SPECIAL ARTICLE

The Canadian Drug Adverse Reaction Reporting Program

EDWARD NAPKE, M.D. and JEFFREY BISHOP, M.B., *Ottawa*

The origins and objectives of the Food and Drug Directorate's Drug Adverse Reaction Reporting Program are reviewed. A brief report from (F&D 123), which has been made available to all physicians, provides the means whereby suspected reactions to drugs can be reported to the Directorate. Information contained in these reports is treated as confidential. Twelve Canadian teaching hospitals have entered into a contractual agreement with the Directorate in order to investigate and evaluate suspected drug reactions occurring in the hospital setting. Manufacturers are notified if a problem appears to be arising in connection with a product, and discussions are held before any regulatory action is taken. Also, under the New Drug Regulations of 1963, pharmaceutical manufacturers are required to notify the F.D.D. if any unexpected reactions occur in association with their products. The Food and Drug Directorate is giving considerable thought to the means by which the interest of the profession in this program may be stimulated.

Les auteurs rappellent les origines et les buts du plan de comptes rendus sur les réactions médicamenteuses défavorables, élaboré par la Direction des Aliments et des Drogues. Une formule abrégée de rapport (F&D 123) a été envoyée à tous les médecins en vue de leur fournir le moyen de signaler à la Direction les réactions défavorables aux médicaments qu'ils auraient constatées. Les renseignements contenus dans ces comptes rendus sont considérés comme confidentiels. Douze hôpitaux canadiens d'enseignement ont signé avec la Direction un contrat par lequel ils s'engagent à étudier et à évaluer les réactions médicamenteuses qui se produiraient dans le milieu hospitalier. On avise les fabricants des difficultés rencontrées dans le maniement d'un produit. Les autorités en discutent avant de prendre des mesures appropriées. De même, d'après les nouveaux règlements de 1963 sur les médicaments, les fabricants de spécialités pharmaceutiques sont tenus d'avertir la DAD (FDD) tout réaction inattendue qui se produit au cours de l'administration de leurs produits. La Direction des Aliments et des Drogues étudie avec beaucoup d'attention les moyens à prendre pour stimuler l'intérêt de la profession médicale pour leur plan.

EARLY in 1965, the Food and Drug Directorate of the Department of National Health and Welfare initiated a program which was designed to collect and evaluate reports of untoward effects associated with the administration of drugs. The program has now been in operation for almost two years and the purpose of the present communication is to review its procedures and to clarify its objectives.

Origins and Objectives

In 1962, a special committee was appointed by the Royal College of Physicians and Surgeons of Canada, at the request of the Minister of National Health and Welfare, to study the procedures by which new drugs were introduced on the Canadian market. In addition to stressing the importance of adequate clinical evaluation of new pharmaceutical products, the committee recommended that the Food and Drug Directorate establish a program whereby drugs reaching the market could be followed up in order to detect any untoward effects which might come to light after their wide distribution and use. In a report to the House of Commons in December 1964, the Special Parliamentary Committee on Food and Drugs recommended that the Food and Drug Directorate design and distribute a form suitable for reporting such reactions and that these reports be studied by the Directorate. The World Health Organization also has requested its member nations to collect information on serious adverse reactions to drugs and to relay such information to all member countries. The Canadian Drug Adverse Reaction Reporting Program was therefore initiated in accordance with these recommendations.

The objectives of the program may be stated as follows:

(a) To assist the Directorate in monitoring drugs in use with a view to early detection of adverse drug effects.

(b) To advise the Directorate on the review of drug labelling and advertising with respect to warnings, contraindications, precautions and adverse effects.

(c) To inform practitioners of the types and, where possible, the incidence and treatment of adverse reactions associated with specific drugs or combinations of drugs.

(d) To provide information to the Adverse Reaction Program of the World Health Organization.

The program consists of two systems, the "Drug Alert System" and the "Evaluation and Research System".

The Drug Alert System

A brief adverse reaction report form (F&D 123) which was devised by the Directorate has been made freely available to the medical and allied health professions. The reporting physician is

From the Division of Medicine and Pharmacology, Food and Drug Directorate, Department of National Health and Welfare, Ottawa, Ontario.

Reprint requests to: Dr. Jeffrey Bishop, Chief, Division of Medicine and Pharmacology, Food and Drug Directorate, Department of National Health and Welfare, Tunney's Pasture, Ottawa 3, Ontario.

asked to give only the bare essentials of the case, i.e. the name of the drug, the daily dose and duration of administration, the suspected reaction to the drug, and concomitant therapy. Over 4500 of these report forms have been returned to the Directorate since the program began. Upon receipt, the reports are acknowledged and filed in a "pigeonhole" file. Coloured markers are attached to reports of severe and unusual reactions; those reactions that resolved when the drug was discontinued and reappeared when the patient was rechallenged with the drug; reports of fetal abnormalities suspected of being due to a drug administered during pregnancy; and reports of deaths associated with the administration of a drug. This system of coloured markers facilitates surveillance of the files and provides an early alert to developing trends.

From time to time, the suggestion is made to the reporting physician that he may wish to submit his report in the form of a letter to the editor or a case report to the medical or scientific journal of his choice. Generally speaking, this suggestion is made when the suspected reaction was previously unknown or if it is of especial severity, importance or interest. It is hoped that the publication of reports of suspected reactions to both old and new drugs will stimulate other physicians to report their experiences in drug therapy and that it will serve a useful purpose by drawing attention to specific reactions, thereby acting as a reminder to the profession.

As its name implies, the "Drug Alert System" is designed to operate only as an alerting mechanism. Each report received by the Directorate represents a clinician's observation together with his own interpretation of the observation. As such, it is suggestive evidence only, and the Directorate does not attempt to substantiate the validity of all reports received. However, it is reasonable to assume that the likelihood of a cause-and-effect relationship is increased if several similar reports of previously unknown reactions, or if an unusually large number of reports of known reactions to a drug, are received. Certainly, it would justify steps being taken to investigate the reaction more thoroughly. In this event, reporting physicians may be asked to supply more complete background information than was contained in their original reports.

THE EVALUATION AND RESEARCH SYSTEM

A contractual arrangement has been made with 12 teaching hospitals. One physician on the staff of each hospital has agreed to locate instances of suspected drug reactions occurring in his hospital and to conduct investigations in order to ascertain the causative or contributory factors in each case. Monthly reports are submitted to the Directorate and a more comprehensive form (F&D 122) is used. Over 550 of these forms have been received to date. In addition, prospective studies designed to determine the extent to which drug reactions occur in hospital patients are planned in several hospitals. Hospitals under contract have also agreed to investigate the occurrence within their own hospitals of suspected drug reactions arising out of the Directorate's "Drug Alert System". Such special requests have, on several occasions, led to discussions being held with the manufacturer concerned and have resulted in changes being made in the package insert and brochure or other appropriate regulatory action.

THE ROLE OF THE MANUFACTURER

Under the New Drug Regulations of 1963, pharmaceutical manufacturers are required to report to the Food and Drug Directorate as soon as possible, and in any event within 15 working days of their receipt by them, reports of "any unexpected side effects, injury, toxicity or sensitivity reaction associated with the clinical uses, studies, investigations and tests respecting that new drug; and any unusual failure of that new drug to produce its expected pharmacological activity. . . ."

Reports of adverse reactions received from private practitioners and from the hospitals under contract are handled in confidence, and the Food and Drug Directorate does not disclose the source of this information to manufacturers. Manufacturers are consulted only if information arising out of the program indicates the need for some action to be taken. This action might consist of the initiation of further studies to elucidate a particular problem, or it might consist of appropriate changes being made in the package insert or brochure, or the issuance of a "Dear Doctor" letter either by the F.D.D. or by the manufacturer concerned. Thus, if the alerting and evaluation systems generate a high degree of suspicion with regard to a specific reaction, the appropriate manufacturer is notified and the problem is discussed before any specific action is taken.

OTHER SOURCES

Reports of suspected drug adverse reactions are also received from the U.S. Food and Drug Administration, the British Committee on Safety of Drugs, and the Australian Drug Evaluation Committee. These reports are scanned and added to the files. Reports of drug reactions appearing in the literature are obtained from various sources and are handled in a similar manner.

FUTURE PLANS

Consideration is being given to the desirability of periodically distributing tabulations of adverse reaction reports to the profession. The misinterpretation that could be placed on information presented in this way is fully realized, and it would be necessary to explain very carefully that the listing of a drug against a suspected reaction would

not necessarily imply that a cause-and-effect relationship had been proved.

At the present time, reports of suspected adverse drug reactions submitted by physicians are acknowledged by a routine "thank-you" letter. Ways and means of providing the reporting physician with some information in return are now being explored. For example, it might be possible for the Directorate to indicate whether or not the reaction was previously known to have occurred in association with the drug in question. Such a feedback of information to the reporting physician would constitute a significant step forward in the Directorate's program, and it is hoped that the receipt of such letters would be an incentive to the practitioner to maintain a continuing interest in the program.

CONCLUSION

The action and interaction of drugs in patients of differing ages and sex with various diseases is highly complex and ill-understood. The incidence of even the more common and well-known drug reactions is not known with any degree of certainty. The few figures that are available indicate that the incidence of drug adverse reactions, at least among patients in hospital, is higher than was previously realized. Thus, some mechanism whereby adverse reactions to drugs can be systematically collected and assessed would seem to be vital. All that can be expected from the program outlined above is the provision of an early alert to a previously unrecognized and unwanted drug effect. Even this goal will not be achieved without the interest and co-operation of all physicians.

VIEWPOINTS

Random Thoughts on a Department of Preventive Medicine in a Canadian Medical School

JAMES M. MATHER, M.D., D.P.H.,* *Vancouver, B.C.*

NOW that I have officially severed my connection with the Faculty of Medicine at the University of British Columbia, I find it possible to sit back and attempt to assess what I have learned in more than 25 years of association with preventive medicine and public health.

One point I want to make abundantly clear from the beginning. Any opinions I express are personal and do not necessarily reflect the official opinion of the faculty or the university at which so many of my concepts were crystallized. As a former faculty member of what I consider to be an excellent medical school, I can, however, in a few words, sum up what I consider to be the prime objective of any medical school. It is to attempt in every way to produce the best possible physician of the future. Everything else is secondary.

What I write about, however, is one specific department. What should this department be called? I am not at all sure that the name really matters. When I came to the University of British Columbia in 1952 it was called the "Department of Public Health". It soon became apparent, however, that we were not interested, primarily, in the specialized training of the graduate student but rather in the teaching of the undergraduate. We had the name changed to the "Department of Preventive Medicine", which in our opinion more accurately typified our objectives. In the last few years similar departments elsewhere have become known as "Community Medicine", "Social Medicine", and by a variety of other titles. I am quite willing to change again, but I must be shown the advantages.

We have not neglected the public health aspects of our community responsibilities. We have regularly held a series of courses at the graduate level. Perhaps the best index of our success in that regard is that British Columbia now has more specialists certified by examination in Public Health than any other single area in Canada.

How much have we been able to direct undergraduate teaching toward preventive medicine rather than public health? Probably here the best index is the examination of the Medical Council of Canada. Ten years ago this was most definitely slanted toward public health. To be successful, one had to know the minutiae of a septic tank. Today this examination bears little resemblance to that of a decade ago; it is now concerned with the preventive aspects of clinical practice.

Who should head a department that has these dual responsibilities? In my day it was quite

From the Faculty of Medicine, University of British Columbia, Vancouver 8, B.C.
*Formerly Professor and Head, Department of Preventive Medicine, and Assistant Dean.
Reprint requests to: Dr. James M. Mather, c/o Dr. D. O. Anderson, Department of Preventive Medicine, Faculty of Medicine, University of British Columbia, Room 300, Wesbrook Bldg., Vancouver 8, B.C.