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WORLD HEALTH ORGANIZATION

TECHNICAL REPORT SERIES

No. 498

INTERNATIONAL DRUG MONITORING: THE ROLE OF NATIONAL CENTRES

Report of a WHO Meeting

WORLD HEALTH ORGANIZATION

GENEVA

1972

PRINTED IN SWITZERLAND

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Geneva, 20–25 September 1971

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INTERNATIONAL DRUG MONITORING : THE ROLE OF NATIONAL CENTRES

Report of a WHO Meeting

A meeting on the role of national centres in international drug monitoring was convened by WHO in Geneva from 20 to 25 September 1971. Dr. V. Fattorusso, Director, Division of Pharmacology and Toxicology, opened the meeting on behalf of the Director-General.

1. BACKGROUND INFORMATION

Adverse reactions to drugs represent a serious health problem. Up to 1 in 20 medical admissions to hospitals have been associated with a drug reaction (Seidl et al., 1966). As many as 1 in 5 patients admitted to medical wards have been reported to experience a reaction during their hopitalization (Hurwitz & Wade, 1969). While the scientific basis for demonstrating the therapeutic effects of drugs has become increasingly firm, relatively little progress has been made in detecting and documenting the toxic effects of drugs in patients.

The basis of scientific knowledge leading to an understanding of certain known adverse effects of drugs has grown, and this should allow the detection of certain reactions before they are manifested clinically. However, the introduction of each new compound into man carries with it the chance of an unexpected adverse effect. Modern animal toxicity studies, even when supplemented by careful human pharmacology studies and clinical trials, still fail to detect certain delayed effects, novel types of toxicity, effects that may be unpredictable owing to genetic variables, interactions between disease and drugs, and interactions among drugs themselves (Gardner & Cluff, 1970 ; Wade, 1970).

It has therefore become increasingly important to obtain much more knowledge about the adverse effects of any drug as well as about its therapeutic effectiveness. Incomplete knowledge of the frequency and severity of adverse effects of drugs is a major weakness of modern therapeutics, and appreciation of this fact and of the responsibility of governments for drug safety has led to the establishment in a number of countries of systems of monitoring drugs for suspected adverse reactions (Royall, 1966).

Because of these considerations, WHO has sought to encourage the development of systems for detecting adverse reactions at both the national and international levels, with the objective of diminishing the time between

the general release of a drug and the full recognition of its capacity to produce undesirable and often dangerous effects.

Most national systems depend upon the spontaneous reporting by physicians of suspected adverse reactions to drugs, the reports being sent to a national drug monitoring centre, as for example in Australia (Walshe, 1968). Careful validation of the data is required, after which analyses and further investigations are carried out in an attempt to confirm or refute the suspected association between a drug and a reaction. The methods adopted by any national centre for this purpose depend upon the facilities of the country concerned and vary according to the drug, the reaction, and the population at risk. For example, prospective and retrospective surveys may be used according to the nature of the problem and the resources available for its study.

The development of an international system was initiated in 1967 by the Twentieth World Health Assembly.[1] First of all, WHO carried out a pilot research project on the feasibility of an international system of monitoring adverse reactions to drugs. Data essential to the development of the project were provided by 10 countries (Australia, Canada, Czechoslovakia, Federal Republic of Germany, Ireland, Netherlands, New Zealand, Sweden, United Kingdom, and USA, later joined by Denmark and Norway) which had established national drug monitoring centres and agreed to participate by forwarding to WHO case reports of adverse reactions to drugs. This information was organized within computer files to allow a variety of analyses.

Some 30 000 case reports of suspected adverse reactions received from 12 countries were recorded by computer methods. A complete input system was developed so that input by means of either a traditional form or magnetic tape has become acceptable.

Certain standards for input have been set : in order to ensure a desirable level of uniformity in the presentation of case reports, the recommendation of the WHO Scientific Group on International Drug Monitoring in 1965 that there should be a basic or minimum content of data was adopted by the participating national centres. Moreover, the preparation by WHO of a comprehensive *Adverse reaction terminology* (see section 5.4) has made it easier to integrate data from systems using different types of methodology. WHO has also compiled a comprehensive list of all drugs reported to the Research Project for International Drug Monitoring that also includes corresponding non-proprietary names and a therapeutic and pharmacological classification, with cross-references. This " drug reference list " is regularly brought up to date.

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[1] Resolution WHA20.51 (*Handbook of resolutions and decisions*, 11th ed., 1971, p. 123) ; see also *Off. Rec. Wld Hlth Org.*, No. 148, p. 65.

Reports of the following type are produced regularly for distribution to the participating national centres :

(1) comprehensive reports for reference purposes ;

(2) concise documents for ready scrutiny ;

(3) signal reports aimed at detecting increases in the reporting of associations between drugs and adverse reactions, or calling attention to serious or unusual reactions reported in small numbers. Lists of those drugs most often reported to the international system are also produced (Royall, 1971).

The programmes and systems that form the basis of the above activities are available to national centres. In a report by the Director-General to the Twenty-third World Health Assembly it was stated : " The conclusion was reached that the WHO pilot project had satisfactorily fulfilled the tasks assigned to it and that ... a system of international monitoring of adverse reactions to drugs was feasible ".[1]

During the period of development of national centres and of the WHO pilot project it became apparent that hospitals were not contributing as much as they might to drug monitoring. It was also realized that it was feasible to carry out intensive monotoring for adverse drug reactions in a number of hospital centres, and that such a development could complement the work of national centres and hence of an international system. With the objectives, therefore, of improving the contribution of hospitals to the international system, WHO held a meeting at which the following recommendations were made : [2]

(1) Hospitals should be encouraged to improve the reporting of suspected adverse reactions to drugs to appropriate centres, for by this means an important contribution to the safe use of drugs will be achieved.

(2) Hospital doctors should accept responsibility to report suspected adverse reactions to drugs. In each hospital or group of hospitals, however, one person or group of persons should be responsible for the development of drug monitoring programmes. Modification of record systems in hospitals may aid this reporting greatly. The importance of adverse reactions to drugs should be taught in all schools of medicine, public health, dentistry, nursing, and pharmacy.

(3) Intensive drug monitoring systems should be established in a number of hospitals which would serve as reference centres in different countries. National centres should be responsible for the promotion and co-ordination of this development with the assistance of WHO.

(4) Drug monitoring activities should be encouraged in countries where they do not at present exist. As national centres are established they should be responsible for developing and improving spontaneous monitoring systems within the country, and should also have a duty to establish intensive hospital monitoring in some hospitals. However,

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[1] *Off. Rec. Wld Hlth Org.*, 1970, No. 184, p. 55.

[2] *Wld Hlth Org. techn. Rep. Ser.*, 1969, No. 425, p. 22.

hospital monitoring activities may also be established with advantage in countries which have no extensive national system.

The Twenty-third World Health Assembly requested that the WHO Research Project for International Drug Monitoring be developed "into a primary operational phase aimed at the establishment of an international system for monitoring adverse reactions".[1] The initiation of this operational phase is likely to be associated with an increased response by Member States to the resolution of the Eighteenth World Health Assembly, which invited Member States "to develop as soon as possible national monitoring systems for adverse drug reactions, with a view to taking part in an international system under the aegis of WHO".[2]

2. GENERAL CONSIDERATIONS

In the light of the above developments and in view of the fact that the effective operation of national centres is the keystone of the international system,[3] it seems opportune to review the role of national centres with 4 objectives in mind:

(1) to provide guidelines for the establishment of national drug monitoring centres and to define their responsibilities and activities;

(2) to advise on measures to increase the effectiveness of the existing spontaneous reporting systems of national centres;

(3) to define the part that national centres should play in the development and coordination of intensive monitoring systems, usually hospital-based;

(4) to identify the methods by which national centres can make the most useful contribution to the international system, including participation in the WHO drug monitoring project, and ways in which the WHO project can facilitate the work of national centres.

2.1 Definitions

For the purposes of the meeting the following definitions were adopted:

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[1] Resolution WHA23.13 (*Handbook of resolutions and decisions*, 11th ed., 1971, p. 124).

[2] Resolution WHA18.42 (*Handbook of resolutions and decisions*, 11th ed., 1971, p. 123).

[3] See *Off. Rec. Wld Hlth Org.*, 1970, No. 184, pp. 54–67.

A *drug* is " any substance or product that is used or intended to be used to modify or explore physiological systems or pathological states for the benefit of the recipient ".[1]

An *adverse reaction* to a drug is one that is noxious, is unintended, and occurs at doses normally used in man.

Drug monitoring, as applied to the field of adverse drug reactions, is defined as any procedure that aims at providing systematic inferences on likely chains of causation linking drugs and adverse reactions within a population. Information on adverse reactions can be obtained by a variety of methods. The 3 major systems are individual reporting, comprehensive monitoring, and population monitoring, as defined below.

Individual reporting. This was previously known as spontaneous monitoring ; the reports fall into two categories :

Isolated individual reports, which are sent direct to the centre by practising physicians and dentists, on their own initiative.

Organized individual reports, which come from groups of practising doctors organized in some manner so as to facilitate their reporting (e.g., doctors in a medical or surgical service, a hospital or group of hospitals, and various types of health centre).

Comprehensive monitoring. In this system a special group of physicians, such as may be found in reference centres, is organized to survey drug use (denominator data) and identify all adverse effects (numerator data). It is also known as intensive hospital monitoring.

Population monitoring. This differs from comprehensive monitoring with respect to the patient population studied and methods of data collection. It is characterized by automatic recording of drug use and patient syndromes or events and by a search for associations between the two.

A *national drug monitoring centre* is an agency charged with the responsibility for drug monitoring in one or more member states.

A *reference centre* is a hospital, group of hospitals, or other medical agency undertaking drug monitoring in collaboration with a national centre and to which specific problems can be referred.

A *special centre* is a hospital or other medical agency with the capacity to carry out drug monitoring in a country without a national centre.

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[1] This definition was first proposed by a WHO Scientific Group on Principles for Pre-Clinical Testing of Drug Safety (*Wld Hlth Org. techn. Rep. Ser.*, 1966, No. 341, p. 7).

It should be noted that the WHO Drug Monitoring Centre (WHO Centre), located in Geneva, is the operational centre responsible for the development of the international system on the basis of a two-way flow of information on suspected adverse reactions to drugs, in collaboration with national centres.

2.2 Objectives of national centres

The primary objectives of a national centre are (*a*) to identify as quickly as possible important or serious adverse reactions to drugs and (*b*) to attempt to establish the causal relationship between the drug and the adverse reaction. The centre should provide data and evaluations calculated to increase the safety of drug use.

To achieve these objectives the national centre should develop and investigate methods for data acquisition, ensuring that information on the association between drugs and adverse reactions is as complete and reliable as possible. Techniques should be developed for data evaluation and interpretation, and for the distribution of information about adverse drug reactions to appropriate professional groups and bodies responsible for drug safety. The centre should also aim to provide other national centres and the WHO Centre with data and information in a suitable form.

3. METHODOLOGY

The methodology and organization of national centres may vary from one country to another. A flexible approach to methodological development is both necessary and desirable. The considerations in this report are intended simply to serve as guidelines.

The essentials of a national centre are: (1) one or more sources of information on adverse reactions (input), (2) a mechanism to analyse this information, and (3) an output to interested parties.

The sources of information will vary. In some countries spontaneous reports from physicians practising outside hospitals are most important; in others, hospital physicians may contribute proportionately more reports; and other patterns may evolve. The nature of the information will also vary. Reports on suspected associations between drugs and adverse reactions in individual patients predominate so far; statistical linkage of drug administration and patient reaction may become more important in the future.

Analysis serves to validate or invalidate the suspected associations, explore other associations, and estimate the clinical importance of the associations. The output will be directed, as appropriate, to those involved in regulating drugs, the drug manufacturer, other monitoring centres,

physicians, and scientists interested in drugs, and may ultimately reach the public.

It should be realized that this is not a simple sequential linear process, but is in a state of constant flux as new information forces the re-examination of old decisions concerning the validity of associations between drugs and adverse reactions.

3.1 Sources of information

The basic principles that underlie most systems are considered in the following sections.

3.1.1 *Individual reporting*

Doctors are the major source of reports. Those whose practice is primarily outside hospitals tend to care for patients for prolonged periods of time and may therefore also see the occurrence of slowly developing or delayed reactions. Since most severe reactions are seen in hospitals, physicians who are hospital-based are often able to ascertain previous drug administration, link it to the reaction, and submit a report.

The physician, during an outpatient or inpatient examination, may decide that the patient has a recognizable syndrome of signs, symptoms, and/or laboratory findings and that this syndrome may be associated with a previously administered drug. He then reports this information to the centre.

There are a number of mechanisms by which individual reports can be made available to the centre. Isolated individual reports and organized individual reports have already been described on page 9. In addition, pharmaceutical companies should report all instances of possible adverse reactions that come to their attention. Many case histories of possible adverse reactions are reported in national medical journals; these could be abstracted and used as a data source. Another source is the WHO Centre's collection of reports from national centres.

3.1.2 *Comprehensive monitoring*

Comprehensive monitoring is typically performed in a hospital setting and the input consists of abstracts of patient identification, drug administration, and patient reactions. Specialized methods are used to ensure that this information is complete, and case reports or tabulated summary data can be supplied to the national centre. Such monitoring was discussed in detail at a previous WHO meeting.[1] Multi-clinic trials may also provide input for comprehensive monitoring.

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[1] *Wld Hlth Org. techn. Rep. Ser.*, 1969, No. 425.

3.1.3 *Population monitoring*

In population monitoring the records of hospital or clinic patients, or of the entire population of a district, may be employed. Such monitoring could be effective when a large stable population is surveyed in an organized medical care system. As rapid advances are being made in the electronic processing of patient documentation and records, there may be unusual opportunities to incorporate a drug monitoring element in these systems.

Population monitoring appears to have much to offer in that actual rates of reactions can be obtained, and truly unexpected reactions may be identified. It is complex and expensive, however, and the patient population may not be large enough for the detection of rare (1 in 10 000–50 000) reactions. This system would automatically record drug use and patient syndromes or events, permitting searches for associations between the two. The results of such searches may be reported to the national centre. Such systems should provide objective and unbiased measures not only of the incidence of particular effects following the use of a specific drug, but also of the incidence of the same effect among persons treated by other methods. Moreover, they may provide a ready means of identifying delayed effects such as carcinogenicity, teratogenicity, and nephropathies. Insufficient attention has so far been paid to the organization of these systems, and high priority should be given to research into the most practicable methods of developing them.

3.1.4 *Other sources*

All potential sources of information should be considered. Each national centre must seize opportunities to exploit old and develop new sources of information. For example, useful information can come from poison control centres, social security records, inquest reports, and from clinical and basic pharmacology, toxicology, and pathology units.

The collection, analysis, and dissemination of national health statistics vary greatly from country to country. In some countries the retrieval and analysis of death certificates can provide useful information. Registers of congenital malformations and cancer can be utilized as a source of case material for retrospective studies and can be scanned for trends over a period of time. It must be ascertained, however, that diagnostic criteria have not been changed during the period. As more and more countries develop national plans for supplying drugs to patients, rosters of prescription drugs can become increasingly useful in providing data on extent of use and in helping to identify populations of patients at risk to adverse drug reactions.

3.2 Nature and analysis of information

3.2.1 *Criteria*

Several centres have experienced some difficulty in deciding whether doctors should be invited to report all reactions, however trivial they may appear to be, or only the more serious or previously unrecognized reactions. To invite reports of all reactions may place an unnecessary burden on the reporters; on the other hand, limitation of reporting to the more serious reactions means that the physician must define their severity in the light of his observation of the individual patient. To exclude the apparently trivial reaction may reduce the possibility of detecting prodromal symptoms of a condition that will later prove serious.

One centre has requested reports of serious or unusual reactions to all drugs, and reports of all reactions to " new " drugs. New drugs should be placed in a special category in official drug lists, and manufacturers should be required to indicate their status in all promotional material until such time as the regulatory agency may release the drug from this category. An old drug used for a new purpose should usually be placed in this category.

Annexes 1 and 2 allow comparison of the criteria hitherto adopted by national centres in Sweden and the United Kingdom.

3.2.2 *Method of reporting*

A variety of report forms have been used by different centres (see Annexes 1 and 2). Ease of completion and simplicity of the data requested have guided the design of these forms.

Most centres request the data regarded as essential by a WHO Scientific Group on Monitoring Adverse Drug Reactions which met in Geneva in 1964 (see table on page 15). These include an identification of the drug administered, its dosage and route of administration, the duration of treatment, the suspected reaction, and the sex, age, and ethnic group of the patient. Additional data of considerable value include the indication for treatment and details of previous or concurrent drug therapy. The amount of detail requested in the initial report may depend on the facilities for follow-up. Centres with limited facilities may, at some risk of deterring reporters, ask for more detail than other centres that have less difficulty in obtaining further information by correspondence or personal interview. The input of data to a national centre may also take the form of detailed correspondence, case-notes, discharge summaries, inquest proceedings, or pre-publication drafts of papers describing adverse reactions.

Centres may need to develop precise methods of patient identification to avoid multiple registration of the same reaction and to facilitate subsequent follow-up.

In some circumstances, direct telephone communication from practising doctors to the centre might be advantageous. The centre could ensure that the necessary information is obtained and if possible establish further communication with each reporting source.

3.2.3 *Validation*

A cluster of reports linking a drug with an adverse reaction or a single report of an unusual or serious reaction can indicate that a drug safety problem may exist. The first step is to validate these reports. Since they indicate only suspected or possible association, they must be checked to ensure, for example, that another cause for the reaction has not been discovered and that the information presented is factual. This may be done by telephone, letter, a personal visit, or a scanning of hospital records.

3.2.4 *Confirmation*

If the reports are valid, it is necessary to confirm whether there is in fact a problem concerning the safety of the drug in question. The experience of a medically qualified person is invaluable. It is a common experience that the possible problems identified at an early stage are too numerous for the staff to investigate each thoroughly. It is generally necessary to decide which possible associations should be selected for confirmation. Serious, new, unusual, or numerous reactions are prime candidates for investigation and confirmation. The extent of use of the suspect drug is also an important consideration.

Studies aimed at confirming a reaction take a variety of forms. Some might be conducted by the national centre, others by outside groups, particularly the reference centres organized for comprehensive monitoring. Problems associated with these confirmatory studies are discussed in sections 4.3 and 4.4.

3.3 Nature of output

To facilitate evaluation of the importance of the information received, data and the results of data analysis should be stored in a form that permits rapid retrieval.

Periodic and cumulative tabulations of suspected drug reactions should be regularly produced. When the validity of the reports has been examined, methods should be devised to include these results in the reviews. The full use of the drug reference list and the recording systems for drugs developed by WHO will facilitate international cooperation.

REPORTING OF SUSPECTED ADVERSE REACTIONS TO DRUGS: DATA INCLUDED IN REPORTING FORMS USED BY NATIONAL CENTRES

Data requested by WHO	Essential datum[a]	Data included in national centre reporting forms											
		Australia	Canada	Czechoslovakia	Denmark	Federal Republic of Germany	Ireland	Netherlands	New Zealand	Norway	Sweden	United Kingdom	USA
Section 1													
Case identification	+	+	+	+		+	+			+			+
Report type (sequence)	+												+
Source of information	+	+	+	+	+	+		+	+	+	+	+	+
Date of birth	} +	+		+	+	+				+	+	} +	+
Age	}	+	+				+	+	+			}	
Sex	+	+	+	+	+	+	+	+	+	+	+	+	+
Height		+	+	+		+			+				+
Weight		+	+	+		+			+			+	+
Ethnic origin						+		+	+				+
Date of onset of reaction		+	+	+		+	+			+	+	+	+
Section 2													
Description of adverse reaction	+	+	+	+	+	+	+	+	+	+	+	+	+
Section 3													
Drug(s) taken by patient	+	+	+	+	+	+	+	+	+	+	+	+	+
Indication of "suspected" or "non-suspected", in relation to the adverse reaction	+	+	+	+	+	+	+	+	+	+	+	+	+
Dosage form (drug form)		+		+	+					+	+		+
Dosage regimen		+	+	+	+	+	+	+	+	+	+	+	+
Route		+	+		+	+	+	+	+		+	+	+
Administration began (date)		+	+	+		+			+	+	+	+	+
Administration terminated (date)		+		+		+			+	+	+	+	+
Duration of administration (as alternative)					+		+	+	+				+
Indication of previous administration		+		+		+	+						+
Disorder or reason for use of drug	+	+		+	+	+	+		+		+	+	+
Section 4													
Other concurrent therapies			+	+		+							
Drug reaction history		+		+		+	+	+	+				+
Laboratory studies		+		+		+	+						+
Other conditions		+		+	+	+	+		+		+		+
Gravidity		+		+		+	+						+
Parity		+		+		+							+
Date last menstrual period began		+				+							
Outcome (of adverse reaction)	+	+		+		+	+	+	+	+		+	+
Date of death				+		+							+
Cause of death				+		+	+						+
Other factors				+		+		+	+			+	+
National centre comments (optional)		+		+		+						+	+

[a] Essential in the opinion of the WHO Scientific Group on Monitoring Adverse Drug Reactions, 1964.

3.4 Problems of individual reporting systems

3.4.1 *Responsibility for reporting*

The responsibility for reporting suspected cases of adverse drug reactions to a national centre should be clearly recognized by individual doctors as a part of their obligations for patient care. It is most desirable to gain the support of national associations of medical personnel, including practitioners, specialists, research workers, and pharmacists, in meeting this responsibility. A variety of procedures are necessary to promote their cooperation. These include meetings and circular letters, in addition to a feedback and communication system between the national centre and those who provide it with information.

Although individual responsibility for reporting is fundamental to the system, national centres should consider reinforcing this in situations where large groups of doctors are working in a cooperative fashion in an establishment such as a hospital, clinic, or health centre. If the establishment is large enough, designated officers may take responsibility for the local collection of reports on adverse drug reactions and for their transmission to the centre. The effect on reporting of a highly motivated individual or group willing to undertake this responsibility should not be underestimated.

3.4.2 *Measures to encourage reporting*

Under-reporting of adverse reactions can be a major defect in individual reporting systems. Under-reporting not only decreases the quantity of the data, making statistical evaluations more difficult, but may introduce bias in that the reports received may not be representative or typical of the reactions that are actually occurring.

Of primary importance in encouraging reporting is the development of rapport between the medical profession and the national centre. The reporting physicians should be made to feel that they are an integral and vital part of the system (as indeed they are). The proper use of follow-up medical officers to validate incoming reports can establish personal contact between the reporting doctor and the centre.

"Feedback" by provision of an information service, by publication of early warnings or more detailed scientific papers, and by answering individual doctors' inquiries is part of the educational function of the monitoring organization and maintains the input of reports into the system. It should be stated unequivocally that effective feedback is fundamental to the establishment of rapport and to the early identification of drug hazards. Several national centres acknowledge each report received and provide information on similar reactions already recorded. Geographic proximity, with increased opportunities for personal contact, should be advantageous. In large countries regionalization may be helpful.

Reporting must be as easy and flexible as is consistent with the transmission of valid data. Practising doctors are very busy and the reporting process must be as simple and swift as possible.

Practising doctors should be advised that *suspicious events* need to be reported. Previously unrecognized associations will be discovered only if the doctor realizes that he should report any possible association.

3.5 Role of reference centres

The case for encouraging the development of hospital centres with the special expertise and facilities to carry out comprehensive monitoring of patients for adverse drug reactions (reference centres) is set out in the report of a previous WHO meeting.[1] That report recommends that " national centres should be responsible for the promotion and coordination of this development with the assistance of WHO ".

It is doubtful if it would be worth while to establish intensive or systematic hospital monitoring solely as a means of detecting previously unsuspected adverse drug reactions. The role of reference centres in complementing the work of a national centre operating an individual reporting system is clear. For example, because of the knowledge of the total number of patients receiving a drug and the availability of information on all other drugs used, a more efficient examination of hypotheses about adverse reactions can be made. In particular, a reference centre is well placed to investigate the peculiarly difficult problems arising from any drug interactions. After identification of a drug safety problem, a hospital-based drug monitoring system linked to a clinical pharmacology group could have the resources to investigate both the epidemiological evidence and the mechanism of the suspected adverse reaction. However, since many of the more serious adverse reactions are often rare, they may not emerge in significant numbers in small populations. This difficulty may be overcome by linking data from a number of reference centres. It should be the function of a national centre to encourage use, and coordinate the activities of reference centres within the country.

4. RESEARCH AND DEVELOPMENT

Since the methodologies involved in drug monitoring have not been perfected, research and development are critical. In all phases of the functioning of a drug monitoring system, serious questions exist as to the most efficient means of extracting, assembling, analysing, and evaluating the

[1] *Wld Hlth Org. techn. Rep. Ser.*, 1969, No. 425.

data. Research in these areas is vital if improved methods of monitoring drug safety are to be developed. The major objectives should include:

(1) continuous review and improvement of the operational system and the development of more efficient operational systems;

(2) improvements in communications, including both input and output;

(3) facilitation of the early identification of drug safety problems;

(4) development and utilization of definitive studies.

4.1 Improvement of operational systems

Major problems include the development of better methods of patient record linkage both inside and outside the hospital and the development of efficient methods of estimating the number of patients taking any particular drug at any time. The meeting agreed that attempts to develop new and more effective systems for monitoring adverse reactions to drugs are necessary and that reliance on any one system is probably undesirable. This view is supported by experience in the USA (Annex 3).

4.2 Improvement of communications

The communications network of a national centre is extremely complex. The most important link is that between the centre and the reporting sources discussed in section 3.4. A major operational research effort must be directed to methods by which reporting can be facilitated and information about adverse reactions fed back to those contributing to the system. The form of presentation of feedback information requires study so as to obtain the maximum educational effect, to maintain the best rapport, and to improve the level of reporting. The optimum method of disseminating information about drug hazards to the health professions as a whole, and in appropriate cases to the public, is also an important subject for study. The most economical and profitable methods of communicating with other national centres and with the WHO Centre should also be developed.

4.3 Early detection of drug safety problems

The use of data processing systems in established national centres is still at an early stage of development, and they are as yet mainly applied to file retrieval.

In one country with an input of 400 reports a month the original reports are scanned by the staff of the centre collectively and decisions on further action are made on the basis of the criteria described in section 3.2.4, i.e., serious, unusual, and numerous reactions and the extent of use of the

drug. Suspicions can be followed up by retrieving relevant information from a computer-stored data bank and by further scanning using the same criteria. Although this method has achieved a significant degree of success in the past, its deficiencies clearly lie in its reliance on the availability of experienced staff, not easily recruited or replaced, and the fallibility of human memory.

Such a scanning and memory recall method can be supplemented by the time-consuming manual sorting of records, which may produce " reaction profiles " for particular groups of drugs. An example of a " reaction profile " is provided in Annex 2 (page 40).

A considerable advance will be made when more refined and fully automated systems are applied to computer-stored data, and work on this is already under way in a few centres and in the WHO Centre. Eventually a variety of automatic " signals " comparable to those developed in the WHO Centre are likely to be devised, and will enable national centres to disseminate more meaningful information to reference centres and other collaborating bodies. Such a procedure is likely to increase the chances of detecting meaningful associations between drugs and reactions and may thus point to the necessity for initiating definitive studies.

4.4 Definitive studies

Not all adverse effects can be detected from the reports of individual events, no matter how carefully the events are investigated and the data are analysed. Sometimes the effects will not be recognized because the events are not reported, while on other occasions relative over-reporting will suggest an association that is entirely spurious. It must be expected, therefore, that national centres will repeatedly have to initiate special inquiries to elucidate such problems (Westerholm & Reizenstein, 1971).

Searches of the WHO Centre's files may provide useful information from a wide range of sources that will assist in determining the type of definitive study to be undertaken. Such data may be especially valuable in instances where definitive studies are not feasible or available to a national centre.

If the suspected effect arises in a high proportion of treated patients, it may be investigated in a laboratory or in a reference centre that undertakes comprehensive hospital monitoring. For example, the suspected association between haemolytic anaemia and methyldopa was confirmed by laboratory experiments (Carstairs et al., 1966). If, however, the reaction is rare, a large number of patients may need to be studied, either by the national centre itself or by epidemiologists at the suggestion of the national centre. Examples of such studies are those conducted in the United Kingdom on mortality and morbidity among women using oral contraceptives: Inman & Vessey (1968) studied mortality in the general population, while

Vessey & Doll (1968) studied morbidity in a smaller hospital population. Alternatively, such studies may be referred to other research organizations. In many instances, however, the problem could be solved more readily if the centre had available a system of population monitoring like that described in section 3.1.3.

5. RESOURCES

5.1 General considerations

The resources required by national centres may vary greatly according to the needs of each country and the resources available. In some countries a valuable addition to drug safety could be made by a small staff of one or two medical officers with clerical help. On the other hand, a fully developed centre would require automatic data processing equipment and a large and highly technical staff.

5.2 National committee on adverse drug reactions

A national committee on adverse reactions is a basic component of the national centre. This should be a permanent committee composed of independent experts in such fields as clinical medicine, pharmacology and toxicology, epidemiology, and statistics. The committee would provide the staff of the centre with expert advice. It should meet regularly in order to examine old and new programmes, suggest the need for further studies, and advise on the importance of new findings. Moreover, a nucleus of members of this committee could provide useful assistance in the establishment of new centres.

Members of the committee, like the permanent staff of the centre, should be independent, and no restrictions should be placed on their medical and scientific evaluation of data obtained from the monitoring activities.

5.3 Staff

In most countries, the permanent staff of the national centre will be government employees working closely with the national committee on adverse reactions. They will be responsible for the operation of the system, for the assessment of safety problems arising from the system, and for the transmission of the national Committee's recommendations to the appropriate individuals or groups.

Because the problems of adverse drug reactions primarily concern clinical medicine, the overall management of the centre should be carried out by medically qualified personnel. Clearly, the medical staff will require sup-

port from other professional personnel, such as medical scientists, pharmacists, computer experts, and administrators.

There is a serious lack of personnel trained in the difficult problems of drug monitoring. Epidemiologists, physicians, and pharmacologists interested in, and with a knowledge of, clinical drug problems are in particularly short supply. The exchange of personnel between centres and the WHO Centre would be highly desirable.

5.4 Computer facilities

The provision of adequate computer facilities is essential if a national monitoring centre is to reach full development.

The automatic data processing system should be used for rapid file retrieval, for " signalling " potential new drug hazards, and for storing and processing additional case-history information obtained during the course of follow-up studies by the national centre. Special provision should be made for the inclusion of statistics on drug use or consumption.

It is highly desirable that national centres should be so designed as to ensure compatibility with the equipment and programmes currently used by WHO. Adoption by the national centre of the *Adverse reaction terminology* [1] prepared by WHO could be a considerable advantage.

5.5 Exchange of information

Facilities should be provided for the regular distribution of information to members of the medical professions. " Feedback " of information may be effected by direct communication between the staff members of the national centre and individual doctors, by direct mailing of circulars to all doctors, or by the publication of commentaries and scientific papers in the national medical journals. Some centres have considered the production of a journal or " broadsheet " dealing with adverse reactions, for regular distribution to all doctors. Consideration may also be given to the holding of seminars sponsored by the national centres, and to the briefing of medical tutors responsible for instructing undergraduates and postgraduates in problems of drug safety.

When evidence of a serious drug hazard has been identified as a result of the national centre's operations, an appropriate warning together with the committee's recommendations should be rapidly communicated to the medical professions, to the authority responsible for drug safety, and subsequently to WHO (in accordance with a resolution of the Sixteenth World Health Assembly).[2]

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[1] Unpublished document DMO/RDM/71.1, available on request from the World Health Organization, 1211 Geneva 27, Switzerland.

[2] Resolution WHA16.36 (*Handbook of resolutions and decisions*, 11th ed., 1971, p. 121).

5.6 Funding

The level of funding will necessarily vary as a function of the needs and resources of each country. Adequate financial provision should be made for the following:

National committee on adverse drug reactions
Professional and supporting staff
Travel, including international travel
Educational activities
Training and exchange of personnel
Communications with: physicians, research groups, other national centres, the WHO Centre, and other agencies
Publications
Library services
Equipment and facilities (including computer time and processing equipment)
Research laboratories
Support for reference centres
Support for special and definitive studies.

6. INTERNATIONAL ASPECTS

International collaboration in the field of drug monitoring has been recognized as a valuable means of improving the usefulness of national centres. Initially the collaboration took the form of an exchange of information between a relatively small number of national centres on particular drug problems. Subsequently, literature searches of medical journals published in other countries have also proved a useful source of information to national centres.

In 1962 WHO initiated a study of methods by which the safe use of drugs could be promoted. A WHO international programme has since been developed in collaboration with Member States; it provides for the following activities:

(1) Advice and assistance to governments to develop drug monitoring systems for the recording and study of the adverse effects of drugs.

(2) Assistance in the training and education of the personnel of national centres, including exchange visits and attendance at WHO meetings and seminars.

(3) The establishment and development of a WHO research project on the establishment of an international system for monitoring adverse reactions to drugs.

(4) The communication to WHO of any official action by a drug registration authority in a Member State to restrict or ban the use of a drug on account of its adverse effect, together with the reason for such action. This information is subsequently passed on to all Member States.

The frequency and nature of adverse reactions to drugs may vary between population groups of different ethnic origin living in different environmental conditions (climate, nutrition, etc.). It is of importance from the point of view of obtaining a representative proportion of the world population to obtain information on adverse reaction patterns from such groups.

It is anticipated that information from comprehensive monitoring systems and the results of definitive studies conducted by national centres could make a useful contribution to the work of the WHO Drug Monitoring Centre.

7. CONCLUSIONS AND RECOMMENDATIONS

The meeting was convened to provide guidelines for countries wishing to establish national centres for drug monitoring, to improve the effectiveness of existing national centres, and to identify the contribution that national centres should make to the international system. The prime objective of drug monitoring systems is to diminish the time necessary to recognize that a drug produces an adverse reaction and to determine the importance of the reaction. It is concluded that national centres should be established or further developed to accomplish this objective.

The main activities of national centres should include :

(1) The collection of data on adverse drug reactions derived from sources such as reporting by individual practising doctors, comprehensive monitoring in hospitals, and systematized collection of data on defined populations. The systematized monitoring of populations and other sources of adverse drug reaction data, e.g., health statistics and drug utilization data, need to be further developed.

(2) The effective analysis of input data. This will be dependent upon the quantity and quality of the reports provided, and upon the system for storage, linkage, and analysis of the data. The quality of reports can be improved by developing satisfactory methods for validation. When the number of adverse reaction reports is large, methods should be developed to determine which reports or groups of reports require further investigation. Special attention should be paid to new drugs.

(3) The support and promotion of reference centres and comprehensive monitoring systems, which can provide additional data and may be especially useful for the investigation of drug safety problems.

It is clear that all activities of the national centres require continuous research and development. The problems involved are sufficiently difficult and important to require methodological, epidemiological, clinical, and laboratory investigation. It should be one of the primary responsibilities of the national centres to promote this type of research.

The national centres will vary in size and complexity, and must have the flexibility to permit innovation. They should have systems to collect, analyse, and evaluate their national data, and these systems should be compatible with the international system. The responsibilities of national centres for supplying information and recommendations on drug hazards to regulatory bodies should not restrict their medical and scientific independence.

The following resources are deemed necessary to permit a national centre to achieve its objectives :

(1) Expertise provided by the national advisory committee.

(2) Adequate medical, scientific, and administrative staff.

(3) Adequate funds for (1) research and development, (2) collecting, processing, and investigating data, (3) training staff, (4) maintaining effective communication with individuals, national groups, and the international system, and (5) disseminating educational information to the health professions.

Achievement of the international objectives of drug monitoring requires surveillance of large populations composed of different ethnic groups, using different drugs, and serviced by different systems of health care. Collaboration between national centres through the international system is therefore essential. The WHO programme for drug monitoring should assist in meeting the needs of national centres by (1) developing systems for recording and processing data for comparative and investigative purposes, (2) assisting in the development of national centres, and (3) supplying information to national centres and aiding them in meeting their responsibilities.

It was concluded that an effective international system for drug monitoring depends mainly upon the ability of national centres to achieve the objectives described in this report.

It is recommended that Member States without national centres explore the feasibility of establishing systems for drug monitoring. In countries that already have national centres, methods for increasing their effectiveness should be investigated. The WHO Drug Monitoring Centre should continue to promote and coordinate existing national centres, and should investigate means for improving the international system of drug monitoring.

ACKNOWLEDGEMENTS

The participants acknowledge the valuable contributions made to their discussions by the following WHO temporary advisers : Dr A. F. Esch, Office of the Associate Commissioner for Science, Food and Drug Administration, Rockville, Md., USA ; Dr W. H. W. Inman, Senior Medical Officer, Committee on Safety of Medicines, London, England ; and Mr Yukitaka Yamada, Chief, Second Drug Manufacturing Section, Pharmaceutical and Supply Bureau, Ministry of Health and Welfare, Tokyo, Japan.

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Annex 1

THE SWEDISH DRUG MONITORING SYSTEM

Barbro Westerholm *

The Swedish Adverse Drug Reaction Committee was established in October 1965 as an advisory body to the National Board of Health and Welfare. The aim was to develop a system by which adverse drug reactions could be discovered with minimum delay, in accordance with the recommendation of WHO.

On 1 January 1971 the drug monitoring system in Sweden completed the pilot phase and it is now run on a regular basis. Its aims are:

(1) to collect, evaluate, and store information on adverse reactions to drugs;

(2) to investigate specific problems that may arise when reports on adverse drug reactions are obtained, and in certain instances to attempt to relate the number of adverse reactions reported to the consumption of the particular drug so that the incidence of the reaction can be estimated;

(3) to stimulate and conduct research on adverse reactions to drugs, their mechanism, diagnosis, treatment, and prevention;

(4) to inform doctors, dentists, and other interested groups about essential adverse reactions and their occurrence, and to take such measures as may be appropriate in the light of the reports;

(5) to revise the reports and send them to the WHO Monitoring Centre; to keep in contact with the WHO Centre and national centres in other countries, and to pass on any information that may be of interest to those centres;

(6) to deal with relevant matters submitted to the Committee by the Swedish National Board of Health and Welfare or the Board of Drugs.

The Committee has 10 members representing pharmacology, clinical pharmacology, internal medicine, paediatrics, psychiatry, dentistry, the drug industry, and drug control. A full-time medical officer acts as secretary to the Committee, which meets 2–4 times a year.

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* Senior Medical Officer, Registration Division, National Board of Health and Welfare, Stockholm, Sweden; *formerly* Medical Officer in Charge, Swedish Adverse Drug Reaction Committee, Stockholm, Sweden.

Within the Committee there is a working group consisting of 5 members who meet every 2 months and make suggestions to the Committee as to what action should be taken on the reports received.

Regular staff

The incoming reports are dealt with by staff members of the Pharmacotherapeutic Division of the Department of Drugs (see chart on page 29).

Three people are employed to deal with the reports : a medical officer, a pharmacist, and a secretary. A part-time secretary is available for the exchange of information with WHO.

Furthermore, computer facilities are available at the Karolinska Institute, Stockholm, where programmers and punch-card operators work part-time on the adverse drug reaction project. The National Board of Health and Welfare finances this service.

Reporting

The medical profession (1965) and later also the dentists (1969) where asked to report all adverse effects, both mild and severe, due to or suspected to be due to " new " drugs, i.e., those registered as pharmaceutical specialties in Sweden for less than 3 years. In the case of " old " drugs, notification was requested of all serious, previously undescribed, or uncommon side effects. A form, reproduced overleaf, was distributed to all doctors together with a letter containing information about how to report adverse drug reactions. It was stressed that the report form could be used but that the Committee also accepted information in the form of hospital records, etc.

It soon became obvious that the definition about what to report was not quite clear. Consequently a circular letter was distributed in 1969 (see Appendix, p. 35) in which it was stressed that reactions of such severity that they led to hospitalization, prolongation of hospital stay, or sick leave should be reported for old drugs. For new drugs all probable or suspected adverse reactions should be notified.

FORM USED IN SWEDEN FOR REPORTING BY PHYSICIANS OF ADVERSE DRUG REACTIONS

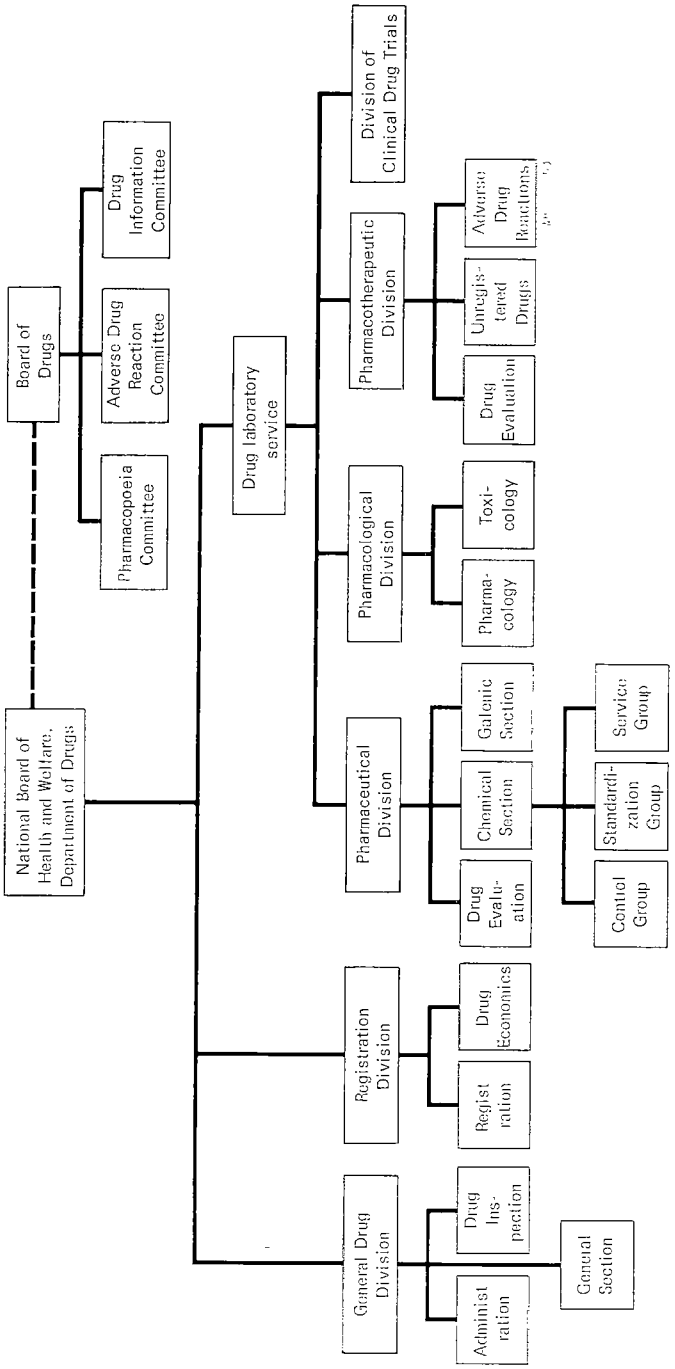
Place, date	Patient, surname, first name, date of birth, identity no.
Name of doctor	
Title	
Name in block letters	
Address	
Telephone no.	☐ Male ☐ Female
Adverse reaction, diagnosis and short description	Date when the adverse reaction was observed:

Main disease

	Dosage form	Route	Dosage	Duration of medication from	Duration of medication to	Disorder or reason for use of drug
Suspected drug						
Other drugs						

One copy should be sent to the Adverse Drug Reaction Committee, Fack, S–104 01 Stockholm 60

ORGANIZATION OF DEPARTMENT OF DRUGS, SWEDEN



The present reporting form was introduced in 1968 and is a modification of the WHO form. As an alternative, doctors may submit discharge notes or copies of medical records.

There has been a steady increase in reporting from about 50 reports per month in 1965–1968 to more than 100 per month in 1970.

Year	*No. of reports received*
1965 (Oct.-Dec.)	155
1966	576
1967	598
1968	657
1969	1103
1970	1303

Most reports come from doctors working in hospitals:

Source of report	*Percentage of total*	
University hospitals	17	88
General hospitals	71	
General practitioners		12
Other		

Experience has shown that the reports come from a very limited number of physicians:

Year	*Doctors reporting adverse reactions (%)*
1965 (Oct.-Dec.)	1.7
1966	6.0
1967	6.5
1968	6.5
1969	7.9
1970	8.5

Very few dentists have notified adverse reactions.

Skin reactions, liver damage, and thromboembolism are the adverse reactions most commonly reported.

Types of reaction most commonly reported, Oct. 1965–Dec. 1970	*Percentage of total (4362 reactions)*
Skin reactions	25
Liver damage	13
Thromboembolism	10
Haematological changes	10

Of these, liver damage and thromboembolism are to a large extent attributed to the use of oral contraceptives. The drugs that most frequently appear in the reports are as follows:

Type of drug	*Percentage of all reports (total 4398)*
Oral contraceptives	25
Chemotherapeutics	19
Analgesics, anaesthetics	14
Psychotropic drugs	12
Cardiovascular drugs	9

Processing of the reports

When a report arrives it is first scrutinized by the responsible medical officer. Complementary information, e.g., in the form of hospital records, may be requested from the reporting doctors. In rare cases the patients are also contacted by the medical officer. Sometimes the manufacturer is asked for information. A literature search is performed if necessary.

At regular intervals (about every 6 weeks) the working party evaluates the reports and makes suggestions to the Committee as to what steps should be taken.

The cause and effect relationship between a drug and a reaction is assessed according to the following classification:

A. Reports that should be classified:

I. Causal relationship probable (provocation test positive, adverse reaction disappeared when medication stopped, adverse reaction resembles other cases reported to the Committee or in the literature).

II. Causal relationship not excluded (criteria under I not fulfilled, several drugs might have been used concomitantly, data might be too scarce to allow a higher classification).

III. Causal relationship unlikely.

B. Reports where only the frequency is of interest (i.e., the well-known drug reactions such as skin rashes due to sulfonamides and jaundice due to oral contraceptives).

C. Reports that cannot be classified because of lack of data.

Since such a classification can never be exact, its value is of course debatable. However, this kind of evalution is of help in deciding what action should follow a reported adverse reaction.

The data in the reports are coded and transferred to punched cards and later to tape. The computer system used for storage and retrieval of the information is developed from the system used by the International Drug Monitoring Centre in Geneva.

Reasons for incomplete reporting

To judge from inquiries, it would seem that there is uncertainty as to what should be reported. For instance, a doctor may not know how long a drug has been on the market and will thus be unable to distinguish between " new " and " old " drugs.

Lack of time is another factor that may keep a doctor from reporting. Fear of legal action, and the fact that reporting is not compulsory, are other causes of incomplete reporting.

The low reporting from dentists may to some extent be due to the fact that they normally prescribe or administer drugs only in small amounts and for short periods. Those patients who experience adverse reactions may be referred to physicians, who may then report the case.

Data from hospital record linkage scheme

Information about the occurrence of adverse reactions can also be obtained through a hospital record linkage scheme that covers about 20 % of the Swedish population. Within a year or two all Swedish hospitals will be included in this scheme.

The data stored in the record linkage system are as follows :

Hospital no.	Date of admission
Department no.	Date of discharge
Medical record no.	Discharge diagnosis
Birth date and no.	Cause of death
Age	Operations
Sex	Anaesthesia
Marital status	Patient's local insurance office

Data and diagnosis are given in words. The diagnosis is also expressed by a 5-digit code according to a Swedish adaptation of the *International Classification of Diseases* (ICD). Coding is carried out at the hospital.

The Swedish adaptation of the ICD also contains code numbers for complications following the use of drugs. Every drug marketed in Sweden has a code number, which is listed in a booklet (*Synonymregister över farmaceutiska specialiteter*) distributed to every doctor.

When a patient has been treated in hospital for an adverse reaction, this is recorded by writing the drug and its code number as a discharge diagnosis. In this way patients treated in hospital for adverse reactions can be traced. The weakness of the scheme is that doctors do not always remember to include the drug in the discharge diagnoses.

By means of this system the frequency with which diseases like agranulocytosis are drug-induced has been investigated. The medical records for all patients hospitalized with this diagnosis during 1964–1968 in the Uppsala

hospital region were searched and examined. About 15% of the Swedish population lives in this area. Some 50% of the patients probably had a drug-induced agranulocytosis (see table), while in the rest other causes (e.g., Feltey's syndrome) were more likely (Westerholm & Reizenstein, 1970). This means that in Sweden there are about 100–140 cases of agranulocytosis per year, half of which are drug-induced. If a change in this rate should be noted, the medical records can be consulted and an investigation carried out to determine whether drugs or other external factors are the cause.

FREQUENCY OF DRUG-INDUCED AGRANULOCYTOSIS IN THE UPPSALA HOSPITAL REGION, 1964–1968 *

Year	No. of cases		
	Drug-induced	Others	Total
1964	10	11	21
1965	10	10	20
1966	8	8	16
1967	10	6	16
1968	9	8	17

* After Westerholm & Reizenstein (1970).

Special investigations

The Committee has initiated or supported several investigations because of reports received from doctors or other monitoring centres or reports in the literature.

For instance, a study has been carried out on the incidence of jaundice and thromboembolism among Swedish women during treatment with oral contraceptives (Westerholm, 1970; Böttiger & Westerholm, 1971). A prospective study has been conducted to reveal the incidence of adverse drug reactions in connexion with the use of injectable contrast media (Bertler et al., 1972).

Surveys have also been made of the incidence of drug-induced agranulocytosis (Westerholm & Reizenstein, 1970) and drug-induced thrombocytopenia (Böttiger & Westerholm, 1972 a, b).

Dissemination of information

Circular letters on the adverse reaction reports received are distributed 2–3 times a year to the medical profession. The letters are simultaneously published in *Läkartidningen*, a leading Swedish medical journal.

Experience has shown that only part of the medical profession reads the letters. The first two warnings about noramidopyrine methanesulfonate sodium and agranulocytosis had no effect on the sales of the drug or on the number of adverse reactions occurring. It was not until after the third warning, when newspapers, radio, and television also mentioned the adverse reaction, that the Committee's report had an effect.

The results of special investigations are published as scientific papers. When it is thought necessary, the Committee publishes its opinion on these investigations as a circular letter and in *Läkartidningen*.

Cooperation with national centres

In a country like Sweden, with a comparatively small population, co-operation with other national and international units is essential in order to solve such questions as "who is at risk" and "how great is the risk" from various preparations. Two examples show the value of cooperation between several centres:

In a cooperative study in the USA, the United Kingdom, and Sweden it was shown that women of blood group O are less likely than others to develop thromboembolism when using oral contraceptives or in pregnancy (Jick et al., 1969).

In another cooperative study in the United Kingdom, Denmark, and Sweden it was demonstrated that women using oral contraceptives containing high-dose oestrogens are at greater risk of developing thromboembolism than women using low-dose preparations (Inman et al., 1970).

Collaboration with WHO

As from January 1968 the Swedish reports were translated, entered on the WHO form, and sent to the International Drug Monitoring Centre. Since July 1971 the reports have been sent on tape, which saves considerable effort and time on both sides. Since Sweden is using the computer system developed at the International Centre, the procedure is very simple. Over the years there have been continuous discussions between WHO and the Swedish national centre about the format and feedback of information from the WHO Centre.

Concluding remarks

It is important to realize the limitations of voluntary reporting systems. The incompleteness of the reporting, together with the fact that in Sweden reporting covers only a small population, might lead to late detection of new and rare adverse reactions. If the data are pooled with data from other countries, however, detection might come earlier.

Once a problem has been detected, various methods have to be used to prove or disprove the suspected cause-and-effect relationship between a reaction and a drug. The incidence of the reaction has to be estimated. The aim should also be to reveal which patients are at risk. In these studies clinical pharmacologists, biostatisticians, and epidemiologists play an important role. At this stage there is some advantage in studying small populations, since both doctors and patients can be more easily reached for follow-up information.

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Appendix

CIRCULAR LETTER FROM THE SWEDISH ADVERSE DRUG REACTION COMMITTEE

The form used for reporting adverse drug reactions has been revised in order to conform more closely with the one used in the international drug monitoring system organized by the World Health Organization. Sweden has taken part in this international scheme since 1 January 1968. The new form is being sent to the medical profession, hospitals, and pharmacies. It can also be ordered from the Adverse Drug Reaction Committee, Fack, S-104 01 Stockholm 60 (Tel. 08/33 33 64). As previously, reports about adverse reactions can also be sent in the form of copies of medical records or discharge notes.

To judge from the large number of inquiries, there is some uncertainty as to which adverse reactions should be reported. When the reporting system was started, the medical profession was requested to report all adverse drug reactions to new drugs, i.e., those

registered in Sweden as pharmaceutical specialties for less than three years, and important or unexpected effects due to the use of old drugs. It was hoped to obtain a picture of the adverse reactions due to new drugs and to limit reporting concerning old drugs. However, it has become evident that the instructions lacked clarity and they have therefore been revised. In future, in the case of *old drugs*, *all probable or suspected adverse reactions that cause hospitalization, prolonged stay in hospital, or sick leave* should be reported. Some well-known adverse effects will thereby be included, but it is important for the Committee to be informed about them if they have led to hospitalization or sick leave. In the case of *new drugs*, *all probable or suspected adverse reactions* should be reported, as before.

The adverse reactions that should be reported include *organotoxic effects* like blood, liver, kidney, and eye damage, as well as neurotoxic effects and cases where *systemic effects* are suspected, e.g., disseminated lupus erythematosus. Furthermore, it is essential to report *allergic reactions* like anaphylactic shock, asthma, and severe skin reactions. If it is suspected that a drug has caused *tumours* or *teratogenic effects* this should be reported, as should *addiction* to drugs not already declared to be narcotics. It is also of interest to receive reports on cases where it is suspected that *drug interaction* has played a part. Symptoms of *overdosage* should, as a rule, not be reported when the reaction is well known. On the other hand, when the drug is new and the symptoms occur in response to a dose that only slightly exceeds the recommended dose, it is of interest to obtain reports about the drug until the nature and frequency of such reactions are established.

The report should contain the diagnosis of the adverse reaction and a short description of its nature, course, and duration. Relevant laboratory data are of interest. If the patient has experienced adverse reactions to the drug earlier, this should be reported, as should allergies towards food and other drugs and chemicals. The trade name, dosage, route of administration, and duration of medication, as well as the reason for medication, should be reported for the suspected drug. The same data should also be given for other drugs given at the time when the adverse drug reaction occurred, to make it possible to evaluate whether several drugs have contributed to the appearance of the adverse drug reaction.

Stockholm, 18 April 1969

Swedish Adverse Drug Reaction Committee

BÖRJE UVNÄS, Chairman BARBRO WESTERHOLM, Medical Officer in Charge

Annex 2

THE UNITED KINGDOM DRUG MONITORING SYSTEM

W. H. W. Inman *

Introduction

Human clinical trials of new drugs frequently reveal the nature and incidence of common side-effects, but the limited number of patients who can be studied usually precludes the detection, except by extreme chance, of the more serious or rare events that may affect only one patient among every 10 000 treated. The early detection of problems arising with new products and of rare reactions to all drugs, new or old, requires some mechanism for monitoring very large populations.

In the United Kingdom this has been attempted by the establishment, in 1963, of an Adverse Reactions Reporting System that is dependent on the spontaneous and voluntary cooperation of all branches of the medical profession. The reporting system is the responsibility of the Adverse Reactions Sub-Committee of the Committee on Safety of Medicines, and is managed by a permanent headquarters staff of three doctors with appropriate clerical assistance. Field work is conducted by a team of 40 doctors employed on a part-time basis in various parts of the country.

Appreciable numbers of notifications of suspected drug reactions were first received in 1964, and some 24 000 reports had been assembled by the end of 1970. The sources of the reports were as follows :

Source of report	*Reports of suspected adverse reactions (%)*
General practitioners	54.0
Hospital residents	17.1
Consultants	17.0
Family planning clinics	7.4
Medical officers of health	1.5
Dental surgeons	0.9
Coroners	0.2
Others	1.9

Useful information has also been obtained from death certificates of patients who died as a result of adverse reactions to drugs, and a small number of events have been reported by the pharmaceutical industry.

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Criteria for reporting

The Committee on Safety of Medicines has requested the notification of all reactions to newly introduced drugs and all serious or unusual reactions to other drugs. In practice, the majority of the reports have described comparatively serious or uncommon events (at least 10% describe fatal events), and much of the Committee's time has been spent on the assessment of conditions such as jaundice, blood dyscrasias, or thromboembolic disease. A recent field survey of a random sample of the reports has shown that they are, on the whole, of high quality and that in the majority of patients drugs are quite likely to have been responsible for the adverse reactions observed.

Registration and coding of reports

All reports to the Committee are processed in strict confidence and material that would identify a patient is never released in any form without the permission of the reporter. The methods by which they have been made are indicated below:

Route	*Percentage of all reports*
"Yellow card"	78.7
Letter from doctor	9.6
Drug company	5.4
Office of Population Statistics	4.2
Royal College of General Practitioners	0.9
Field workers	0.8
Case report in major journal	0.3
Others	0.1

It can be seen that the pre-paid reply card (Fig. 1), usually referred to as the "yellow card", has proved a most effective means for reporting, accounting for nearly 80% of the input. The format of the yellow card is very similar to that of the document used by national centres for reporting adverse reactions to the WHO Drug Monitoring Project. The coding procedure is also similar. All possible combinations of drug and reaction are processed, using a therapeutically based drug code and a simple adverse reaction code. The yellow cards and other documents relating to individual patients are filed chronologically in approximately 600 drug files. Where a patient has received more than one drug, tracer cards are placed in appropriate files so that all the documents relating to a single drug can be retrieved manually. The documents are stored in transparent plastic wallets, and the essential details can be read without removing them from the wallets. By this simple device the documents are rarely lost or misfiled, and can be assessed very rapidly.

FIG. 1. "YELLOW CARD" USED FOR REPORTING ADVERSE DRUG REACTIONS IN THE UNITED KINGDOM

IN CONFIDENCE — REPORT ON SUSPECTED TOXICITY OR SIDE-EFFECTS

NOTES FOR GUIDANCE

1 For all drugs, please record serious or unusual reactions. For new drugs record all reactions.
2. Record, on the top line, the drug suspected of causing harmful effects to the patient at normal dosage.
3. Record all other drugs, including self-medication, taken in the previous 3 months. With congenital abnormalities, record all drugs taken during pregnancy.
4. Please do not be deterred from reporting because some details are not known.

Name of Patient: (Required in confidence to allow linkage with other reports for same patient)			From: (Name, Address & Tel. No.)	
Sex	Age or Date of Birth	Weight if known	Signed:	Date:

DRUGS* (Give brand name if known)	ROUTE	DOSE	DATES From	DATES To	INDICATIONS
(*For Vaccines give Batch No.)					

REACTIONS (List separately)	Started	Ended	OUTCOME (e.g. fatal; recovered)

Additional Notes

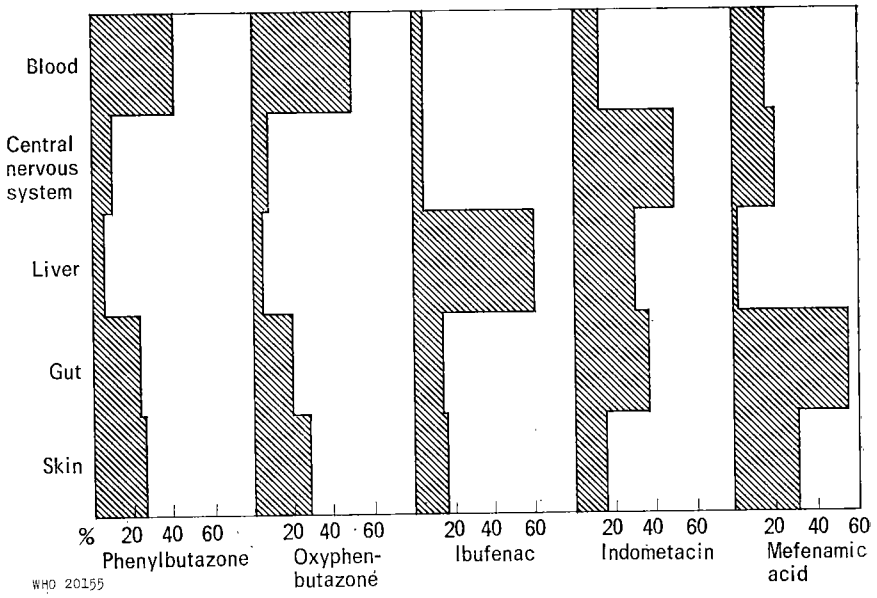
Recognition of new drug-safety problems

The computer programme currently in use enables the Committee to obtain tabulations of the reactions that have been reported and can also be used for simple file-retrieval operations. It is not yet possible to perform detailed analyses of the data in such a way as to generate "signals" that would draw the attention of the monitoring staff to potential hazards they might not have identified during the routine inspection of the reports. New computer programmes currently being developed will speed up file-retrieval and also, it is hoped, enable automatic signals to be generated.

On several occasions new hazards have come to light as a result of comparisons between the reaction patterns of related drugs. The "reaction

profile" of each member of a group of drugs is prepared by calculating the proportion of reports of each type of reaction among the total number of reports received. As an example, the profiles for 5 analgesic drugs are shown in Fig. 2. The profiles of phenylbutazone and oxyphenbutazone

FIG. 2. REACTION PROFILES OF FIVE ANALGESIC DRUGS



are clearly very similar, but show quite marked differences from the profiles of the other drugs. Indometacin shows a high proportion of central nervous disturbances, mefenamic acid a high proportion of gastrointestinal symptoms. With ibufenac, there was a marked predominance of reports of liver disturbances. These reports led to the voluntary withdrawal of ibufenac from the market by its manufacturers.

In the United Kingdom it is possible to obtain accurate estimates for the number of prescriptions and for the total quantity of drugs prescribed by general practitioners, using data collected by governmental drug pricing bureaux. These estimates cover perhaps 85% of all drug use in the country. Similar data may also be obtained from the pharmaceutical industry. In many situations it is possible to estimate the reported incidence, using a denominator expressed as "patient-years" of exposure to a drug, though it has not usually been possible to estimate the total number of patients actually exposed.

The importance of drug-use estimates is illustrated by the apparent difference noted in 1966 in the pattern of reactions to oral contraceptives containing mestranol as compared to those containing ethinylestradiol.

While the sales of the two types of contraceptive were known to be almost equal, there were appreciably more reports of thromboembolic disease following the use of preparations containing mestranol. Some three years later it was possible to demonstrate that the increased risk of thromboembolism was related to the oestrogen content of oral contraceptives rather than to chemical differences between the two oestrogens. Similar data were supplied by the Swedish Adverse Drug Reaction Committee and the Danish Adverse Reactions Board, and yielded comparable results (Inman et al., 1970).

The "reported incidence" of adverse reactions is much less than the actual incidence, because only a small proportion of events are reported. For example, in the course of a retrospective inquiry by its team of field workers, the Committee found that, of 53 general practitioners who were aware that their patient had been using oral contraceptives at the time of her death from thrombosis, only 2 had reported the death to the Committee (Inman & Vessey, 1968). In another situation that attracted much less publicity, it was suggested that perhaps 3500 asthmatics had died as a result of over-use of pressurized aerosols containing bronchodilator drugs (Inman & Adelstein, 1969). Only a handful of reports of sudden death had been sent to the Committee over a period of several years before the hazard became generally recognized as the result of publications in the medical journals (e.g., Doll et al., 1967 ; Speizer et al., 1968).

Probably because of the long interval between exposure to a drug during early pregnancy and the subsequent birth of a deformed baby, few doctors have suspected and reported possible associations of this kind, so that the voluntary system cannot be regarded at present as an effective means of detecting teratogens. For similar reasons it seems unlikely that carcinogenic or mutagenic effects of drugs will be detected by the voluntary reporting system.

Investigation of a new hazard

The term "early warning" has been used to describe the early recognition of a possible new drug safety problem. The warning is usually internal to the monitoring system and should not be confused with public statements made by official bodies. So many internal early warnings are derived from the voluntary reports that it is often difficult to decide on the priorities for their further investigation. It is usually necessary to follow up or validate individual reports in order to ascertain the outcome of the reaction and to search for other factors, including the use of concurrently administered drugs, which might provide an alternative explanation for the reported event. The use of medically qualified field officers for this work has proved invaluable.

When preliminary investigation suggests that reactions may be causally related to the use of a drug, the Committee may decide that it is necessary

to bring this immediately to the attention of the medical profession or may delay notification until further studies have established the incidence and importance of the reaction.

Occasionally it may be possible to study a problem in relatively small numbers of patients, using laboratory techniques. If the reaction occurs infrequently, the Committee may request the assistance of groups of doctors conducting intensive monitoring of large populations of patients, usually in hospitals, under conditions where both numerator and denominator can be measured. If the reaction is rarer still, much larger populations may need to be studied either prospectively or retrospectively. The Committee has undertaken one such epidemiological study of the influence of oral contraceptives on mortality from thrombosis, and has encouraged outside workers to conduct a number of other studies. Using retrospective methods, it has also completed a pilot study of the drug histories of mothers of congenitally abnormal babies and plans to continue the inquiry on a larger scale to facilitate early detection of teratogens.

Provision of information to the medical profession

The Committee's professional staff undertake correspondence with individual physicians who have reported adverse reactions or who inquire about drug safety problems. The Committee has issued 9 pamphlets in its *Adverse Reactions Series* and its officers have published several letters and papers in the medical journals. As a matter of routine, each time a doctor reports an adverse reaction he receives an acknowledgement together with lists of previously reported reactions to the group of drugs concerned.

The unpredictable response of the national news media to statements made by the Committee has led to difficulties. When the medical profession is informed about the existence of hazards associated with the use of drugs, there is always the risk that patients taking the drugs may read about this warning in the public press and become unduly alarmed.

The Committee endeavours to keep the pharmaceutical companies informed of any dangers that come to its attention, and frequently checks sales literature to ensure that the information concerning side-effects and adverse reactions is correct.

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Annex 3

THE PLANNING OF A NATIONAL DRUG MONITORING SYSTEM

Albert F. Esch *

For more than a decade, the United States Food and Drug Administration (FDA) has participated in a number of programmes for acquiring and processing information concerning adverse reactions to drugs. These have ranged from the most fundamental procedures for assimilating individual case reports to complex methodologies utilizing computer technology. With the wealth of experience gained from these investigations, the FDA is currently formulating a comprehensive plan to meet future requirements for ensuring safety in drug therapy. Furthermore, a broadened safety information system can now be visualized.

On the basis of data patterns, previous FDA studies can be divided into 3 general categories : (1) spontaneous isolated case report programmes, (2) drug reaction incidence studies (e.g., using intensive monitoring techniques), and (3) comprehensive surveillance efforts that have been incorporated into major health plans. Each has been found to have the potential for providing data unobtainable by other means, together with qualitative or quantitative advantages in applied methodologies. In addition, there have been characteristic patterns of reporting and wide variations in the cost per unit of useful information.

The first category, individual case report systems, can be further divided into systems providing drug experience data through contractual agreements and sources submitting reports on their own initiative or as the result of regulatory requirements. In the USA, the former group consists primarily of the Hospital Reporting Program subsidized by the FDA, while the latter group includes data from the pharmaceutical manufacturers, military hospitals, and professional organizations, and spontaneous communications from physicians. During the 10 years of experience with the Hospital Reporting Program, several hundred institutions have participated and more than 100 000 reports have been elicited. To obtain uniformity of case reports, a continuous effort has been made to facilitate the retrieval of information in a standardized form.

Although the origins of isolated case reports received by the Food and Drug Administration are diverse, many general characteristics have become

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evident. Using the guidelines for "significant" cases as proposed by the FDA, a relatively constant level of reporting has been observed. Institutions under contract consistently report drug reactions affecting approximately 5–7% of the hospital patients under observation, and this is believed to reflect closely the true incidence of significant adverse effects. Payment for reports, although on a modest scale, increased the yield approximately tenfold. The quality of such reports was comparable with that of reports provided free of charge.

The WHO Research Project for International Drug Monitoring is of particular significance. Primarily based on spontaneous reporting, this programme has demonstrated the feasibility of collaboration between a number of nations and has developed a unique system of "signals" for critical cases based on preselected criteria. It now operates as a single programme with facilities for exchange and retrieval of information.

Isolated reports have been found to yield a relatively high incidence of unprecedented, or comparatively undocumented, suspected associations of drugs and side effects. Consequently, this type of reporting is believed to be highly suitable for incorporation into a comprehensive monitoring system. Its utilization for the "early warning" sector of a comprehensive programme, moreover, is a relatively cheap method of identifying new problems of potential significance. Attempts have been made to subject this type of reporting to statistical analyses through the establishment of trends on which predictions could be based. Owing to the complexity of drug reaction cases, however, even relatively large quantities of material have not yet proved satisfactory for this purpose.

The second general category comprises drug reaction incidence studies, which provide both numerator and a denominator data. Such programmes have demonstrated their potential for providing the next level of documentation for unprecedented ("early warning") reports or for drug/reaction associations that are of particular interest and for which preliminary numerical indicators are needed. Up to now the number of suspected associations to which attention was first drawn by these programmes is small, because logistic and economic considerations make it difficult to study populations of sufficient size. Many contemporary systems have accumulated data on adverse reactions to drugs, but so far difficulty has been experienced in obtaining specific results from the processed information.

The Food and Drug Administration has directly funded three investigations within this category and maintained an active interest in at least two other established programmes. One of the earliest of the funded studies was carried out in 1965, utilizing records of prescriptions and physician-recorded drug reactions. The sources of data were 30 pharmacies and a medical society of 83 physicians in a county with an area of 950 km^2 (population 115 000). A relatively low yield of drug reaction reports was obtained

during the survey. Another early project of several years' duration was undertaken in a major hospital, using two approaches to drug side effects (Koch-Weser et al., 1969). This investigation provided a comparison between the results of intensive surveillance procedures employing nurse surveillance officers and the results of voluntary reporting from other wards, using the protocols specified by the FDA Hospital Reporting Program. During a subsequent phase of this study, special monitoring projects were conducted on classes of drugs or individual agents specified by the FDA. In another medical centre, a study that has been in progress since 1967 has developed an intensive surveillance methodology that is considered to have shown maximum accuracy for retrieving clinical information. These investigators, employing a basic pharmacist/physician team for the direct monitoring of inpatients, have established a consistent rate of drug reactions and drawn up a protocol that is possibly applicable to other centres. Other studies in which the FDA has had an interest have employed nurse monitors as the basic personnel for the collection of clinical material or have used a pharmacy service common to several hospitals as a focal point for collecting reports on drug reactions from attending physicians.

Although these studies do not provide the FDA with large quantities of significant information, their practical value has been to demonstrate the comparative merits of each methodology. It is envisaged that those methods with potentially productive protocols can be widely applied in the future to establish the intermediate level of documentation needed within a comprehensive system. This would facilitate the monitoring, where necessary, of specific classes of drugs or suspected adverse reactions.

The third category of investigations comprises surveys designed for major population segments and compilations of data from an unusually large number of hospitals. Positive interest in such studies was expressed as early as 1963, but the clinical information assembled in such repositories as existed was found to be of a more general administrative nature. Medical literature is a potential source of data on the required scale. As with statistical surveys, an early difficulty was found to be the lack of relevant data for comparison. In addition to the successful efforts carried out within the Agency, work on this problem has also been done on a commercial basis. In 1966, the Food and Drug Administration began funding a major programme directed towards epidemiological surveillance for drug reactions, using computer-based medical records. The study was unique in that it monitored an outpatient population, and its results have been promising (Friedman et al., 1971). With the increasing emphasis on comprehensive health plans, this epidemiological approach may become the principal method for the detection of major problems within the population.

Contrary to the earliest expectations, it has proved more difficult to identify adverse reactions than to obtain data on the extent of drug use. The diversity of interpretations and the forensic constraints on such infor-

mation have been described elsewhere (Esch, 1969). In addition to these limitations on volume, qualitative requirements also present difficulties. In the three categories, a consistent inverse relationship has been observed between the specificity of the subject matter and the volume of both the numerator and denominator data. Consequently, while the direct use of professional expertise in the subjective detection of cases has restricted the breadth of any survey, epidemiological approaches that incorporate large segments of general clinical information have not effectively isolated the precise data that are necessary. When further developed, large-scale epidemiological systems may prove more useful than isolated clinical conclusions, but their adoption should not preclude the use of the numerous professional assessments that are readily apparent and directly adaptable to the task. A comprehensive monitoring system must incorporate a full range of techniques. The use of each procedure must be determined by the specified objectives of the system. The alternatives to be balanced include acquisition of early knowledge of isolated "first" cases as against the detection of products presenting a statistically significant danger to public health, monitoring of drug categories used predominantly by outpatients as against those used mainly by inpatients, and monitoring of all products as opposed to selected categories, e.g., newly approved drugs. The design of a proposed system may be further influenced by economic factors, since the cost of obtaining useful data has been observed to increase exponentially when spontaneous reporting is extended into intensive monitoring and ultimately into comprehensive monitoring. Consequently, while there is ample theoretical justification for the method that produces reports of new suspected associations by means of epidemiologically derived hypotheses reinforced by statistical data, it may be necessary to modify the design if the system is required for the surveillance of drug interactions covering all therapeutic agents.

In conclusion, future systems to ensure that marketed products can be used safely must be designed to coordinate adverse drug reaction data, toxicological findings, records of the misuse of drugs, and data on adverse effects of other potentially hazardous products.

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