression, internal bleeding, and loss of hearing or vision' as a result of wrong or unnecessary prescriptions.

Other medical opinions in America hold that the varied estimates of 30000–140000 deaths from drug therapy each year are a misleading and unsubstantiated extrapolation of actual but limited survey data. In particular Koch-Weser (1974) emphasized that anyone who had studied the mechanisms and epidemiology of adverse drug reactions realized that, no matter how carefully the course of such patients was analysed, it was often difficult to decide whether they died because of, in spite of, or unrelated to the administration of certain drugs. Especially since the most dangerous drugs were often used in seriously ill or moribund patients.

Techniques of monitoring

Registers of adverse drug reactions, which are based upon practitioner reporting or journal surveillance, are generally now regarded as being inadequate; the information is incomplete and the degree of incompleteness is uncertain (Doll, 1971). In particular the total number of individuals exposed to a drug in question is undetermined. Moreover, the proportion of those who develop an adverse reaction that goes unnotified is unknown, as also is the type of adverse reaction occurring in these persons (Lawson and Wilson, 1974).

Other techniques of monitoring have therefore been evolved to augment (but not replace) the function of the national drug regulation bodies, like the Committee on Safety of Medicines, which largely adopts practitioner reporting and journal surveillance as their primary mechanisms of monitoring. Such additional techniques include the detailed follow-up of recipients of selected drugs to assess the frequency and nature of adverse reactions in this group of patients (drug-orientated system), the follow-up of patients with specific diseases to assess the nature and frequency of any side-effects of therapy occurring in such patients (disease-orientated systems), and the review of patients experiencing a suspected adverse event to ascertain possible drug association in its production (complication-orientated system) (Lawson and Wilson, 1974).

Drug-orientated monitoring

This approach involves the study of individuals exposed to a drug or group of drugs in order to detect the frequency and nature of any adverse reactions attributable to the drugs. Such studies may be undertaken by the manufacturer of the drug, either to assess the overall frequency of reactions or to report on the frequency of a specific adverse event. Alternatively, the studies may be carried out by practising physicians investigating consecutive recipients of a selected drug. Examples of this type include detailed cohort analysis of recipients of colistin, sulphonamides, and nitrofurantoin (Koch-Weser *et al.*, 1970, 1971), adverse reactions to the tricyclic antidepressant drugs (Boston Collaborative Drug Surveillance Program, 1972*a*), aspirin and the kidney (New Zealand Rheumatism Association Study 1974), central nervous system effects of pentazocine (Wood *et al.*, 1974), adverse reactions to cephalothin and cephapirin (Sanders *et al.*, 1974), and adverse reactions to potassium chloride (Lawson, 1974). Some of these studies have also involved a direct investigation of drug–drug interactions, for example interaction between chloral hydrate and warfarin (Boston Collaborative Drug Surveillance Program, 1972*b*), drug interaction in general practice (Petrie *et al.*, 1974), and effects of concomitantly administered drugs on control of long-term anticoagulant therapy (Williams *et al.*, 1975).

As Lawson and Wilson (1974) have explained, the drug-orientated approach to monitoring side-effects is of most value when a hypothesis exists as to the damage or otherwise of a drug or group of drugs. The approach is usually a hypothesis-testing one rather than a hypothesis-generating one. A drawback of this type of investigation, however, is usually the absence of a control group of individuals. This may well bias the conclusions drawn from the study since it has been observed (Reidenberg and Lowenthal, 1968) that untreated healthy volunteers often experience those very symptoms which in an uncontrolled study are attributed to the drug under examination.

Disease-orientated monitoring

An alternative approach to monitoring is a disease-orientated study. This is of value where there is difficulty in operating a drug-orientated system, and is of greatest use when the drug or drugs being investigated are ones likely to be used almost exclusively in the treatment of a single condition or group of conditions (Lawson and Wilson, 1974).

The technique of this latter approach is also that of a cohort analysis. However, in this system, instead of reviewing the frequency of adverse reactions to a drug used specifically in the treatment of a particular disease, it is more convenient to examine all cases of that disease seen in the hospital and from that list select all recipients of the drug being examined. The remaining patients serve as control subjects. Simple examples of such a system in operation were the demonstration of hypokalaemia following therapy for megaloblastic anaemias (Lawson *et al.*, 1970, 1972), and the perinatal study in America (Slone *et al.*, 1973), which analysed data from over 50000 consecutive pregnancies on drug exposure and foetal outcome. Data on selected congenital malformations to maternal exposure to phenytoin (Monson *et al.*, 1973), and on the risk of childhood malignancy to maternal immunization during pregnancy (Heinonen *et al.*, 1973) were gained from this type of monitoring approach. Other studies of this type include that by the Boston Collaborative Drug Surveillance Program (Levy, 1974) on aspirin use in patients with major gastrointestinal bleeding and peptic ulcer disease, and on regular aspirin intake and acute myocardial infarction (Boston Collaborative Drug Surveillance Program, 1974*a*).

Complication-orientated monitoring

The complication-orientated system involves the study of individuals who are suffering from a specific disease or from a clearly defined syndrome which is thought to be drug-related. The most regularly applied technique is the classic case-control study of epidemiology in which the cases are clearly defined and compared with another group or groups of individuals, the controls. The cases and controls are then questioned regarding their past drug exposures (Lawson and Wilson, 1974).

There are many examples of this type of monitoring, for example the association between smoking and lung cancer (Doll and Hill, 1952), the association between maternal exposure to thalidomide and phocomelia of the new-born (Lenz, 1962), the linkage between use of oral contraceptives and diseases of the circulatory system (Vessey and Doll, 1968, 1969; Inman and Vessey, 1968; Royal College of General Practitioners' Oral Contraception Study, 1977; Vessey *et al.*, 1977; *British Medical Journal*, 1977*c*), and the relationship between clioquinol and the development of subacute myelo-opticoneuropathy (SMON), notably in Japan where it has reached epidemic proportions (Tsubaki *et al.*, 1971). This latter side-effect is discussed later in this text (Chapters 17 and 22), and it is of particular interest since it may indicate a regional factor in some iatrogenic diseases.

Lawson and Wilson (1974) have emphasized that, as with all epidemiological or non-interventive research, the demonstration of a statistical association between drug exposure and disease does not necessarily mean that this association is causal since other factors might explain the relationship. The strength of the association is the critical factor and in the examples that have been cited this was so striking as to preclude anything but a causal interpretation of the evidence, especially since withdrawal of the drug under investigation, or as in the case of oral contraceptives, of reducing the oestrogen content, effectively reduced the number of cases and so proved the connection.

Not all such linkages are so clear cut, and indeed some may never be absolutely established; such an example was the suggested link between the excessive use of bronchodilator aerosols and the recorded rise in the death rate of asthmatics (see Chapters 6 and 21) especially in the younger age-group during 1961–6 (Smith *et al.*, 1966; Speizer and Doll, 1968; Speizer, Doll, and Heaf, 1968; Speizer *et al.*, 1968; Inman and Adelstein, 1969). This type of problem in complication-orientated monitoring was well explained by Inman and Adelstein (1969) in the final paragraph of their paper on the rise and fall of asthma mortality in relation to the use of pressurized aerosols:

> Fortunately, the high mortality has now been reduced (although it is still higher than it was before the introduction of the aerosols). This in itself is likely to make it difficult or impossible in the future to evaluate all the factors that were responsible or to prove a direct link with aerosol bronchodilators. In the absence, however, of any other satisfactory explanation for the changes that have been observed, it is concluded that the increase in mortality from asthma that was observed during the years 1961 to 1966, was likely to have been due to the excessive use of pressurized aerosol bronchodilators and that the subsequent reduction in mortality resulted from a greater awareness among the medical profession and the patients themselves of the hazards of these devices if improperly used.

An interaction between propellents and sympathomimetic amines was later suggested, in which the propellent system of the bronchodilator aerosol formulation might further sensitize the heart to sympathomimetic amines during an anoxic state (Bass, 1970; Taylor and Harris, 1970) and so contribute to the mortality. Support was given to this view by a number of studies which established that some halogenated hydrocarbon propellents were capable of sensitizing the heart to circulating sympathomimetic amines (Clark and Tinston, 1972; Aviado and Belej, 1974) and also by the demonstration in patients and animals that detectable levels of individual propellents were evident after exposure to inhalers (Dollery *et al.*, 1970; Paterson *et al.*, 1971; Morgan *et al.*, 1972).

These parallel studies, although of interest, were largely inconclusive in relation to the participation of the propellent system in the aerosol–asthma hazard and added virtually nothing to the evidence supporting a causal relationship between aerosols and asthma mortality. The explanation of the rise in death rate of asthmatics during the mid to late 1960s has still not been fully explained and, in this respect, work on the cardiotoxicity of isoprenaline during hypoxia (Shanks and Swanton, 1970; McDevitt *et al.*, 1974) may offer additional leads.

The aerosol–asthma mortality study has, however, demonstrated clearly that from a practical view point absolute establishment of a causal relationship may be only of academic interest; the strong suggestion or likely association and the inherent interest that such an investigation provokes are in themselves adequate to bring about practical solutions to the primary problem. With the bronchodilator aerosols, these factors obviously created a greater respect and an awareness of potential hazards of aerosol medication in both patient and prescriber and the mortality dropped.

Lawson and Wilson (1974) have commented that complication-orientated systems of monitoring are of

particular interest when the event under investigation is rare and when the condition is clearly defined and relatively easy to diagnose. Success is most likely to attend such a study when the time relationship between drug exposure and disease detection is short or if continued long-term exposure to the drug is necessary for development of the disease. While such criteria are normally present in studies of this type, there are exceptions as has been well illustrated by the demonstration of a strong association between maternal exposure to diethylstilboestrol and vaginal adenocarcinoma in the progeny (see also Chapter 20, Drug-induced neoplasia).

Herbst *et al.* (1971), in a case-control epidemiologic investigation associated the occurrence of clear-cell adenocarcinoma of the vagina of young women to intrauterine exposure to diethylstilboestrol administered to their mothers for the therapy of high-risk pregnancies. The results of this investigation were soon confirmed (Greenwald *et al.*, 1971) and since then over 170 cases of vaginal and cervical clear-cell adenocarcinomas have been collected with a definite history of maternal exposure to non-steroid oestrogens in 65 per cent of the investigated cases (Herbst *et al.*, 1975).

The time from drug exposure to disease onset was some 15–20 years in this example, but the study was successful because the circumstances of drug exposure were sufficiently well defined to be easily recalled by both cases and controls, and the event (vaginal carcinoma in premenarchial females) was so rare as to be virtually never otherwise reported (Lawson and Wilson, 1974).

Comprehensive drug surveillance programmes

In an attempt to circumvent some of the problems inherent in the monitoring by practitioner reporting, journal surveillance, and drug-, disease-, or complication-orientated systems, several groups of workers have set up hospital-based comprehensive drug-surveillance programmes. The basis of such investigations is that the adverse drug reaction is actively sought by the hospital doctor or nurse, often in collaboration with the clinical or ward pharmacist. The general format of these programmes is the investigation of the hazards of drug therapy experienced by consecutive patients admitted to a study area such as a hospital ward. There is a much higher return of results with this system than with the largely passive system of practitioner reporting to a central body. It must be emphasized, however, that these two systems are not mutually exclusive; indeed they should continue to operate in parallel especially relative to patients discharged from hospital into the drug care of the community physician.

Pioneer work on the hospital-based active system of monitoring was done by Cluff and his colleagues in Baltimore (Cluff *et al.*, 1964; Seidl *et al.*, 1966; Smith *et al.*, 1966) who instituted the first major intensive in-patient hospital drug-monitoring programme. Initially this group surveyed the available methods of surveillance for adverse drug reactions, using spontaneous recording procedures as well as prospective follow-up of target drugs. They finally decided, however, to concentrate on recording only data linked by physicians to special drugs. They characterized the reactions and documented the reaction rates of some of the offending medicines. In 1967, Ogilvie and Ruedy in Montreal published the results of their study on adverse drug reactions during hospitalization. For a 12-month period from July 1965, all patients admitted to a public medical service of the Montreal General Hospital were surveyed for adverse drug reactions occurring during their hospital stay. They defined an adverse drug reaction as an undesirable consequence of drug therapy, but did not consider that failure to achieve an expected therapeutic effect was an adverse reaction. Reports of possible reactions were made in writing by the resident and nursing staffs. Each shift of nurses listed information on medication alterations, diagnostic and therapeutic procedures, and adverse reactions observed. These reports were used as a daily alerting system whereby the evaluator, a resident physician on the ward, could further investigate, evaluate, and record the events. Severity of reactions was classified using a system modified after Schimmel (1964) and reactions were classified according to two types: Type I being quantitative abnormalities in drug effects, usually dose-related and predictable, and Type II, adverse reactions due to a combination of the effect of a drug and special predisposing factors in the host which altered the response to the drug.

It is of interest to note that 81 per cent of reactions recorded were of Type I. The authors of the report thus concluded that a better knowledge of dose requirements, recognition of factors which potentiate drug action, and awareness of side-effects of drugs should aid in decreasing the incidence of these reactions. Reduction in the number of drugs used and greater knowledge of their pharmacological action was also emphasized. Also of significance was the finding that 38 per cent of all adverse drug reactions were due to three drugs, digoxin, quinidine, and insulin, which at the time of the report had been used extensively in medical practice for over 30 years. Indeed, a wider spectrum of older drugs, including aspirin, phenobarbitone, paraldehyde, adrenaline, heparin, thyroid extract, and purgatives, brought

the percentage of reactions to over 50 per cent. It was not found that the high incidence of reactions was due to new drugs with which the doctor possibly had little experience.

The Belfast study of Hurwitz and Wade (1969) followed soon afterwards; a total of 1268 patients admitted to hospital wards were kept under surveillance by one observer during their stay in hospital. All drugs given to them and the occurrence of adverse reactions were recorded. Drug reactions were found in 10·2 per cent of the 1160 patients who received drug therapy. Most reactions were due to known pharmacological actions of the drugs, and digitalis preparations, bronchodilator drugs and ampicillin had the highest reaction rates. Although only four reactions were of life-threatening seriousness, 80 per cent of the 129 reactions observed were of moderate severity.

Hurwitz followed up this monitoring exercise by investigating predisposing factors in adverse reactions to drugs (Hurwitz, 1969*a*). These factors were sought in 118 patients who developed adverse drug reactions in hospital. Significantly more patients of 60 years and over, and more women than men, developed reactions. Patients with reactions had received more drugs before the development of the reaction than patients who did not develop reactions. A previous adverse drug reaction and a history of allergic disease were significant factors, while a history of jaundice or the presence of diabetes mellitus and renal disease were not.

Hurwitz also monitored admissions to hospital due to drugs (Hurwitz, 1969*b*). During a period of 12 months, of 1268 patients admitted to hospital, 37 patients (2·9 per cent) were admitted because of adverse reactions to drugs taken for therapeutic reasons. During the same period a further 27 patients (2·1 per cent) were admitted because of self-poisoning. Patients admitted because of adverse drug reactions were older than those admitted because of self-poisoning and they stayed in hospital longer. Among the drugs which caused the adverse reactions were digitalis preparations, antibiotics, corticosteroids, anticoagulants, analgesics, and tranquillizers. Hypersensitivity and side-effect types of reactions were the most common. Barbiturates were the most frequently used drugs in suicide attempts.

This latter study of Hurwitz advanced the concept of adverse reaction monitoring a good way forward because it gave preliminary data on the extent to which patients in the community suffer serious adverse effects of drugs. Hurwitz commented that some of the admissions due to adverse reactions were due to misuse of drugs by patients and could possibly be avoided by better instructions being given with their medication. This whole question of patient compliance is currently still giving concern, especially in the elderly patient, and non-compliance undoubtedly is still responsible for a sizeable proportion of adverse drug reactions and interactions (Smith, 1976; Waters *et al.*, 1976; Wandless and Davie, 1977). An indication of the extent to which patient non-compliance in following medication instructions occurs was given by Stewart and Cluff (1972) in their review of medication errors in patients at home. Not less than 25 per cent of patients made errors in self-administration of prescribed drugs, and in some instances the figure was as high as 59 per cent.

Several other groups of investigators have also set up comprehensive drug-surveillance programmes either in medical wards (Miller, 1973; Boston Collaborative Drug Surveillance Program, 1972*c*), in paediatric wards (Boston Collaborative Drug Surveillance Program, 1972*d*) or in psychiatric wards (Swett, 1974). Their format has been much the same as that used by the Baltimore, Montreal, and Belfast groups and much useful information has been generated by this approach. Caranasos *et al.* (1974), Miller (1974), and McKenny and Harrison (1976) have also investigated drug-induced illness leading to hospitalization.

Without doubt the Boston Collaborative Drug Surveillance Program is the largest scheme of this type and a description of the work of this team is appropriate in this text. Some of the data generated by this group is further discussed in Chapter 2, Epidemiological aspects of iatrogenic disease.

The Boston group collects quantitative information on consecutive patients admitted to medical wards; a detailed explanation of the working of this programme has been presented by the Director, Hershel Jick, and his colleagues (1970). The group was formed in 1966, and since then have published numerous reports on simple documentation of adverse drug reaction frequencies (Boston Collaborative Drug Surveillance Program, 1968, 1972*c*, 1973*a*, 1974*b*; Levy *et al.*, 1977) as well as data on specific adverse drug reactions, for example ampicillin (Shapiro *et al.*, 1969; Boston Collaborative Drug Surveillance Program, 1972*e*), prednisone (Boston Collaborative Drug Surveillance Program, 1972*f*), tricyclic anti-depressants (Boston Collaborative Drug Surveillance Program, 1972*a*), spironolactone (Greenblatt and Koch-Weser, 1973), potassium chloride (Lawson, 1974), and aspirin (Lawson, 1973; Boston Collaborative Drug Surveillance Program, 1974*a*).

The programme has also included studies on clinically significant drug interactions, for example chloral hydrate and warfarin (Boston Collaborative Drug Surveillance Program, 1972*b*), smoking and drug efficacy (Boston Collaborative Drug Surveillance Program, 1973*b*, *c*), elevated blood urea nitrogen levels in patients receiving