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**INTERNATIONAL DRUG
MONITORING**

THE ROLE OF THE HOSPITAL

Report of a WHO Meeting

WORLD HEALTH ORGANIZATION

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CONTENTS

	Page
1. Introduction	5
2. General considerations	6
3. Methodological problems	8
3.1 Spontaneous hospital reporting	9
3.2 Intensive hospital monitoring	11
4. Resources and organization required for drug monitoring in hospital	14
4.1 Spontaneous hospital reporting	14
4.2 Intensive hospital monitoring	15
5. The uses of intensive drug monitoring systems	16
5.1 Epidemiology of adverse reactions	16
5.2 Efficacy of drugs	18
5.3 Long-term effects of drugs	18
5.4 Patients predisposed to drug reactions	19
5.5 Pharmacological studies	19
5.6 Prescribing habits	20
5.7 Drug management in hospitals	20
6. Dissemination of information about drugs	20
7. International aspects	21
8. Conclusions and recommendations	21
References	23

WHO MEETING ON THE ROLE
OF THE HOSPITAL IN INTERNATIONAL DRUG MONITORING

Geneva, 18-23 November 1968

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INTERNATIONAL DRUG MONITORING

THE ROLE OF THE HOSPITAL

Report of a WHO Meeting

A meeting on international drug monitoring was convened by WHO in Geneva from 18 to 23 November 1968. Dr H. Halbach, Director, Division of Pharmacology and Toxicology, opened the meeting on behalf of the Director-General.

1. INTRODUCTION

The Eighteenth World Health Assembly requested the Director-General "to study further the requirements of an international programme for the collection, analysis and dissemination to Member States of information on adverse drug reactions." This decision was a consequence of the vast number of pharmacologically active and therapeutically effective drugs which have become available and which, although transforming the practice of medicine, have brought a number of unwanted effects.

Many of the adverse effects of drugs in man that occur infrequently are not predictable by toxicological experiments on animals or controlled clinical trials, if the populations exposed to the drug differ from the population participating in the clinical trial in characteristics such as age, sex, pathology, etc., or if the specifications of a drug are modified after the trial. The primary object of drug monitoring for adverse reactions is to define as soon as possible the capacity of a drug to produce undesirable effects.

A number of member countries have developed national systems to receive reports of adverse drug reactions, from doctors in practice and in hospitals, at drug monitoring centres. Efficient operation of such systems is impaired by a number of difficulties. For example, the quality of clinical observation, particularly outside hospitals, is frequently reduced by high work loads and deficiencies in clinical, laboratory and administrative facilities. Overwork and the absence of any immediate benefit to the doctor diminishes his motivation and leads to under-reporting. In addition, under-reporting by doctors in hospital is the result of not knowing which member of the medical team is responsible for making a report. The position is made worse by the inadequacy of the medical record as a complete account of clinical observations.

Another and different approach to monitoring drugs for adverse reactions is to use epidemiological techniques in hospital populations, and the report of the WHO Scientific Group on Principles for the Clinical Evaluation of Drugs (1968) states that this is a subject which deserves study.

The purpose of the present meeting is, therefore, (1) to consider methods of increasing the efficiency of hospitals in detecting and reporting adverse reactions to drugs within national systems; (2) to discuss the methodological problems associated with the development of epidemiological techniques aimed at systematic drug monitoring of hospital populations; (3) to assess the potential advantages to clinical medicine and pharmacology of such a development; (4) to indicate the part national and international organizations concerned with drug monitoring may play in this development.

2. GENERAL CONSIDERATIONS

Terminology

The meeting agreed on the following terminology :

(a) *A drug* is defined as 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 This definition thus includes vaccines, sera and diagnostic agents.

(b) *An adverse reaction* is defined, for the purposes of this report, as one which is noxious and unintended, and which occurs at doses used in man for prophylaxis, diagnosis or therapy. It was the consensus of opinion that this definition should not be applied rigidly but may vary for different centres and under different circumstances, provided that such variations do not result in ambiguity.

(c) *Drug monitoring* is defined as the systematic reporting, recording, and evaluation of adverse reactions to drugs generally available with or without prescription. Information on adverse reactions can be obtained either through voluntary reporting by practising doctors and hospitals to designated centres (*spontaneous monitoring*), or by epidemiological techniques aimed at systematic coverage of separate hospitals, representative samples of the physician population, etc. (*intensive monitoring*).

(d) *The WHO Drug Monitoring Centre* is a pilot organization located in Alexandria, Va., USA, which is intended to be responsible ultimately for facilitating a two-way flow of information concerning adverse reactions to drugs between WHO and centres at the national level.

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).

(e) *A national centre* is an agency, commonly (but not necessarily) governmental, or quasi-governmental, charged with the responsibility for drug monitoring in one or more member states. At present these centres use spontaneous reporting by doctors as the basis for their surveillance systems.

(f) *A special centre* is a hospital, or other medical agency, which has the capacity to carry out drug monitoring in a country without a national centre.

Objectives

Ideally, drug monitoring in hospitals should have two major objectives, firstly to establish the frequency and incidence of adverse reactions, both well-recognized or newly discovered, in relation to the use of a drug, and secondly to detect serious and unexpected adverse reactions as early as possible.

To achieve the first objective requires the identification of a hospital population which has received a drug suspected of producing a well-recognized or newly discovered adverse reaction, and to determine which individuals in that population develop the reaction. One of the main difficulties of identifying a population at risk is a direct consequence of the deficiencies in existing systems of recording the administration of drugs to patients. When such a population is identified in a retrospective study the lack of awareness of doctors of the need to look for and to record the occurrence of adverse reactions to drugs considerably diminishes the value of any data obtained. On the other hand, in what might be considered the most favourable circumstances, when a population currently receiving the suspected drug has been identified, an observer actively looking for an effect may distort the findings and the need remains for properly controlled studies of a suspected association between a drug and an adverse reaction.

The detection of previously unknown or unexpected adverse reactions requires careful observation of patients and the recording of any happening or "event" (as defined by Finney, 1965) that is not part of the normal course of the disease or diseases from which the patient suffers, an intended consequence of treatment, or a recognized adverse reaction to the drugs the patient is taking. The drugs being taken at the time must also be recorded. Some "events" may be explained on the basis of unrecognized pathology from which the patient suffers, and the remainder should be suspected as unrecognized effects of the drugs the patient is receiving. The ascertainment of the unexplained "events" presents great difficulties, even when they are manifest by the development of obvious signs and symptoms, since it cannot be assumed that when they are observed they are always recorded and reported (Lasagna, 1964). The position is

further complicated by the fact that patients frequently receive a number of drugs at the same time, and any combination of two or more drugs may be responsible for an "event". Furthermore, account must be taken of the possible effects of drugs in relation to different pathological conditions from which patients may suffer and which may not necessarily be the disease under treatment. Adverse reactions may occur only after a patient has been discharged from hospital and can only be detected by follow-up.

The collection of the type of information described above also presents other difficulties : for example, because a drug has been prescribed it does not necessarily follow that it has in fact been administered or that the dose administered was correct. Furthermore, prescriptions are frequently written in a form that allows neither easy recognition nor abstraction, and the sheer volume both of drugs and potential adverse reactions produces a formidable problem in data-handling.

It is clear that there is a vast amount of information on the effects of drugs obtained in the course of the medical care of patients in hospital which is, as yet, unavailable for systematic study because of the difficulties described above of drug monitoring in hospital. Hospitals on the other hand have some special advantages in the field of drug monitoring since they lend themselves to the application of new methods of obtaining, recording and handling clinical and laboratory information.

The methodological problems which must be resolved to obtain data for monitoring adverse reactions to drugs administered in hospitals include :

(a) the development of a standard way of writing the prescription that can be easily abstracted;

(b) the development of a method of recording and checking the actual administration of drugs;

(c) the linkage of data on all drugs prescribed, together with details such as age, sex, disease, etc., of individual patients;

(d) the ascertainment of "events" occurring in patients, both explained and unexplained, using procedures which will allow comparison of the relative accuracy of the various sources providing such information;

(e) the development of computer techniques for the handling, storage and analysis of the large volume of information; and

(f) the confidential nature of reports on individual patients.

3. METHODOLOGICAL PROBLEMS

The subject matter of this section falls into two broad categories. The first concerns the development of methods which will improve the reporting of adverse reactions by all hospitals within the framework of

established national monitoring or early warning schemes. The second is the development of methods of more intensive surveillance in a number of centres. These centres, in addition to providing information to national centres, would have the capacity to produce "numerator" (adverse reactions) and "denominator" (patients at risk) data which would be complementary to an "early warning" system nationally or internationally based.

3.1 Spontaneous hospital reporting

At present there are two broad approaches which are influenced by the organization of hospitals in different countries. The first is to consider the hospital doctor as part of the total physician population and to request spontaneous reporting to national centres without payment, as in the United Kingdom of Great Britain and Northern Ireland and in New Zealand. The second is to designate certain hospitals as "reporting hospitals" (as in the USA and Canada) and to associate this with a payment element. Neither of these methods has been satisfactory, and the contribution of hospitals to spontaneous reporting systems has been small considering the number and severity of adverse reactions and of drug-induced diseases which are known to occur in hospital populations.

If improvement in the contribution of hospitals to spontaneous reporting schemes is to be achieved, attention must be devoted to the items discussed below.

3.1.1. *Responsibility for reporting*

It should be emphasized that the doctor responsible for the patient has the primary responsibility to report adverse reactions. However, in addition, one person or team in every hospital or group of hospitals should be made responsible for the organisation and co-ordination of reporting. For example, many hospitals have prescribing committees which could appropriately undertake this task. Highly motivated individuals, such as clinical pharmacologists or medical administrators, could also carry out these functions. The emergence of the clinical pharmacologist in many centres is a development which should improve reporting in general, and it might be appropriate, depending on local circumstances, for him to adopt the function of co-ordinator. In hospitals unlikely to establish clinical pharmacology departments, hospital pharmacists might well be encouraged to assist hospital doctors in this area. The potential contribution of hospital pathologists should not be neglected.

3.1.2. *Method of reporting*

Any form of reporting which is not built into the routine documentation procedure for patient care is likely to produce a low yield. At the present

time in many countries there is intense activity in the field of reorganization of medical documentation and the opportunity should be taken to incorporate the reporting of adverse reactions to national centres in such schemes. Experience so far suggests that reporting forms should be brief and simple. These brief reports could be the basis for retrieving the more detailed information easily provided by hospitals and required by the national centres.

3.1.3 *Time of reporting*

The time when a doctor is most highly motivated to assemble adverse reaction data in a critical and responsible manner is when the event occurs, and this factor should be taken into account in evolving hospital reporting schemes. The data recorded at the time of the event can be best linked to other relevant information at the time of discharge, when the opportunity can also be taken to identify and report on adverse reactions which may not have been recorded at the time. Thus both these occasions during a patient's stay in hospital should be used to identify and report adverse reactions. Any system devised should permit urgent reporting of adverse reactions according to local circumstances.

3.1.4 *Criteria for reporting*

Previously unknown and unexpected reactions, together with serious known reactions, should be reported. The suggestion was made by some members of the group that spontaneous reporting should be used primarily for those in the former category.

3.1.5 *Follow-up of reporting*

The ability of national centres to follow up initial reports of suspected adverse reactions and evaluate them from their own resources is limited. As far as possible the evaluation of a suspected reaction to a drug should be undertaken soon after reporting. The investigation of such alerting reports could well be an important way in which hospitals could assist national centres in evaluation of the relationship of the drug to the reported adverse reaction.

3.1.6 *Education*

The importance of drug hazards and the responsibility of the hospital professions to participate in drug monitoring programmes should be part of the teaching schedule of all schools of medicine, public health, dentistry, nursing and pharmacy. Reinforcement of these principles should be conveyed to hospital staffs at regular intervals and a variety of methods can be used to achieve this goal.

3.1.7 *Payment and reporting systems*

In those countries where payment has been made for spontaneous reporting, experience has shown that it has no advantage over reporting without payment. Financial resources used for this purpose in the past could be utilized more effectively to support follow-up studies and to develop intensive hospital reporting systems.

3.2 **Intensive hospital monitoring**

A number of hospital centres in different countries, besides making their contribution to national monitoring schemes, have been engaged over the last few years in intensive monitoring. Such centres can make a special contribution to national and international systems of drug monitoring because of their special facilities and interests.

The potentialities of intensive hospital monitoring of drugs are illustrated by the work of Cluff and his colleagues at the Johns Hopkins Hospital, who found by intensive surveillance of 714 patients that drug reactions were present on admission in 5% and reactions during hospitalization occurred in 13% (Seidl et al., 1966). Similar findings have been obtained by Hurwitz & Wade (1969) in Northern Ireland, the comparable figures being 5% and 10% respectively in a hospital population of 1300 patients. Another intensive monitoring system has found a 35% incidence of adverse drug reactions (Borda, Slone & Jick, 1968), this figure being considerably higher than the generally reported incidence of from 5% to 20%. In a large general hospital intensive monitoring resulted in an increase from the ordinarily reported 5% to 30% (Koch-Weser, 1969).

This type of monitoring has the following advantages. It can answer the question whether adverse reactions occur, and thereby contribute to the data gained through a spontaneous reporting system. By its nature it can provide data not otherwise available as to how often reactions occur in relation to the use of a drug and in addition it may answer the question why reactions occur and provide leads for investigation of the mechanisms underlying certain reactions.

Three interrelated types of intensive hospital monitoring can be distinguished depending on the method of ascertainment — drug, patient or adverse reaction.

3.2.1 *Ascertainment by drug*

In this type of surveillance an individual drug or group of drugs is monitored for known, suspected or previously unsuspected adverse reactions. Drugs should be identified by manufacturer where possible. In the case of known reactions, both the incidence and characteristics of

the reaction can be established. Numerator data (number of patients with adverse reactions) and denominator data (number of patients exposed to drug) can be obtained, and this information would make an important contribution to the follow-up measures of an early-warning system in the case of suspected reactions.

In the detection of previously unknown reactions it would supplement the spontaneous reporting of the conventional early-warning system as well as provide numerator and denominator information. This would be particularly useful in the case of drugs under investigation and newly marketed drugs, since many drugs of this type are used more extensively in hospitals. Surveillance of this type would also allow dose of drug, patient weight and other relationships to be studied. It would be both possible and desirable to obtain control data matched for selected patient characteristics as discussed in more detail in section 5, which deals with the uses of intensive drug monitoring systems.

Two variations of this type of surveillance may be used separately or together, as follows :

(a) *Prospective*

This procedure would aim at identifying a population of patients currently receiving an individual drug, alone or in combination with other drugs, and keeping these patients under close surveillance by a staff member while they receive the medication, in order to detect a known or unknown adverse reaction if and when it occurs. This staff member may be a doctor engaged full-time on the project (Seidl et al., 1966), a specially trained nurse, i.e., the "nurse monitor" described by Slone et al., (1966) or the "nurse surveillance officer" described by Sidel et al. (1967), or a ward pharmacist (Crooks, Calder & Weir, 1967). In the case of the adverse reaction being noted by a nurse or pharmacist it is essential to have it verified by a doctor, preferably a clinical pharmacologist when available, as described by Sidel et al. (1967).

A number of sources can be used to identify the population receiving an individual drug or group of drugs, but each involves using the record of a patient's daily treatment. The development of automated ordering systems for drugs where the order itself would create a computer-stored record, would facilitate this procedure (Seibert et al., 1967).

The approach described above can also be used to validate the results of retrospective studies, as described by Sidel et al. (1967). The prospective method is likely to be very effective but requires special staff. It appears to be worthwhile for specific objectives such as reinforcement of suspicions raised by the early-warning systems for monitoring certain new drugs and for verification of the validity of data obtained by other methods. Control data must be obtained for the more meaningful interpretation of results.

(b) *Retrospective*

The basis of this method is the identification of patients exposed to an individual drug or group of drugs while in hospital, and identification of any "events" which might be adverse reactions to drugs. These items of information might be linked at the time of discharge of the patient. The denominator, being the number of patients at risk, can be accurately established, but the accuracy of the numerator, the number of the adverse reactions, is a function of the completeness and accuracy of medical and nursing records. Unfortunately the quality of such data tends to be poor, but various devices may be employed to improve it, such as completion of an "adverse reaction" report on discharge (Sidel et al., 1967), or incorporation of such reports in the discharge summary itself.

This method may be developed by linking drug records pertaining to individual patients to diagnoses and other information concerning an admission to hospital, to allow more sophisticated types of analyses to be carried out. One particular way in which this approach can be exploited is to identify from the medical record those patients who are likely to continue taking the drug that is being surveyed, after discharge from hospital, and to further identify the population at risk by direct interview in collaboration with the doctor responsible for the care of the patient (Coull et al., 1968). As in (a) control data should be obtained.

A combination of the prospective and retrospective approach for individual drugs may be used to validate suspected associations between a drug and an adverse reaction, and may prove a powerful complementary tool to spontaneous reporting systems on a national or international basis.

3.2.2. *Ascertainment by patient*

These procedures focus mainly on patient populations and not on individual drugs. The possibility exists that susceptible patient populations (identified by genetic factors, diseases, age, sex, etc.) can be detected and predicted, e.g., the incidence of bleeding from heparin has been found to be significantly higher in women above the age of sixty (Jick et al., 1968). This approach has been particularly effective when special measures are taken to improve and maintain the standard of reporting (Sidel et al., 1967). Such studies may be either retrospective or prospective. They are capable of supplying "numerator" and "denominator" data and could make an important contribution to national systems of drug monitoring.

3.2.3 *Ascertainment by adverse reaction*

In the hospital environment the use of this type of ascertainment is important in those patients whose admission to hospital is wholly or

partly due to an adverse drug reaction. This is a particularly important group since the reactions are usually severe, e.g., agranulocytosis and aplastic anaemia, and may provide the lead information on which intensive monitoring by drug ascertainment could be based. Usually the suspected drug has been administered outside hospital and may be a drug not commonly used in hospitals. Methods of recording and checking the exposure of patients to drugs in this situation should be devised. Since it is usually the function of the hospital to establish the diagnosis in such cases, it should be the duty of the hospital to report such adverse reactions to the national centre. Ascertainment by adverse reactions may be directed towards analysis of the types of reactions which are occurring in the hospital population and could provide useful information both on new and well established drugs.

Information concerning adverse reactions obtained in this way can be compared with control data, as in the other forms of ascertainment, and so raise the suspicion of a previously unrecognized adverse effect of a particular drug. Changes in the frequency or pattern of adverse reactions may also raise such suspicions.

4. RESOURCES AND ORGANIZATION REQUIRED FOR DRUG MONITORING IN HOSPITAL

To improve the contribution of hospitals to nationally based spontaneous reporting systems, and to establish intensive hospital monitoring in hospitals with special facilities, will require resources and organizational changes. National centres, and the WHO Drug Monitoring Centre in the case of countries without national centres, should be responsible for the promotion and co-ordination of the developments described below.

4.1 Spontaneous hospital reporting

Spontaneous reporting by hospitals to national early-warning systems need not require additional staff, and an increase in the quality and quantity of reporting is primarily an educational and organizational problem. It is suggested, therefore, that those countries with national reporting systems consider the implementation of the proposals made under item 3.1. In countries without organized national monitoring programmes, resources may be available in one or more hospitals (special centres) for reporting adverse reactions to drugs. Such programmes should be encouraged, particularly in developing countries.

4.2 Intensive hospital monitoring

4.2.1 *Staffing and organization*

While it is appreciated that the attainment of a comprehensive drug monitoring system with the objectives listed on page 8 will not be practicable or necessary in all hospitals, it is suggested that the development of (a) a standard and clear way of writing a prescription, and (b) a standard method of recording and checking the actual administration of drugs, would be an investment in improved patient care irrespective of drug monitoring facilities. Objectives (c), (d) and (e), dealing with intensive surveillance systems and the processing, storage and recovery of the large volume of data generated, however, require special resources of staff and equipment not found in the ordinary hospital, and which, for reasons of economy, are likely to be made available only in certain centres. In drug surveillance schemes the participation of full-time medical staff with special training (clinical pharmacology), nursing and pharmacy staff, will usually be necessary to achieve these objectives since such staff will have an interest in the detection of adverse drug reactions. Such staff will have to be supported by data processing facilities with staff trained in computer technology and with appropriate computer software and access to a computer. Indeed, it might be appropriate to describe these organizations as "reference centres" and such centres should be established in a number of countries with the active support of national and international agencies which have responsibilities for collecting and disseminating information in the field of adverse drug reactions.

4.2.2 *Data processing*

It is now generally accepted that the attainment of the objectives of drug monitoring in hospital, particularly in those designated as reference centres, depends upon data processing facilities. In this context a report by the Director-General of WHO on International Monitoring of Adverse Reactions to Drugs (World Health Organization, 1966) indicates that national centres will need to collaborate closely with the WHO Drug Monitoring Centre "in the preparation of vocabulary lists and dictionary files necessary for the translation of information from their original form into the internal language and format of the data processing system." This statement underlines the advantages of standard terminology and data processing procedures in the three fields with which the meeting is concerned, i.e., drugs, adverse reactions, and patients.

In the context of the collaborative efforts of national centres and the WHO Centre, compatibility of data handling would also be to the advantage of reference centres. If such standardization of computer

input data is agreed upon by several hospital centres, the potentialities of intensive drug monitoring in hospital would be substantially increased. This would be particularly true of adverse reactions of infrequent occurrence, which a single centre would be unable to identify as being significant. In such an operation it would be possible to predict the frequencies of reactions which would be detectable at various levels of ascertainment, and improved communication between centres in different countries co-operating in a common problem would be an additional bonus, e.g., input material might become interchangeable between centres.

5. THE USES OF INTENSIVE DRUG MONITORING SYSTEMS

The epidemiological approach to the assessment of the benefits and adverse effects of drugs differs from the clinical trial in that the material studied comprises populations of patients each of whom will probably be receiving a number of drugs, suffering from different pathological conditions and who are often under the control of different physicians.

The effective use of such an epidemiological approach would require statistical methods, some of which may have to be developed. It would be advantageous to have a team consisting of an epidemiologist, a statistician and a clinical pharmacologist to collaborate on the design of intensive monitoring methods. Emphasis should be laid on the necessity of including methods of data validation in such schemes. Additional benefits of such an approach would be stimulation of clinical and basic scientific research as well as a more realistic appraisal of the harmful potentialities of a drug. Some of the potential uses of intensive hospital monitoring methods are summarized below.

5.1 Epidemiology of adverse reactions

5.1.1 *Rates and patterns of adverse reactions*

Both over-all reaction rates and the rates of specific reactions may be calculated for whole populations in the hospital environment, and this would heighten the physician's awareness of the problem, thereby improving patient care. Furthermore, populations at risk from known adverse reactions to drugs can be identified.

The finding that an adverse reaction occurs with a certain frequency in a population in association with the administration of a particular drug is only significant in the context of the frequency with which the manifestations of the adverse reaction occurs in a similar population not receiving

the drug. For example, the significance of the foetal abnormalities associated with the use of thalidomide was, and to some extent still is, obscured by a lack of information on the numbers of spontaneously occurring foetal defects.

The ability to link information on the use of all drugs to patient information (including diagnosis) in a hospital population, which is foreseen in one type of intensive hospital monitoring (section 3.2.1), may make it possible to obtain adverse reaction rates in matched controls; the control patients being subjected to the same type of surveillance, prospective or retrospective, as the group at risk. Some of the information so collected could be applicable to studies of patients discharged from hospital and out-patients.

Patterns of adverse reactions could be established for a population exposed to drugs, which would increase the probability of detecting previously unsuspected reactions. Such reactions, and their association with drug exposure, may involve pharmacogenetic and pharmacokinetic relationships. For example, the kinetics of a drug are not necessarily the same in healthy persons as in patients with disease. An example of such a relationship is the increased blood levels of certain antibiotics found in patients with impaired renal function (Kunin & Finland, 1959). Drug kinetics may also be modified by different physiological states, and low glucuronidase levels within the physiological range in the newborn can result in impaired metabolism of certain drugs (Gillette, 1967). Attention should be paid to instances of sudden death, since patients who have severe disease may die suddenly as a consequence of drug effects and the event may be ascribed to the pre-existing pathological state. In such cases pathologists can contribute to the recognition of unsuspected reactions. Teratogenicity presents particular problems that require special study and possibly the establishment of a registry to link foetal abnormalities with drug exposure. Such studies would be assisted by the establishment of registries both on a national and an international basis. Drug dependence should be considered a special type of adverse reaction, and attempts should be made in intensive monitoring systems to develop mechanisms for its detection.

5.1.2 *Drug interactions*

The number of adverse reactions increases proportionally with the number of drugs used in individual patients (Hurwitz & Wade, 1969). Since multiple drug prescriptions are common in hospitals, drug interactions producing adverse reactions can be studied through intensive monitoring systems. Such interactions do not occur only between drugs, since drug action can be modified by other factors, such as food products, alcohol and sunlight.

5.1.3 *Excessive and inappropriate use of drugs*

This is believed by many to contribute to the occurrence of adverse reactions. Such misuse of drugs includes the prescribing of an inappropriate drug or drugs for a particular condition, the use of excessive doses or unnecessary prolongation of treatment regimes, use of potent drugs as placebos and lack of awareness of known drug reactions or interactions. Investigation of this problem by epidemiological means might confirm or refute this belief and could assist, by its educational element, in diminishing the frequency of reactions due to this cause. While it is recognized that the effects of accidental or intentional overdose should not be regarded as an adverse reaction, consideration should be given to the use of experience gained in poison and toxicological reference centres. Collaboration between such centres and adverse reaction monitoring programmes would be mutually beneficial.

5.2 Efficacy of drugs

The evaluation of a drug requires a consideration of its efficacy and toxicity in relation to the hazards of the disease which is being treated. The efficacy of a drug in clinical practice may vary greatly from that established by controlled clinical trials, since the patient selection, the environment and the drug regimen are often markedly different.

Intensive monitoring systems can yield valuable data on drug efficacy. It is to be emphasized, however, that such methods are at an early stage of development and methods of validation must be developed. This is of particular importance since drug interactions may often affect efficacy. One approach to this problem is to use epidemiological data and to ask why the drug was started and why it was stopped. The answer to the second question in particular may throw some light on the efficacy of the drug in general clinical practice and reveal possible adverse reactions.

5.3 Long-term effects of drugs

This is an area in which knowledge is very limited, but there are some examples of harmful reactions becoming manifest many months or years after exposure to drugs. Many drugs have been identified as the cause of delayed reactions, e.g., chloroquine and retinal degeneration, phenacetin and nephropathy, oral contraceptives and thromboembolism, steroids and osteoporosis. The long-term effect of drugs on growth and development are also very important. In intensive drug monitoring systems it must therefore be recognized that there may be a time interval between

the first administration of a drug and the appearance of an adverse reaction. This is particularly relevant to carcinogenic, mutagenic and teratogenic effects.

5.4 Patients predisposed to drug reactions

Many physicians are aware that certain patients seem predisposed to develop adverse reactions to drugs, but information is scanty concerning the factors which increase susceptibility. It is known, however, that genetically determined variations in the metabolism of drugs are important in determining the steady-state blood concentrations of some drugs and thus influence both the efficacy and the frequency of adverse reactions. A recognized example of this type of genetic polymorphism is that which determines whether persons are rapid or slow acetylators of the drugs isoniazid, sulfadimidine and hydralazine (Evans & White, 1964). Furthermore, patients with renal and hepatic disease show an increased incidence of adverse reactions to many drugs.

It would be a considerable advance to be able to predict those patients who were prone to develop an adverse reaction to a particular drug or group of drugs, using clinical, biochemical, genetic, immunological or other biological criteria. Certain individuals may be prone to develop particular adverse reactions, e.g., blood dyscrasias, as a non-specific response to a number of drugs, and may have some identifiable biological characteristics in common. Thus, one facet of drug epidemiology lies in the area of the prevention, as opposed to the detection of adverse reactions. Such an activity is also likely to stimulate research in a number of the basic biological sciences, including pharmacology, genetics, biochemistry and immunology.

5.5 Pharmacological studies

The epidemiological method in the field of drug usage can never establish a cause-and-effect relationship between a drug and an adverse reaction with certainty. It can only produce the suspicion that such a relationship exists or confirm the significance of an association between the two. Confirmation of the relationship can come only through detailed study of the pharmacokinetics of the drug in man and its biological effects. Well-designed studies of drug epidemiology will present the pharmacologist with many new ideas and orientate the development of the subject towards a more rational and therefore safer use of drugs. This exchange is unlikely to be only in one direction since the activities of the clinical pharmacologist might well stimulate the initiation of an epidemiological project to determine the significance of his findings in relation to the wider clinical use of the drugs under study.

5.6 Prescribing habits

The reasons why doctors prescribe certain drugs in preference to others are important. Even within the same hospital or even the same ward or service, there is a wider variation in prescribing habits than can be accounted for by rational choice. Few data are available on the relative influence of the sources from which doctors obtain information concerning new drugs. Studies of the prescribing patterns of individuals, services, hospitals and countries would be an exercise, with an epidemiological basis, which would illuminate many of the problems of drug safety and efficacy. In this connexion, patient attitudes to drugs would be an important complementary field of investigation. Such work would be likely to interest the behavioural scientist. The help of educationalists might also be enlisted to find the most effective forms of feeding back information concerning drugs and their effects to doctors, a procedure which is necessary for the success of any drug monitoring system. This development is particularly desirable in view of intensive drug promotion to physicians as this tends to produce excessive use of certain drugs and potentially increases the incidence of adverse reactions.

5.7 Drug management in hospitals

In a number of centres where intensive drug monitoring using epidemiological methods is carried out, it is significant that there has been simultaneous development in the production of more efficient methods of supplying, prescribing and administering drugs (Crooks, Calder & Weir, 1967). The same data can then be used in the context of operational research and such drug-handling procedures might well be models for the reorganization of medical care in hospitals at present being considered in many countries.

6. DISSEMINATION OF INFORMATION ABOUT DRUGS

Accurate and unbiased information about drugs is essential if good medicine is to be practised. In these days when many new and potent drugs are being introduced, such information must be readily available and should include all facts relevant to the use of the drug, including both efficacy and adverse reactions. Such educational information can best be provided through a drug information service on a national basis. It would be the function of such a drug information service to evaluate the evidence on which its reports were based, using appropriate panels of experts. The combined resources of national early-warning systems

for drug monitoring and intensive hospital monitoring schemes would facilitate such evaluations and accelerate the early dissemination of urgent and important drug information to doctors, industry and the public.

7. INTERNATIONAL ASPECTS

Well-developed systems of monitoring adverse reactions to drugs in hospitals, preferably of the intensive type, can make considerable contributions to international drug monitoring. By reporting previously unknown and also serious cases of adverse reactions to national centres, the information currently available for international drug monitoring through the WHO Drug Monitoring Centre will be augmented.

Resources may be available for systematic drug monitoring in one or two hospitals in countries without national monitoring programmes. Such hospitals may be of a type suitable for designation as special centres under the WHO international drug monitoring programme (World Health Organization, 1966).

A pilot study on the value of existing surveys on the frequency and incidence of drug reactions in hospitals, which have been carried out in relatively few centres in three or four countries, may contribute useful information if carried out on an international basis.

The possibility of internationally linking information on drug reactions from hospitals with intensive monitoring systems would present many methodological problems and the feasibility of such an undertaking has not been determined. However, in view of the potential value of detecting and linking new types of information by bringing together a larger number of patient-drug experiences, the possibility of such an undertaking should be explored.

8. CONCLUSIONS AND RECOMMENDATIONS

The meeting was convened to examine the role of hospitals in the field of monitoring adverse reactions to drugs. The prime objective of such monitoring is to diminish the time necessary to define the capacity of a drug to produce an adverse reaction.

Spontaneous reporting of adverse reactions to drugs has certain deficiencies and intensive drug monitoring in hospitals can supplement monitoring that is dependent on spontaneous reporting in six important ways :

(a) it will improve the early-warning system by the detection of adverse reactions to drugs which are difficult or impossible to detect by systems that rely on spontaneous reporting;

(b) by the use of epidemiological techniques, it will provide quantitative data about the over-all incidence of adverse reactions and specific reactions found with certain drugs;

(c) by the provision of numerator and denominator data it will have the capacity to evaluate reports of suspected adverse reactions to drugs brought to light by national or international centres or other sources;

(d) it will identify certain groups of patients at high risk or pre-disposed to adverse reactions to drugs;

(e) it will identify and elucidate the occurrence of adverse reactions produced by drug interactions, a matter of increasing importance as a hospital patient often receives a number of drugs simultaneously;

(f) it may determine whether adverse reactions are related to the dosage, source or quality of certain drugs.

The development of intensive hospital monitoring of adverse reactions to drugs will stimulate the basic pharmacological, biochemical, immunological and genetical studies necessary to elucidate the mechanisms of such reactions.

Intensive hospital monitoring, to be effective, requires skilled staff and may be helped by the development of sophisticated systems of ordering and recording the administration of drugs. Generally accepted terminology and classifications for drugs, adverse reactions and diseases will be required. Hospitals with intensive monitoring systems may become designated reference centres as national and international systems develop.

The meeting recommended that :

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

(5) WHO should encourage the development of drug monitoring in hospitals by :

- (a) assisting in the establishment of drug monitoring in developing countries (if some hospitals in these countries were to develop intensive monitoring systems, they might function as reference centres in relation to the international monitoring system as it develops);
- (b) preparing guidelines for internationally acceptable terminology, classifications and codes necessary for data processing;
- (c) assisting in the training of personnel;
- (d) encouraging the examination of the results already available from the few centres where intensive hospital monitoring systems exist, to determine whether they can be combined with advantage.

(6) WHO should explore the means by which information from national monitoring centres, through spontaneous reporting and intensive hospital monitoring or from special centres, might best be collected and integrated. The methodological problems involved should rank highly in the priorities of such developments.

(7) WHO, in collaboration with national centres and special centres, should study methods by which accurate and unbiased information about drugs and their adverse reactions can be made available to the medical profession, industry and the public.

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