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The Study of Adverse Reactions to Drugs [*Abridged*]

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Monitoring of Adverse Reactions to Drugs in the United Kingdom

All drugs with any worth-while therapeutic activity produce adverse reactions in a proportion of patients treated with them. Ideally, no doctor would prescribe a drug until he had carefully considered whether the risks inherent in its use outweighed its benefits, or whether there were equally effective but safer alternatives. Sadly and all too frequently, however, reactions occur because the prescriber is ignorant of the risks or even of the pharmacological properties of the drugs he has prescribed. It should of course be said that he is often placed at a considerable disadvantage in his choice of treatment because the range of drugs available to him is vast, and commercial advertising emphasizes their alleged merits while minimizing their potential dangers. Many important hazards have yet to be identified and the incidence of most of the known hazards has not yet been measured.

Several countries have established drug safety committees for the purpose of screening laboratory and clinical trials of new drugs. Tests in laboratory animals or clinical trials in limited numbers of human patients cannot, unfortunately, always predict the toxic effects that may be encountered in large-scale human use, and for this reason some of these countries have also established drug monitoring systems for the purpose of detecting and investigating safety problems that are encountered after a drug has been put on the market. In the United Kingdom, the monitoring system is directed by a subcommittee of the Committee on Safety of Drugs which is supported by a small permanent staff of doctors and a small number of administrative and clerical staff. Its functions include those of problem-identification or 'early warning', the conduct of epidemiological investigations and the provision of an information service.

Early Warning

A drug safety problem may come to the attention of the Committee in several ways. Sometimes an enquiry from a doctor stimulates a search of the accumulated data and uncovers a previously unnoted hazard. More often, problems are identified as a result of scrutiny of the reports by the permanent staff at the time they are first received. To perform this function effectively, automatic data processing is being developed for rapid retrieval and analysis of previous records relating to similar drugs or reactions.

The new hazard may be recognized because a number of similar reports appear in the computer printout or because a reaction is new to the experience of the monitoring staff. Alternatively the hazard may be identified because the rate of the reporting has changed suddenly or because the reports show some kind of unexpected preponderance of certain reactions in relation to those reported with other drugs used for similar therapeutic purposes. This last approach is especially interesting and has brought several important hazards to light. For example, in a report to the Committee in February 1968, it was noted that while anticonvulsants comprised about 5% of the drugs listed as taken by the mothers in all reported congenital abnormalities, they accounted for no fewer than 33% of the drugs in reports of cleft palate or hare lip. The total number of such cases was small and no special importance was attached to them at the time, but it was interesting that almost a year after this observation Meadow (1968) independently reported an association between anticonvulsants and cleft palate. As long ago as 1966 it was noted that there was a disproportionately large number of reports of thrombosis among women using oral contraceptives containing the œstrogen, mestranol; more recently it became apparent that the total dose of œstrogen, rather than its chemical structure, was more closely correlated with the risk of thrombosis (Inman *et al.* 1970).

Full evaluation of a drug safety problem generally demands estimation of drug usage, so that the incidence of the reactions can be measured. It is often also necessary to study vital statistics, especially when the suspected reaction

to a drug is itself a disease or symptom that has a natural or spontaneous incidence, independent of drug therapy.

There are several obvious defects in any system of monitoring based on voluntary reporting of adverse reactions. First, while some doctors report events such as jaundice or blood dyscrasia which are commonly associated with drug therapy, many more will not even consider the possibility that a drug was responsible for the patient's condition. Secondly, there is no doubt that reactions are seriously under-reported. For example, in 1966 when the possible thromboembolic hazards of oral contraceptives were frequently discussed, both in the medical journals and in the public news media, only 15% of deaths of women using oral contraceptives were reported spontaneously to the Committee on Safety of Drugs. It seems likely that reporting of less dramatic adverse reactions will be even more defective and it is possible that many unsuspected hazards will not be identified at all by voluntary reporting. Thirdly, the majority of serious or fatal adverse reactions are comparatively rare, with an incidence of perhaps one reaction in 1,000 to one in 1,000,000 courses of treatment and a 'reported incidence' which may easily be ten or a hundred times less than this. Because of their rarity, serious reactions are therefore likely to be detected only by a national or international monitoring organization collecting information from very large populations of patients. Hazards of lesser severity and greater frequency may sometimes be evaluated by intensive monitoring schemes in hospitals, in which both the adverse reactions (the numerator) and the drug usage (the denominator) are measured. Continuous hospital monitoring schemes tend to be expensive to operate, and motivation and efficiency may be difficult to maintain in view of the comparatively small chance that they will succeed in identifying a new drug safety problem. The specialized equipment and skills available in hospitals are best employed on the investigation, in depth, of hazards that have been identified elsewhere, rather than attempting to detect previously unrecognized hazards.

Follow Up

Drug monitoring is an exercise in epidemiology. Once a potential hazard has been identified, it is usually necessary to undertake detailed case work by personal discussion with physicians who have reported the adverse events, in order to decide how much time and resources should be allocated to further investigation. In 1965, the Committee appointed 40 part-time medical officers whose main activity is interviewing doctors who have reported adverse reactions. This has been found to be an extremely effective way of obtaining a better insight into the likely importance of the reports. These officers were also engaged in the first epidemiological investigation to provide proof of the causal relationship between oral contraceptives and death from thrombosis (Inman & Vessey 1968).

Although the possibility of a link between cleft palate and the use of anticonvulsants was suggested by the scrutiny of the voluntary reports, it must be admitted that this method of obtaining information cannot be regarded as a reliable means of early detection of human teratogenicity. Most pregnant women are probably exposed to one drug or another during pregnancy, but less than 1% of congenitally abnormal births are reported to the Committee. The Registrar General's Office collects reports of congenital abnormalities from all over the country and the Committee's medical officers are currently investigating a sample of these and obtaining control data on normal children born in the same practices. This is a pilot study at the moment, and if successful the Committee may decide to extend the scope of the investigation considerably in the future.

Experience has shown that the drug monitor, notwithstanding its limited resources and small staff, is likely to throw up more drug safety problems than it can possibly evaluate. For this reason the Committee is anxious to encourage doctors working in hospital or other institutions to undertake the responsibility for follow up of specific problems to which the monitoring system had drawn attention. Always, however, we are faced with the fact that the incidence of adverse reactions determines the size of the investigation that is necessary to evaluate them. In general, the more serious the reaction, the rarer it is, the larger the study needed to evaluate it and the greater the responsibility of the national monitor to take the lead in the essential investigations.

Feed-back

There would be little point in maintaining a system for detecting and investigating drug hazards if the results were not made available to the medical professions as early as possible. It is unfortunate that public opinion and the response of the national press is so fickle. For example, the Committee's statement that the dose of œstrogen in oral contraceptive preparations was a factor in determining the risk of thrombosis attracted widespread publicity while, on the other hand, the publication of a paper suggesting that more than 3,500 deaths of asthmatics had occurred as a

probable result of the overuse of pressurized aerosols, raised hardly a ripple of interest in the public sector.

Personal contact between the Committee's staff and members of the medical profession who have reported adverse reactions or who have enquired about them has proved to be of incalculable value. As a matter of routine, each doctor reporting a reaction receives a summary of all the reactions that have been previously reported with the relevant group of drugs.

As soon as possible, the Committee intends to publish the whole of its Register of Adverse Reactions so that doctors may be apprised of the considerable amount of data that have already accumulated.

The Committee has encouraged doctors to make use of the available data. Recently, for example, an investigator studying the problem of post-anæsthetic jaundice discovered that as many detailed case reports were found in the Committee's files as in the whole of the world literature on this topic.

Summary
Three major activities of a drug monitor, early warning, follow up and feed-back, are aimed at detecting and investigating drug safety problems within the limits imposed by the available staff and equipment, stimulating research by others and providing an information service for prescribers.

Among the limitations of drug monitoring based on voluntary reports, that imposed by the comparative rarity of the more serious reactions, as a result of which very large populations have to be studied, is seen to be the most important. Adverse reactions are seriously under-reported but, in spite of this, the drug monitor is capable of detecting more new drug safety problems than it can evaluate. Workers in many disciplines are encouraged to take an active part in the evaluation of the drug safety problems that come to light as a result of operating the drug monitor.

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Monitoring of Adverse Reactions to Drugs in the United Kingdom: Some Illustrative Examples of the Work Done by the Committee on Safety of Drugs

Studies undertaken by the Committee on Safety of Drugs have played a major part in establishing the relationship between oral contraceptives and thromboembolic disease. The epidemiological and statistical problems involved in four such studies (Cahal 1965, Inman & Vessey 1968, Jick *et al.* 1969, Inman *et al.* 1970) were discussed. Particular attention was paid to a recent analysis (Inman *et al.* 1970), which utilized routinely submitted reports of suspected adverse reactions to oral contraceptives, and demonstrated that the risk of thromboembolism is related to the œstrogen content of the preparations.

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