Papers and Originals

Adverse Reactions to Drugs*

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There have been two alarming outbreaks of adverse reactions to drugs in our time. In 1937, as a result of the ingestion of an elixir of sulphanilamide containing diethylene glycol, 93 deaths occurred in 15 States of the U.S.A. (Locket, 1957). This was an example of an adverse reaction from failure to study the toxicity of a drug, in this case the excipient, before marketing. The second was the epidemic of congenital deformities in Western Europe which followed the discovery of thalidomide in 1956. Thalidomide was introduced into this country in 1958 and withdrawn at the end of 1961. At least 349 deformed children were born to mothers who had certainly or probably taken thalidomide (Ministry of Health, 1964). This was like the disaster to the first Comet aircraft in that the epidemic could not have been predicted from the tests used at that time.

I have begun by talking about deaths and congenital deformities from adverse reactions to drugs. The great majority of adverse reactions are less serious than this, though deaths from familiar drugs such as penicillin, corticosteroids, and phenylbutazone are commoner than we sometimes realize. To have a complete picture of adverse reactions to drugs we must keep both the non-fatal and the fatal reactions in mind. No one who has suffered from a haematemesis, a troublesome diarrhoea, or a protracted attack of jaundice or dermatitis after taking a new drug will be ready to minimize reactions just because they are not fatal.

A series of tests is necessary to ensure maximum safety, though it can never be complete safety, in the use of drugs in man. These tests are, in succession, toxicity studies in animals, pharmacological studies in human volunteers, clinical trials, and, finally, a watch for any ill-effects when the drug is marketed and used on a large scale. In the first three stages the drug is given to hundreds of animals and men for relatively short periods of time. In stage 4, with which we are particularly concerned to-day, it is given to tens of thousands, or hundreds of thousands, or even millions of men and women of different ages, in different states of nutrition, and with different concomitants which may profoundly modify its actions. It may be given for long periods of time, and we are still learning about previously unsuspected reactions to protracted treatment with chlorpromazine, which was introduced in 1953.

When a drug is manufactured in bulk it may contain impurities which were not present in the samples used in the original trials and which are toxic. For example, the nephrotoxic effect of phenacetin may be due not to phenacetin itself but to *p*-chloroacetanilide, an impurity which did not arise in the original process of manufacturing the drug but only with a subsequent modification (Harvald, Valdorf-Hansen, and Nielsen, 1960). Methods of controlling the quality of drugs have improved greatly in the last year or two, but clinical supervision of patients under treatment with a drug is just as necessary as quality control.

It was stage 4 and the arrangements for keeping a new drug under close scrutiny which were defective on the introduction of thalidomide. Stage 4 cannot be carried out by the manufacturers alone: it requires the co-operation of all those who administer drugs to patients. It is therefore unfortunate that Lady Summerskill, speaking in the House of Lords, should have said that the latest burden on the back of the doctor was as a tester to pharmaceutical firms who were more concerned with quick profits than with the medical service; the medical practitioner was being asked to report on the side-effects of drugs which should have been adequately tested before release (Summerskill, 1965). The final test of the safety of a drug is in fact its release for general use.

Since the thalidomide incident it has been learned that it is difficult to predict teratogenesis in man by animal experiments; some of our most useful drugs are embryopathic in some animals. However, if a drug has no other toxic effects in man it is unlikely to be teratogenic. The best safeguard is not to use new drugs in women who are likely to be pregnant for the first two years after the introduction of the drug on the market and to keep a watchful eye for adverse reactions during this period. If this had been done in the case of thalidomide its tendency to produce peripheral neuritis would have been noted and the drug would either have been given up or regarded as unsafe for pregnant women.

Types of Adverse Reactions

Adverse reactions are usually classified under the headings of intolerance, idiosyncrasy, and allergy. In *drug intolerance* the characteristic effects of the drug are produced by an unusually small dose; this is merely an example of the normal variation that is found in all biological phenomena. In *drug idiosyncrasy* the subject reacts to the drug in an uncharacteristic way which could not have been predicted from animal experiments. In *drug allergy* the patient becomes sensitized to the drug and responds to it with an allergic or anaphylactic type of reaction; drug allergy is particularly apt to develop with penicillin. In all three types of reaction it is probable that there is usually if not always a genetic component which in the first two at any rate is probably an abnormal enzymatic constitution of the body (Evans, 1965). In the Subcommittee on Adverse Reactions to Drugs we hope that as our register of adverse reactions grows we may be able to find out why fractions of the population react adversely to certain drugs. We may also discover why some groups of drugs produce idiosyncratic reactions more commonly than others. Examples are the antirheumatic drugs

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which are related to amidopyrine (phenylbutazone, oxyphenbutazone, nifenazone, and sulphinpyrazone), the antidepressants which contain the hydrazine group, and some of the more recently introduced anticonvulsants.

Rational and Irrational Fears

There is no doubt that patients and doctors have strong emotional and often irrational feelings about the use of drugs, and reports of adverse reactions are greeted with something like *Schadenfreude*. In the eighteenth and nineteenth centuries the drug most widely used was opium, and it was still known as the Grand Old Medicine up to the beginning of the therapeutic revolution which followed the introduction of the sulphonamides in 1935. Sir Walter Scott and his household imbibed a quart of laudanum or its equivalent and a pint of castor oil a month, and de Quincey, writing in 1856, referred to the large number of famous literary people who had taken laudanum (Dewhurst, 1963). As a result the word drug still has overtones derived from opium addiction and its unpleasant effects.

Some writers, like Aldous Huxley, seem to suggest that the amount of suffering in the world is a constant and that as one disease is conquered it is replaced by another. Such theories are probably manifestations of the Oedipus complex and are similar to the fears of impotence among soldiers and sailors who are given antiscorbutics or antimalarials. Most of us would agree with the Director of the Office of Health Economics that the conquest of disease is worth while and that new and effective drugs have contributed much to the happiness of mankind (Teeling-Smith, 1964). One does not have to read extensively in the biographical literature of the first half of the nineteenth century to realize how much suffering we have been spared since the discovery of potent anti-infective and analgesic drugs.

For a variety of reasons, some of which are rational, as, for example, the fact that drugs are used widely and repeatedly, and some of which, as I have hinted, are not, the dangers due to treatment with drugs are given more prominence than those from other forms of therapy. A mortality of 1 or 2 per 100 is not regarded as excessive for operations such as cholecystectomy or partial gastrectomy. With drugs the limits of tolerable lethality are set much higher and death rates of 1 in 10,000 to 1 in 100,000, such as have been estimated to follow the use of chloramphenicol and monoamine oxidase inhibitors, are the maximum that is generally acceptable. For comparison it can be noted that each of us has on an average a bigger than a 1 in 10,000 chance a year of being killed in a road accident and a 1 in 500 chance of being badly injured. Indeed, the risks of modern drugs are small in comparison with those of the motor-car and the cigarette.

We are setting the pharmaceutical industry a hard task when we ask it to produce drugs which are effective against serious diseases and yet non-toxic. Circumstances alter cases, and there is a direct ratio between the severity of the disease under treatment and the frequency of reactions that can be tolerated. In other words we have to think also of the risks of *not* using the drug. Osgood (1964) has given his opinion that radioactive phosphorus is the best treatment for polycythaemia, even though it may provoke leukaemia in some patients, because on the average patients with polycythaemia who are treated with radioactive phosphorus live longer than those who are not. Special care must be taken when the same drug can be used for two purposes, as chloramphenicol can be used both for typhoid fever and for respiratory infection, or antimitotic agents both for neoplastic disease and for suppression of immune reactions in less fatal diseases. The use for the more dangerous disease is obviously right but the use for the less dangerous disease may not be.

The Statistical Problem

The low limit of lethality which is permissible for drug therapy in the majority of diseases sets a difficult statistical problem for the observer of adverse reactions. When the risks are of the order of 1 in 10,000 to 1 in 100,000 it is not always easy to prove that an adverse reaction suspected to be due to a drug is actually more common in those who take the drug than in those who do not. The solution of the problem depends on the adequacy of the data available. For example, Custer (1946) determined the incidence of aplastic anaemia in the second world war in American troops stationed in Asia and the South Pacific area, where mepacrine was used as an antimalarial, and in other theatres of war or the U.S.A., where mepacrine was not used, and showed that it reached a level of 2.84 per 100,000 in troops taking mepacrine as compared with approximately 0.1 per 100,000 in troops not taking mepacrine. In spite of the low incidence, the observations are regarded as convincing evidence that mepacrine can produce aplastic anaemia. The proof was possible because Custer was surveying millions of troops with excellent medical records.

Chloramphenicol probably carries about the same danger of damaging the bone-marrow as mepacrine. It has been estimated that the risk of fatal aplastic anaemia in patients receiving chloramphenicol is at least 1 in 60,000, but we do not have reliable figures because we cannot at present use Custer's technique, dividing the population into those taking chloramphenicol and those not, and comparing the mortality from aplastic anaemia in the two groups. We can, however, see how often chloramphenicol has been taken by those who die of aplastic anaemia. In a study of deaths from aplastic anaemia in California it was found that 30 out of the 137 patients who died had been exposed to chloramphenicol (Smick, Condit, Proctor, and Sutcher, 1964). For most of us this is sufficient evidence that chloramphenicol is not an antibiotic to be used routinely or to be advertised as the antibiotic of choice, but there are still those who refuse to accept the association between chloramphenicol and aplastic anaemia (Report of Senate Committee, 1963).

The monoamine oxidase inhibitors (M.A.O.I.) which are used in the treatment of depression have offered a similar difficulty in assessment of risk. The dangers attributed to these drugs are, firstly, hypertensive crises and intracranial haemorrhage from tranylcypromine, and to a less extent from other M.A.O.I., particularly when sympathomimetic amines in medicines or foods are taken at the same time; and, secondly, severe and sometimes fatal jaundice from the compounds which contain the hydrazine radicle. The incidence of hypertensive reactions to tranylcypromine has been reported to lie between 2% and 10%, though this may well be an overestimate (*Brit. med. J.*, 1964). The Food and Drug Administration of the U.S.A. was sufficiently alarmed to withdraw permission for marketing of tranylcypromine in February 1964, though they restored it again in June 1964.

There has been little controversy about the hypertensive crises during tranylcypromine therapy but a great deal over the attribution of fatal jaundice to M.A.O.I. This controversy stems in part from the fact that the pathological appearances in the liver in M.A.O.I. poisoning cannot be distinguished from those in fatal virus hepatitis. It is in fact possible that some hepatotoxic drugs may damage the liver by activating a virus which was already present. Over the last decade or so death certification figures have run fairly consistently at a level of 0.6 per 100,000 of the population for infectious hepatitis and 0.25 per 100,000 for acute and subacute yellow atrophy of the liver. Figures supplied by the manufacturers suggest that the incidence of fatal jaundice with the hydrazine-containing M.A.O.I. probably lies between 1 in 10,000 and 1 in 100,000, though some publications suggest that it occurs more often. The data are not reliable enough for an accurate comparison

of incidence rates in those taking the drugs and in the general population. There is, however, enough evidence to justify the suspicion that the M.A.O.I. are hepatotoxic in some people. Cook and Sherlock (1965) have reported that of 29 patients admitted under their care with acute hepatic necrosis eight had received psychotropic drugs and three halothane. The shows that there is an association between psychotropic drugs and acute hepatic necrosis but it leaves us guessing about its frequency.

Committee on Safety of Drugs

The thalidomide incident caused concern throughout the civilized world, and there was a flurry of articles and letters in the lay press and the medical journals. A more permanent effect was that governments and professional organizations in a number of countries began to review their procedure for ensuring the safety of drugs. In this country the Committee on Safety of Drugs was appointed by the Secretary of State for Scotland, the Minister of Health, and the Minister of Health and Local Government, Northern Ireland. The Committee on Safety of Drugs formed three subcommittees—on toxicity, on clinical trials, and on adverse reactions.

The task of the Subcommittee on Adverse Reactions to Drugs is to assemble and assess reports about adverse effects of drugs in use and prepare information thereon which may be brought to the notice of doctors and others concerned. It is a small expert committee or working party and not a representative body. It is designed to function as an operational research group. A subcommittee on which every branch of the profession was represented would be too unwieldy for this purpose. This has the corollary that the subcommittee must take the advice of experts in particular fields and it must discuss its decisions with the people who will be affected by them.

When the Committee on Safety of Drugs was set up many people grumbled because its powers were only permissive, and it is quite possible that in the future the committee may be reconstituted and given statutory powers to enforce its decisions. Nevertheless, the absence of such powers has in no way hampered the work of the committee. It has been a useful discipline for us to learn to proceed by consultation, and we have been able to execute our task and carry the medical profession and the pharmaceutical industry with us in a way that has not always happened in countries where bodies corresponding to ours have been given and have used strong legal powers.

Early Warning System

The task of the Subcommittee on Adverse Reactions has been to discover and record the occurrence of adverse reactions to drugs and to relate the number of adverse reactions to the frequency with which a drug is prescribed. I must emphasize that we are nearly always dealing with *alleged* or *suspected* reactions, and if I later omit these adjectives it is only to avoid repetition. In beginning our work we were much helped by the report of a committee of the Medical Research Council, which had considered the assessment of drug toxicity in man, though in practice we have diverged rather widely from their recommendations. The first thing we did was to set up an early warning system to make use of the experience of all doctors using drugs. A business reply-card for the notification of adverse reactions was designed and copies were sent through the executive councils and hospital management committees to all doctors and dentists in the National Health Service. The number of questions was deliberately kept short, as it was felt that other items could be left for further inquiry. The card is of a distinctive yellow colour, which is also used for other papers of the subcommittee.

Our intention to build up a register of adverse reactions was announced in November 1963, but it was not until the end of May 1964 that the register became fully operational. The number of reports was at first relatively small, but has recently shown a considerable up-swing. The processing of the data and the coding of the reactions and the drugs have now become the subject of active research, as it is necessary to look forward to the future use of computers and a possible conversion to an international system. A good deal of international co-operation on an informal basis is already occurring and the Committee on Safety of Drugs exchanges information with a number of other countries. It is probable that international standards will eventually be established for testing drugs before marketing, monitoring the use of drugs in practice, and reporting adverse reactions (Finney, 1963, 1964).

What is a Reaction for the Purpose of Notification?

Neither the profession nor the subcommittee would wish to be bothered with notification of well-known reactions to established drugs, such as extrasystoles from digitalis or dry mouth from belladonna, and we therefore suggested that the subcommittee should always be notified of suspected reactions to new drugs, no matter how trivial, and of suspected reactions to established drugs which are either unusual or serious or both.

What Justification is there for Believing that a Reaction is Due to a Particular Drug?

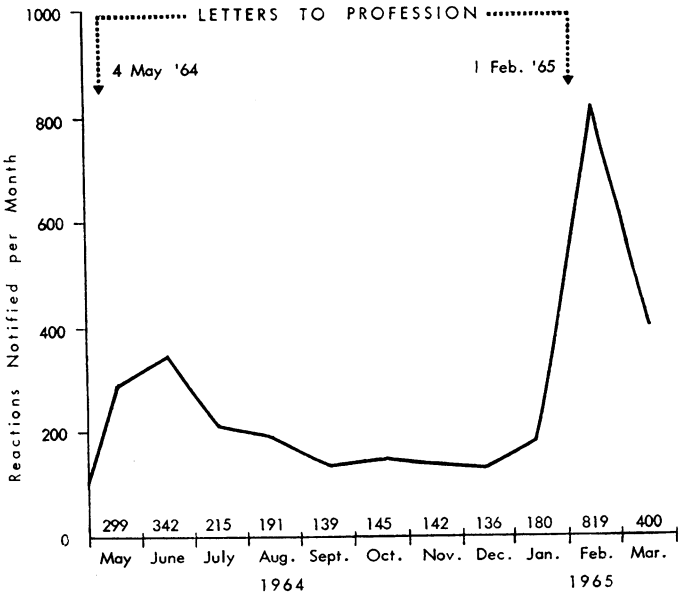
Drugs are rarely given alone, and in a study at the Johns Hopkins Hospital, where sodium methicillin was used as the marker drug, it was found that the average number of drugs administered to patients receiving sodium methicillin was 14, with a range of 6 to 32 (Cluff, Thornton, and Seidl, 1964). Fortunately for our purpose multiple prescribing of this order is uncommon in general practice in this country, though disorders such as hypertension and oedema may require the simultaneous administration of a number of powerful drugs (Vere, 1965). Multiple prescribing should be avoided if possible because we know little about the interactions of drugs and there is mounting evidence that combinations of drugs may produce new and unexpected reactions. The Subcommittee on Adverse Reactions has appointed part-time medical officers in every region of the United Kingdom to act for our medical assessor, and with the help of these medical officers and follow-up letters to the notifying doctors we can collect data about other drugs given at the same time, the disease under treatment, and the possibility of some intercurrent event or illness. The individual case will always remain uncertain unless the patient is deliberately challenged again with the drug, but when the same type of reaction to a drug occurs in a number of patients in different circumstances, there is a prima facie case that we are dealing with an adverse reaction.

What is the Frequency of Reporting?

Doctors are busy people, and we all know how easy it is to put off writing letters. It has been stated that about 15% to 20% of patients admitted to an acute general hospital suffer unfavourable effects from the drugs administered to them, and that only about a quarter of these reactions are reported, even though cards for this purpose are attached to the patients' records (Cluff *et al.*, 1964). Most of these unfavourable effects, however, are of a type on which our committee would not expect reports. They are phenomena such as the side-effects of corticosteroids or symptoms of overdosage of anticoagulants or allergic reactions to penicillin, which are already well known and some of which are inevitable when powerful drugs are used and optimal doses are being worked out.

Nevertheless, we have evidence that many of the reactions to new drugs and unexpected reactions to old drugs are not reported. For a new drug in which we have recently been interested adverse reactions, none of them serious, were reported in 7.5% of patients when the drug was undergoing clinical trials. The drug has been on the market in this country for just about the same time as the Committee on Safety of Drugs has been in existence, and, making rather arbitrary calculations from the amount of the drug sold and the probable duration of treatment, the number of adverse reactions reported has been of the order of 0.3% of patients treated. Again, the number of reports received under the early warning system has fluctuated considerably from month to month (see Chart). These fluctuations have been chiefly dependent on the amount of publicity given to the activities of the Subcommittee on Adverse Reactions, and letters to the profession from the chairman of the Committee on Safety of Drugs, Sir Derrick Dunlop, asking for notification of all suspected adverse reactions and dated 4 May 1964 and 1 February 1965 were followed by gratifying rises.

The best method of maintaining a high level of reporting is therefore for the committee to keep the profession regularly informed about its work and the data it is collecting. A feed-back of information is essential because reports of adverse reactions which in earlier days might have been published in the form of a letter to the medical journals may now be sent direct to the committee. Doctors reporting adverse reactions to the committee receive a reply giving the committee's experience to date with the drug in question, and these replies are undoubtedly appreciated. Manufacturers have been encouraged to write to the press or direct to the profession when unexpected reactions to one of their drugs have been observed. The committee itself has written similar letters. A committee has to be more guarded than an individual in reporting suspected adverse reactions, as its words carry more weight, but now that we are beginning to accummulate significant numbers of reports in our register of adverse reactions we hope to send the profession communications at regular intervals in our adverse reactions series, commenting on adverse reactions to particular drugs or groups of drugs.



Variation in notifications of adverse reactions. The figure for March 1965 is provisional.

The Numerator and the Denominator

The value of the early warning system is in alerting us to the possibility that a drug is capable of producing adverse reactions. What we then need to know is the ratio between the number of reactions (the numerator) and the number of patients treated (the denominator). If we looked only at the number of reactions reported we might think that chlorpromazine and phenylbutazone were extremely toxic drugs, but when we take into account the large amounts of these drugs prescribed we see the numbers in a different perspective. We can get an approximate figure for the number of patients treated from the amount of a drug moving into the market and the number of prescriptions for the drug written by general practitioners. The early warning system cannot, however, give us even an approximate figure for the numerator.

Spontaneous reporting must inevitably be biased and incomplete. At the present time there is great interest in oral contraceptives, and thrombosis is more likely to be reported as an adverse reaction if it occurs in a woman who is taking an oral contraceptive than if it occurs in a woman who is taking an anti-emetic or a haematinic. Complete recording cannot be secured by exhortation. Experiments are being made in America in which all prescriptions in a hospital are recorded in a computer and special medical staff is employed to see that all adverse reactions are reported. However, the rules of chance being what they are, several hundred patients might need to be treated with a drug before it was discovered that it produced noxious side-effects in 1% of people, and the population of a single hospital will usually be too small to detect such a risk.

In the foreseeable future all prescriptions in the N.H.S. might be recorded by computer and all conditions commonly due to drug toxicity, such as agranulocytosis, aplastic anaemia, hepatitis, peripheral neuritis, and congenital abnormalities, might be made notifiable and correlated with the prescriptions by record linkage (Acheson, 1964; Finney, 1965), but this is unlikely to reveal an unusual type of reaction such as the pigmentation and the oral dyskinesia which may occur after treatment with phenothiazine derivatives (Hunter, Earl, and Janz, 1964), and in any event these arrangements are still in the future. What we can do here and now is to study possible ill-effects of a limited number of drugs in defined populations by prospective or retrospective surveys.

List of Specially Monitored Drugs

Over 600 new preparations were submitted by the drug manufacturers to the Committee on Safety of Drugs in 1964. Many of these were combinations or reformulations of old drugs and probably no more than 50 could properly be called new drugs. It is unpractical and undesirable to impose restrictions on the prescription of new drugs or the distribution of samples, but for the first two years after their release for marketing they are kept by the subcommittee on a list of specially monitored drugs. The list also includes older drugs for which we have received reports of adverse reactions which seem serious or frequent enough to require assessment. Indeed, we have so far had more problems from drugs that were on the market when the committee started work than from those that have been introduced since. In one case it was eight years after marketing before a highly unpleasant side-effect was recognized. In addition, a few selected old drugs which are believed to be free of side-effects are used as markers. At the present time the list comprises about 100 drugs.

Monitoring Mechanisms

All methods of recording and monitoring drug reactions require the correct identification of patients to avoid duplicate reporting of the same patient by different observers and to enable follow-up studies to be carried out. All such information is treated as confidential. Whenever possible it is

translated into code at an early date and no further inquiries are pursued without obtaining the co-operation of the doctors or institutions concerned. Although the ideal would be to record all prescriptions and all reactions, this is not at present practicable and we have had to devise techniques whereby samples of the population can be studied.

Northern Ireland

The Northern Ireland General Health Services Board has for many years used mechanical methods of coding and tabulating prescriptions. It is therefore possible to trace rapidly all prescriptions for a given drug issued by general practitioners in Northern Ireland and to get in touch with the doctors concerned. The population of Northern Ireland is approximately 1,500,000 and there are about 750 general practitioners under contract with the Board. About 3,500,000 prescriptions for drugs are written each year. All prescriptions are examined at the Pricing Bureau and the following data are transferred on to Hollerith punch cards: the code number of the pharmacist, the serial identification number of the prescription, and the code numbers of the doctor, the preparation, and the quantity of drug prescribed. These data can then be analysed as required by the use of sorting and tabulating machines. It is expected that a computer will be installed in the future. At present about 60 persons are employed in the bureau ; the coding and analysis of prescriptions from a relatively small population is thus an elaborate and expensive business.

The Committee on Safety of Drugs has been offered co-operation by the Northern Ireland Ministry of Health and Local Government and the General Health Services Board in the use of this machinery for its work. If suspicions arise that a drug may be causing serious adverse reactions it is possible for us to trace immediately all prescriptions for that drug issued by general practitioners in Northern Ireland and then to write to the doctors concerned or to inquire from them through our part-time medical officers to ask whether patients have or have not had any ill-effects that might be due to the drug. The committee is especially grateful to the practitioners in Northern Ireland for their co-operation. It has already been possible to carry out surveys on drugs such as chloramphenicol, phenylbutazone, and long-acting sulphonamides.

England and Wales

The Northern Ireland scheme is at present unique, but it might be criticized on the grounds that the population is relatively small and that it may not be representative of the United Kingdom as a whole. We have therefore sought ways of supplementing it on this side of the Irish Sea. The possibility was considered of enrolling 500 volunteer practitioners who would keep copies of all prescriptions, notify all adverse reactions, and check on patients who had received a particular drug when asked, but an *ad hoc* scheme of this kind covering all drugs would be unduly expensive.

A volunteer panel is of great value for making prospective or retrospective inquiries about a single drug, and no expensive coding of prescriptions is then necessary. The College of General Practitioners maintains a register of general practitioners interested in research and prepared to take part in group studies, now numbering about 850. Means exist to circulate those on this register for special information. They have helped us greatly on several occasions when we wished to make a rapid assessment of the possible dangers of a particular drug.

The virtue of the Northern Ireland Scheme is that it makes use of a mechanism that was already in existence for another purpose. Fortunately we have been able to discover a similar, though by no means so elaborate, mechanism in this country. A redesigned method for sampling prescriptions was introduced recently by the Joint Pricing Committee for England and Wales. It provides for the monthly analysis of approximately 1 in 12 prescriptions ordered by a sample of over 1,000 general practitioners. Chemists sort their prescriptions into doctor order before submitting them for pricing, and the pricing bureaux are therefore able to assemble prescriptions ordered by sample doctors.

This revised method of sampling prescriptions was designed primarily for the provision of information about variations in prescribing between doctors, as indeed was the Northern Ireland scheme, but it seemed to us that with some modification it could be used for the monitoring of adverse reactions. We have therefore sought and obtained the co-operation of the Joint Pricing Committee to allow us to do this. The system is not so convenient for us as that in Northern Ireland, as the sample of general practitioners is changed from time to time, and even if all the doctors in the sample co-operated we should obtain only one-twelfth of the prescriptions for a population of approximately 2,000,000. However, I am a great believer in getting pilot schemes working. A few sound experiments are worth more than a lot of theorizing, and it is only by producing concrete results that we shall persuade our masters, as Lord Snow (1964) calls them, of the wonderful opportunities for operational research which the National Health Service provides.

Recording of Prescriptions in Hospital

Hitherto I have been talking about monitoring drugs used in general practice. However, one-fifth of all drugs and a larger fraction of some of the new ones are used in hospital. In some ways it is more difficult to monitor drugs in hospital than in general practice. Records of prescriptions are difficult to retrieve, patients for whom medicines have been prescribed are often not easily identifiable, there is a tendency for some departments to stay outside the unit record system, important drugs may be issued from stock on the wards, there are frequent changes of junior medical staff, and dispensaries often suffer from crippling shortages of pharmacists. A great deal of work is currently being done on the improvement of hospital case-notes and records so that they can be analysed by modern methods of data processing. Under one system which is already widely used a copy of every prescription is retained by the hospital pharmacist. In general, however, records of prescription of drugs in hospital are still much inferior to those in general practice, where they have to be accurate enough to determine the remuneration of the chemist. To monitor a drug in hospital it is at present necessary to put the drug on a restricted list so that the pharmacist can keep a copy of the prescription, as he does for dangerous drugs.

A pilot study carried out with the help of the Guild of Public Pharmacists, in which the prescription of 18 drugs was monitored at each of 17 hospitals, showed that the information recorded had been adequate for any approach to hospitals that would have been necessary if the subcommittee had decided to follow up any of the drugs under review. At the present time plans are being made for some 200 hospitals to begin continuous monitoring on these lines. Each hospital will monitor a selection of the drugs on our list which will be appropriate to the type of work the hospital is doing and will not impose too heavy a burden on the dispensary or inconvenience to the hospital staff. We shall thus have a denominator of usage for the drugs in which we are specially interested and we shall be able to determine the numerator of reactions by a prospective or retrospective survey of the patients in cases in which we require this information. Moreover, it should be easily possible to allot new drugs for

monitoring at short notice and to remove others from the list when their time of trial is over.

Anaesthesia and Radiology.—Two of the most active fields of research into new drugs are anaesthesia and radiology. About 10,000,000 anaesthetics a year are administered in this country, and in the average 700-bed teaching hospital there will be 10,000 anaesthetics a year. There are two special features of anaesthetics and of diagnostic agents used in radiology which make them of interest to our committee. They are not usually supplied on individual prescription from the pharmacy but from stocks kept in the operating theatres and x-ray departments and would therefore bypass our new monitoring mechanism. Secondly, while anaesthetists and radiologists are on the watch for immediate or early reactions they will not normally have the opportunity to observe delayed reactions. If, therefore, there was a delayed reaction which occurred two to three months later, like homologous serum hepatitis after transfusion or aplastic anaemia after gold or chloramphenicol, it might well be missed. Records of anaesthetics and diagnostic reagents used in radiology are, of course, already kept, but anaesthetists and radiologists are now carrying out pilot studies to see whether data such as the identification of the patient, the drug used, the dose and batch number where applicable, and the occurrence of reactions can be collected in a standardized form and made easy to retrieve. Fortunately the hospitals to which new drugs in these categories have been supplied can usually be quickly pinpointed.

Summary

Adverse reactions to drugs can be divided into intolerance, allergy, and idiosyncrasy. With modern methods of testing before marketing, severe and unexpected adverse reactions to new drugs should be uncommon and deaths from intolerance or anaphylaxis should be avoidable by ordinary therapeutic caution.

Idiosyncratic reactions may not be discovered till a drug is marketed on a large scale. For this reason a period of surveillance is necessary, during which new drugs are kept under special scrutiny and adverse reactions are promptly reported.

Non-fatal or mild reactions to drugs are relatively frequent. It is important that they should be reported so that the relative frequency of their occurrence with different drugs of similar action can be revealed and the more toxic ones can be discarded.

The methods at present being used by the Committee on Safety of Drugs are described. The determination of the ratio between the frequency of reactions (the numerator) and the number of patients treated with a drug (the denominator) is at present difficult, but with the steady improvement in the recording and processing of data in the National Health Service it should become progressively easier.

The opinions expressed in this paper are personal but the work it refers to has almost entirely been done by others. I must therefore declare my indebtedness to my colleagues on the Committee on Safety of Drugs, its secretariat, and the Subcommittee on Adverse Reactions, with whom I have worked so happily and from all of whom I have learned so much.

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Heller-valve Method of Intravenous Fluid Administration in Neonatal Surgery

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Accurate administration of intravenous fluid in the newborn infant can present one of the major problems of paediatric surgery. It is often extremely difficult to adapt the usual "gravity-drip" system to the relatively minute fluid requirements of the infant. A drip rate of as low as 2 ml. per hour is almost impossible to regulate, and predisposes to clotting within the vein, cannula, or both. The flow rate is also sensitive to change in the infant's posture and to the effects of temperature and viscosity variations. By incorporating a form of burette, or graduated chamber, in the drip set, Rickham (1959) facilitated greater accuracy, but constant supervision and adjustment was required, and the likelihood of early vein/cannula thrombosis was unaffected.

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The problems of efficient intravenous infusion are equally apparent during operation. It is not uncommon to find the anaesthetist wriggling under the operation drapes, trying to revive a stubborn "drip" so that he can then resuscitate the infant. The need to have a reliable route available for the administration of blood, sometimes rapidly, during major surgery in infants has been emphasized in a leading article in the *British Medical Journal* (1964). This need was dramatically illustrated in the account of the operations for the separation of craniopagus twins (Ballantine and Jackson, 1964). During one such operation no less than 10 litres of blood was transfused. It is probably fair to say that the administration of blood and other fluids has often proved as troublesome as the operation itself.

It was therefore a welcome relief to the surgical and nursing staff of this hospital when our colleagues in the anaesthetic