The Detection of Adverse Drug Reactions

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Before a drug is marketed it must undergo rigorous tests in animal models. Many drugs are discarded during testing, while those considered to have reasonable efficacy in relation to toxicity are then studied in human volunteers, and progress to clinical trials if judged to have an acceptable benefit-to-risk ratio; subsequently a licence to market may be granted (W.H.O., 1975).

However, despite every precaution on the part of the manufacturers and the Committee on Safety of Medicines, unexpected and sometimes serious adverse drug reactions do occur for the following reasons. Animal toxicological studies do not necessarily reflect all human hazards and clinical trials may not demonstrate the full adverse reaction potential of a drug. The latter is a special problem when potential reactions have a low incidence, a common occurrence with many serious adverse reactions. Reactions with a long latent period may also be missed by conventional clinical trials. Furthermore, the populations exposed in clinical trials may differ from those exposed after general marketing, e.g. the very young, the elderly, pregnant women, etc.

Apart from the difficulty of predicting from animal experimentation and clinical trials the likelihood of adverse reactions to a particular drug after marketing, there are considerable problems in identifying a cause and effect relationship between a drug and an adverse reaction because many of the latter are non-specific and could be produced by disease or by other drugs given at the same time. Thus, the practice of medicine today, where not uncommonly multiple pathology is treated by polypharmacy, has produced formidable problems in identifying cause and effect relationships between drugs and adverse reactions of clinical importance.

One factor immediately related to the size of the problem of adverse drug reactions is the very large number of drugs available, and another is the extensive use of these drugs. There are between 30,000 to 40,000 medicinal products available on prescription or directly to the public. Approximately 2,200 branded products are advertised in MIMS and about 45 per cent of these contain two or more pharmacologically active ingredients. Furthermore, the National Health Service pricing bureau statistics show that about 400 active agents are prescribed on more than 50,000 occasions each year and that 250 others are prescribed
between 1,000 and 50,000 times. They also show that the total number of prescriptions dispensed by chemists in England and Wales in 1970 was 247 millions and the figure for 1974 was almost 270 millions. The scale of drug use in the community and therefore of potential hazards is also shown by a survey carried out by Dunnell and Cartwright (1972) where 1,400 households in the U.K. were studied. It was found that four-fifths of all adults and more than half the children had used some kind of medication in the preceding two weeks. As evidence of the chronicity of treatment, 50 per cent of drugs had been prescribed more than a year previously and 75 per cent had been obtained on repeat prescriptions. The evidence of such widespread drug use underlines the limitations of pre-marketing clinical trials and makes it understandable why many features of drug performance, including adverse effects, may be revealed only at the post-marketing stage.

It is against the background of this brief review of the size and nature of the problem of detecting adverse drug reactions that the development of monitoring systems for their detection should be viewed.

THE VOLUNTARY REPORTING SYSTEM – UNITED KINGDOM
This is a national system run by the Adverse Reactions Sub-Committee of the Committee on Safety of Medicines. Although reports concerning suspected adverse drug reactions (serious in the case of ‘old’ drugs and mild or serious for ‘new’ drugs) come from many sources, more than 80 per cent originate from general practitioners and hospital doctors, who forward reports on a standardised ‘yellow card’, and manufacturers who, as a rule, co-operate by forwarding reports of adverse reactions to their drugs, and assist the Committee in further investigations. This spontaneous or voluntary reporting system was pioneered in the U.K., and similar systems now exist in a number of other countries. In any discussion of how to detect adverse drug reactions a description of how this reporting system operates is merited (Inman, 1972).

Completion of the ‘yellow card’ by the reporting doctor enables the collection of standard items of information, and pre-paid return postage simplifies handling. The pharmaceutical industry has co-operated with the Committee on Safety of Medicines in encouraging reporting of suspected adverse reactions by labelling recently introduced products with a special symbol (an inverted triangle) in their index of proprietary preparations (MIMS) linked to a request to report using the ‘yellow card’. Although the effectiveness of this procedure in improving reporting is doubtful, in the direction of monitored release of new drugs it is a tentative step that presages the development of new methods of detecting adverse drug reactions.

On receipt, ‘yellow card’ reports are reviewed on a twice-weekly basis by medically qualified staff and prepared for processing by clerical and coding staff. This allows an early scrutiny of the reported event by a doctor and involves
checking of reported parameters, coding of drugs and adverse reactions, patient identification, and vital statistics data prior to computer input. In some instances a report may be selected for validation and contact with the reporting doctor made, usually by one of a team of field workers who may be called upon on an ad hoc basis to investigate a case. All reports are acknowledged by the monitoring centre and information relevant to the reported reaction or drug is routinely fed back to the reporter. The level of reporting of systems of this type is dependent upon good feedback to the medical profession; selected types of feedback include information on drug reaction hazards, established and potential, which are distributed to all doctors on a nationwide scale, e.g., the 'adverse reaction series' and the 'current problem series'. As a consequence of clues provided by the reporting system, many studies have been carried out, leading to publications in the medical press. On the basis of reports, the Adverse Reaction Sub-Committee may also make direct requests to manufacturers, which not infrequently result in the circulation to practising doctors of 'Dear Doctor' letters from the manufacturers, or modifications to their drug literature, e.g. the Data Sheet. Finally, acting on the recommendation of the Committee on Safety of Medicines, the Licensing Authority of the Department of Health and Social Security may withdraw a drug from the market.

In brief, the advantages of a spontaneous or voluntary monitoring system of the type used in the United Kingdom may be summarised as follows.

The operative costs are relatively low and a small central staff with a core of medically qualified personnel, data-processing staff with a computer facility, and a team of part-time field workers (medically qualified) covering most areas of the country can effectively run the system. The facility of validating reports of interest by the field workers is unique to the U.K. system. Confidentiality is easily maintained and the computer probably contributes to rather than detracts from this. A particular advantage lies in the potentially wide coverage of the population that is possible.

The two main disadvantages of voluntary systems lie in the type of data obtained and in under-reporting. The quality of the data varies, depending on the reporter; inadequate information leads to increased time and manpower costs in the follow-up of cases and possible delay in identifying problems. In addition, biases may occur owing to the variability of factors that influence reporting. Differences in the frequency of reporting any given association may be related to factors such as excessive publicity, a specific request to report, publishing of a 'first' case, etc., which may be independent of the actual frequency of occurrence of the event. Furthermore, without knowing the total number of patients exposed to a drug, it is not possible to determine the incidence of reactions to it. Approximations may be made relative to total numbers of prescriptions or doses issued annually or manufacturers' data on drug production or supply, but such extrapolations can only be made with due consideration of their limitations.
Clearly, under-reporting is the major problem faced by spontaneous or voluntary adverse reaction monitoring systems and its extent and significance is shown by the following example. Of 53 women identified by the Committee on Safety of Medicines as having died from thrombo-embolic disease in 1966 and whose general practitioners knew they were taking the oral contraceptive at the time of death, only two of the deaths had been reported by the general practitioner. Another six cases were reported retrospectively by pathologists.

There are many reasons for under-reporting by doctors, including pressure of work, lack of motivation, administrative defects (e.g. ‘yellow card’ not to hand), but there is hope that the increasing awareness of doctors about the problems of detecting adverse drug reactions will improve reporting.

In spite of the shortcomings outlined above, the potential of voluntary reporting of adverse drug reactions is apparent by a number of successes recorded by the system. For example, a dose-response relationship between the oestrogen content of oral contraceptives and thrombo-embolic phenomena has been established; and the association between jaundice and two drugs, benziodarone (a coronary vasodilator) and ibufenac (an analgesic) has resulted in the voluntary withdrawal of these drugs from the market by the companies concerned (Inman, 1976).

**INTENSIVE MONITORING SYSTEMS**

These systems are almost exclusively hospital based and tend to be complementary to the voluntary reporting systems. The most successful scheme of this type, which is used to detect previously unsuspected adverse reactions, is the Boston Collaborative Drug Surveillance Program (BCDSP) (Jick, 1972; Miller, 1974). In this programme, a nurse-monitor collects patient data on special collecting forms. More than 130 different items of data are collected for each patient and seven data collection forms are used. Each nurse-monitor supervises a ward of about 24 patients. Input forms are checked for completeness, with the assistance of a medical team, and all data items entered into a central computer. Tabulations of a high degree of sophistication are produced incorporating statistical tests to highlight trends between batches and significant variations from the batch averages; these print-outs are carefully studied by a multi-disciplinary monitoring team of clinical, epidemiological, biomedical and statistical experts and further computer-aided analyses of the data are carried out as required. Approximately 20 wards have been monitored using this system and at present data are available on magnetic tape relating to 35,000 patient admissions, from hospitals in the U.S.A., Canada, New Zealand, Scotland, Germany and Italy.

Much published work has resulted from in-depth studies of the data file of the Boston group including –

1. accounts of the frequency of occurrence of adverse reactions to specific drugs; e.g. ampicillin, propranolol, heparin, digoxin and antidepressants, etc;
2. articles on drug interactions; e.g. the potentiation of ampicillin rashes by allopurinol; elevation of blood urea in patients receiving tetracycline and diuretics;

3. history of previous drug use and an associated event; e.g. reserpine intake and breast cancer.

Another type of intensive hospital monitoring system is based on the major hospitals in the East and North-East of Scotland, the Aberdeen-Dundee Medicines Evaluation and Monitoring Group (MEMO) (Crooks et al., 1967; Moir, 1972; Moir et al., 1975).

This system differs from the Boston system in a number of respects; for example, a much reduced amount of data is collected for each patient with items that are recorded as routine in hospital practice. Such items include patient identification and associated vital statistics, discharge diagnoses, and drug data derived from a standardised prescription sheet made in duplicate. The collection of the patient identification and diagnostic data is designed to allow direct key-punching and computer input of data; the drug information contained on the prescription sheet, however, is coded on to a drug coding sheet then entered on to a computerised drug file. Computer programs allow data linkage of those items in a variety of forms dependent upon the drug problem being tackled. The MEMO system thus allows a large hospital population to be covered at relatively low cost. Furthermore, adverse effects do not form part of the data input to the computer but are studied as part of specially designed projects. The file is therefore used mainly to investigate problems associated with the suspicion that a drug may be producing a particular adverse effect. To do this it can identify patients with given characteristics, e.g. given disease group, within a given age range, etc., or identify patients who have received a given drug, drugs within a given group, or any drug or drug-disease combination. At present the files contain information on over 250,000 discharges and cover one million prescriptions.

Many studies have been undertaken by the Aberdeen-Dundee centre and some examples are shown below.

1. Association of amitriptyline and sudden death.
2. Adverse effects of pentazocine on the central nervous system.
3. Cold extremities and beta-blockers.
4. Reserpine use and breast cancer.
5. Frusemide and thrombocytopenia.
6. Direct Coombs positive test and methyldopa.
7. The clinical significance of the interaction of tetracycline and iron.

The reserpine and breast cancer study provides some indication of the difficulties involved in the evaluation of a suspected drug adverse reaction association. The initial reports were published in The Lancet in 1974 from three centres that found a positive association, the strongest evidence coming from the
Boston group with an estimated relative risk ratio in the breast cancer group of 3.5 to 1 (Boston Collaborative Drug Surveillance Program, 1974). The Finnish and Bristol workers both had the somewhat lower figures of 2.0 to 1 (Armstrong et al., 1974; Heinonen et al., 1974). Subsequent studies from Los Angeles, New York, the Mayo Clinic and Aberdeen-Dundee failed to show an association (O'Fallon et al., 1975; Laska et al., 1975; Mack et al., 1975; Aberdeen-Dundee Medicines Evaluation, 1977). Further work by the Bristol group did not provide evidence of a significant association (Armstrong et al., 1976) and a similar type of study in Helsinki showed no evidence of an association (Aromaa et al., 1977). Such a picture demonstrates how confounding factors can play an important part in the collation and evaluation of data from various sources and the hiatus that exists between a suspected association and a proven one. The conclusion is that any association between the use of rauwolfia alkaloids and breast cancer is minimal and no conclusive cause and effect relationship has been demonstrated. In spite of this at least one country has banned the marketing of the drug group on the basis of the first reports. It seems inescapable that in such circumstances a well co-ordinated multi-centre approach will have many advantages that individual centres cannot match.

OTHER METHODS
Apart from spontaneous and intensive systems of detecting adverse drug reactions, a number of other methods have been used with varying degrees of success. In the main they comprise a variety of epidemiological surveys, and recent outstanding examples of this approach are the survey of the adverse reactions to oral contraceptives carried out by the Royal College of General Practitioners in the U.K., and the study of drugs used in the management of diabetes by the University Group Diabetes Program in the U.S.A. Such epidemiological studies make use of vital statistics including mortality rates, death certificates, and information derived from cancer registries and registries of congenital abnormalities. While epidemiological methods are valuable tools in the detection of adverse drug reactions and in the reinforcement of suspicions of an association between a drug and a reaction, both the quality of the data and often its retrospective nature can lead to difficulties of interpretation.

CONCLUSION
It must now be clear that the methods at present available for the detection of adverse drug reactions are basically unsatisfactory. Spontaneous reporting systems suffer from gross under-reporting and reports of variable quality, intensive hospital monitoring with higher quality reports do not cover a large enough population in terms of patient numbers and drug exposure events, while the primarily epidemiological approach is suited to investigate suspected associations between a drug and a reaction rather than identifying previously unsuspected ones.
It is probable, therefore, that a new methodology for detecting adverse drug reactions requires to be developed, with the greatest effort directed towards newly marketed medicines and those that are extensively prescribed, using long-term regimes requiring repeat prescriptions. It seems likely that both the medical profession and the pharmaceutical industry have arrived at an appreciation of the intractable nature of the problem of detecting adverse drug reactions, which will allow new methods of post-marketing surveillance of medicines to be developed. Such methods would involve 'monitored' or 'recorded' release of designated drugs and the medical and/or other health professions would be under an obligation to follow up and report on the events that occur to patients on such drugs over a reasonable period of time. Finally, the problem of adverse drug reactions must be kept in perspective. All pharmacologically active drugs are potentially capable of producing unwanted effects and this potential must be balanced against their potential for producing therapeutic effects. Appreciation of this fact by the public will avoid the emotional overtones associated with the problem and the danger of inhibiting new drug development by unnecessarily restrictive pre-marketing regulations.

DISCUSSION
Dame Elizabeth Ackroyd (Patients Association) wanted patients to be better instructed in drug hazards and drug usage. There was the temptation to take two tablets instead of one or to hoard medicines for a long time, perhaps hoping that they would mature. She did not think that GPs did enough to instruct their patients, and came back to the point of prescriptions being written by receptionists. Dr Crooks agreed that there should be more education of patients and of doctors. In fact there had been a major expansion in the number of departments of clinical pharmacology. The public exerted strong pressures on doctors to prescribe, a drug being the symbol of the interaction between doctor and patient. The interaction was complex. It had been shown that there was no correlation between what the patient knew about a drug and what he did with it.

Dr Dollery came back to the question of the monitored release of drugs and thought it unfortunate that it had got tied up with promotional activities. A register of patients taking a new drug was needed. A large initial quota of patients was required and not until that quota had been filled should a drug go on general sale. Information on symptoms could be obtained by postal questionnaire from the patients. Mrs Jean Robinson was pleased to think that the patients should provide information. She thought that a group of consumer associations should set up their own reporting agency and send the collected data to the Medicines Commission. The Patients Association post-bag was full of complaints about the adverse effect of drugs, which indicated a very real public anxiety about the standard of medical care.

Dr D. R. Laurence said that the Medicines Commission was at present working
on a monitoring scheme to include the first 2,500 patients to take a new drug. He was also worried by the tremendous pressure on the doctor to prescribe. This led to over-prescribing.

Dr Herxheimer thought that the resources to study adverse reactions should be increased to match those for the study of therapeutic effects.

Dr Inman pointed out that the Food and Drug Administration in the U.S.A. had just voted itself another 16.4 million dollars and created an extra 600 posts in its already large organisation. The British effort was based on four people at headquarters and 60 in the field. Monitored release of drugs would need much larger resources. Monitoring the release of a drug needed a standardised form, monitoring all patients for a specified period and laying down the total number of patients to be treated; ideally this should be done without limiting the freedom of the doctor to prescribe the drug or the freedom of the patient to take it. All adverse events should be recorded and not merely those events thought to be drug reactions. There must be rapid communication between doctors using the drug, the monitoring committee, and the pharmaceutical industry. Somehow the cost of such monitoring must be kept reasonably low.

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