

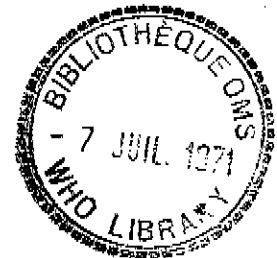


WORLD HEALTH ORGANIZATION  
ORGANISATION MONDIALE DE LA SANTÉ

INDEXED

MEETING ON INTERNATIONAL DRUG MONITORING  
- The Role of National Co-ordinating  
Centres -

Geneva, 20-25 September 1971



The Swedish Drug Monitoring System  
by Barbro Westerholm, M.D.

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 a minimum of delay, in accordance with the recommendation of the WHO.

On January 1st, 1971 the drug monitoring in Sweden left its pilot phase and is now run on a regular basis. The task of the organization is :

1. To collect, evaluate and store information on adverse reactions to drugs.
2. To investigate specific problems which may have arisen when reports on adverse drug reactions have been obtained and in certain instances make attempts 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 measures which the reports may lead to.
5. To revise the reports and send them to the WHO monitoring centre. To be in contact with the WHO centre and national centres in other countries and to send any information which may be of interest to these centres.

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6. To deal with matters within the field that are submitted to the Committee by the Swedish National Board of Health and Welfare or the Board of Drugs.

#### Committee members

The Committee is an advisory Committee to the Swedish National Board of Health and Welfare and has ten members representing pharmacology, clinical pharmacology, internal medicine, pediatrics, psychiatry, drug industry and drug control. A full time medical officer acts as secretary to the committee which meets two-four times a year.

Within the Committee there is a working group consisting of five members who meet every six weeks and who make suggestions to the Committee on what action should be taken of the reports received.

#### Regular staff

The staff dealing with the incoming reports belong to the Pharmacotherapeutic Division of the Department of Drugs (Figure 1).

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, where programmers and punch card operators work part time with the adverse drug reaction project. The National Board of Health and Welfare provides the money for this service.

#### What to report

The medical profession (1965) and later also the dentists (1969) were 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 specialities in Sweden for less than three years. In the case of "old" drugs notification was requested of all serious, previously-undescribed or uncommon side effects. A form (Appendix I) 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. Therefore a circulatory letter was distributed in 1969 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 (Appendix II).

### Reporting form

The present reporting form was introduced in 1968 and is a modification of the WHD form. As an alternative the doctors can send in discharge notes or copies of medical records.

### Source and content of reports

There has been a steady increase of the reporting from about fifty reports per month in 1965-1968 to more than a hundred per month in 1970 (Table I). Most reports come from doctors working in hospital (Table II). Experience has shown us that the reports come from a very limited number of doctors. In 1970 8.5 per cent of the medical profession sent in reports. (Table III) Very few dentists have notified adverse reactions.

Skin reactions, liver damage and thromboembolism are the adverse reactions most commonly reported to us (Table IV). The two latter are to a large extent attributed to the use of oral contraceptives. The drugs which most often appear in the reports are chemotherapeutics, oral contraceptives and cardiovascular drugs (Table V).

### Processing of the Reports

When a report arrives it is first scrutinized by the Medical Officer in Charge. 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 six weeks) the working party goes through and evaluates the reports. Suggestions are made to the Committee as to what steps should be taken.

The cause-effect relationship between a drug and a reaction is classified into one of six groups (Appendix III). The value of such a classification can of course be debated since it can never be exact. However, this kind of evaluation is of help when decisions are made about what action should follow such a report.

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 thus will be unable to distinguish between "new" and "old" drugs.

Lack of time is another factor which may withhold a doctor from reporting. Fear for legal action is another cause of incomplete reporting as is the fact that the reporting is not compulsory.

That there is such low reporting from the dentist may to some extent be due to the fact that drugs are not prescribed or administered by them to any great extent. When their patients experience adverse reactions the patients are referred to physicians who then may report the case.

### Data from hospital record linkage scheme

Information about the occurrence of adverse reactions can also be obtained by a hospital record linkage scheme which covers about 20 per cent of the Swedish population. In a couple of years all Swedish hospitals will be included in this scheme.

The data recorded are the hospital, the department and the case record number (which is filled in for each discharge) and the patients identification number<sup>1</sup>). Besides this identification, which makes it possible to find the case record in which data for more intensive research is available, the form also contains certain data of medical interest in themselves (Table VI). Data and diagnosis are given in words and a five digit code according to a Swedish adaptation for indexing hospital records of the International Classification of Diseases (ICD). The coding is carried out at the hospital.

The Swedish adaptation of the ICD also contains code numbers for complications following the use of drugs. In Sweden every drug has a code number which can be found in a booklet (Synonymregister över farmaceutiska specialiteter), which is distributed to every doctor, containing information about drugs marketed in Sweden.

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. This gives us a system by which we can trace the patients treated in hospital because of adverse reactions. The weakness in this scheme is that doctors do not always remember to put the drug among the discharge diagnoses.

By means of this system it has been investigated how often diseases like agranulocytosis have been drug-induced. The medical records for all patients hospitalized with this diagnosis during 1964 - 1968 were searched and examined.

<sup>1</sup> Every Swedish citizen has an identification number which consists of the date of birth and four figures denoting sex among other things.

Fifty per cent of the patients probably had a drug-induced agranulocytosis (Table VII) which in the rest other causes (e.g. Felty's syndrome) were more likely (Westerholm and Reizenstein 1971). This means that in Sweden there are about 100 to 140 cases of agranulocytosis per year, half of which are drug-induced. If a change in this rate should be noted one can go back to the medical records and investigate whether drugs or other external factors are the cause.

#### Special investigations

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

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

Surveys have also been made of the incidence of drug-induced agranulocytosis (Westerholm and Reizenstein 1971) and drug-induced thrombocytopenia (Böttiger and Westerholm 1971 b.c).

#### Dissemination of information

Circular letters on the adverse reaction reports received are distributed 2 - 3 times per year to the medical profession. The letters are simultaneously published in the Swedish Medical Journal.

Experience has shown us that only part of the medical profession reads our reports. As an example it can be mentioned that our first two warnings about metamizol and agranulocytosis had no effect on the sales of the drug or on the number of cases occurring. It was not until after the third warning when newspapers, radio and television also mentioned the adverse reaction that our report had an effect.

The 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 the medical journal.

#### Cooperation with national centres

In a country like Sweden with a comparably small population cooperation with other national and international units is essential in order to solve questions like "who is at risk" and "how big is the risk" with various preparations.

There are two examples showing the value of cooperation between several centres.

In a cooperative study in the USA, the United Kingdom and Sweden it was shown that women belonging to blood type O run a less risk 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 could be demonstrated that women using oral contraceptives containing high dose oestrogens run a greater risk to develop thromboembolism than women using low-dose preparations (Inman et al 1970).

#### Collaboration with WHO

Since January 1968 the Swedish reports have been translated and filled in the WHO form and sent to the international drug monitoring centre. From July 1971 the reports will be sent on tape which will save 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 the WHO and the Swedish national centre about the formate and the feed back of information from the WHO centre.

#### Concluding remarks

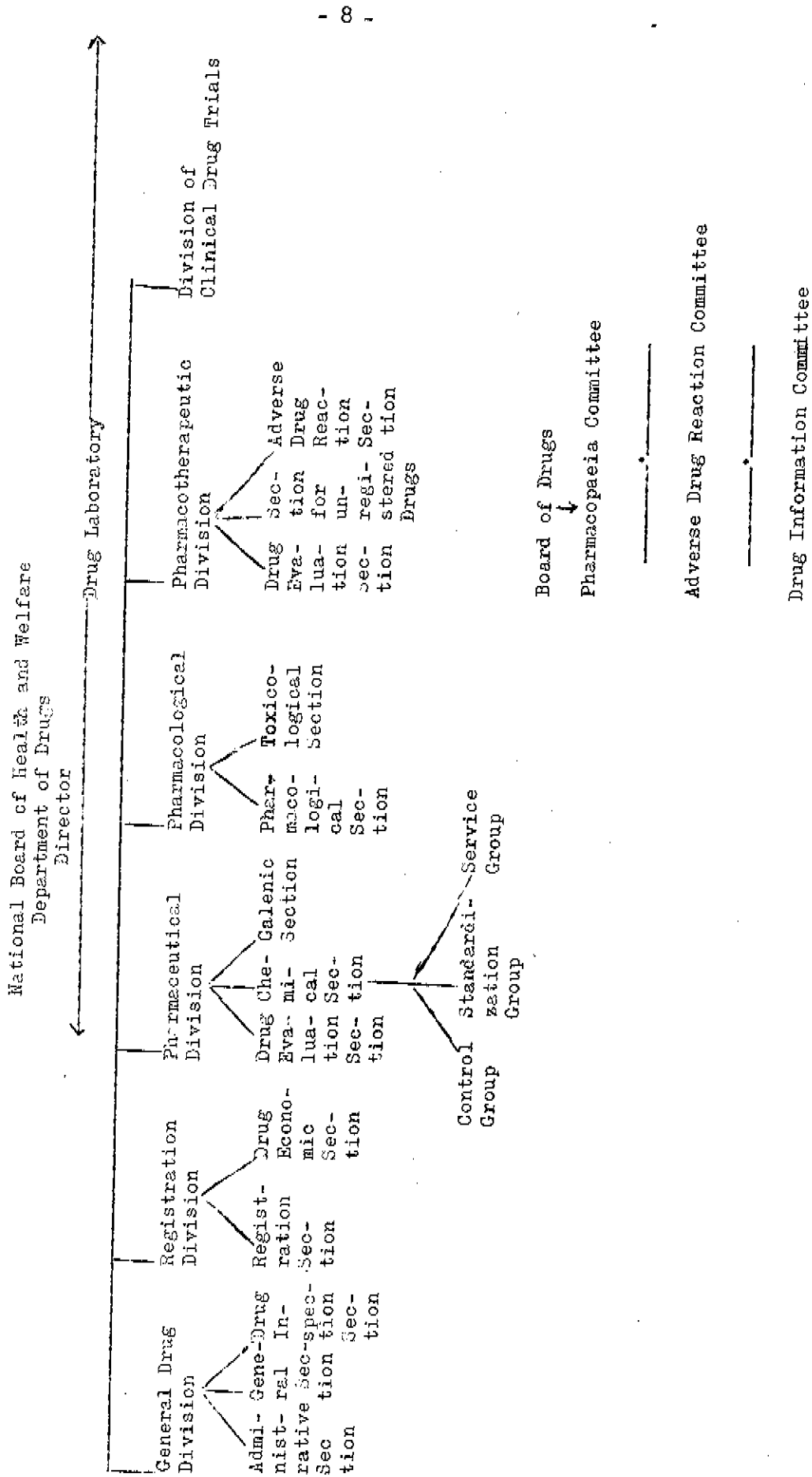
It is important to realize the limitations of voluntary reporting systems. The incompleteness of the reporting in combination with the fact that in Sweden the reporting covers only a small population might lead to late detection of new and rare adverse reactions. If, however, the data are pooled together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

When a problem has been detected various methods have to be used to prove or disprove the suspected cause-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 rôle. At this stage there is some advantage to study small populations both doctors and patients can be more easily reached for follow-up information.

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- FIGURE 1 -

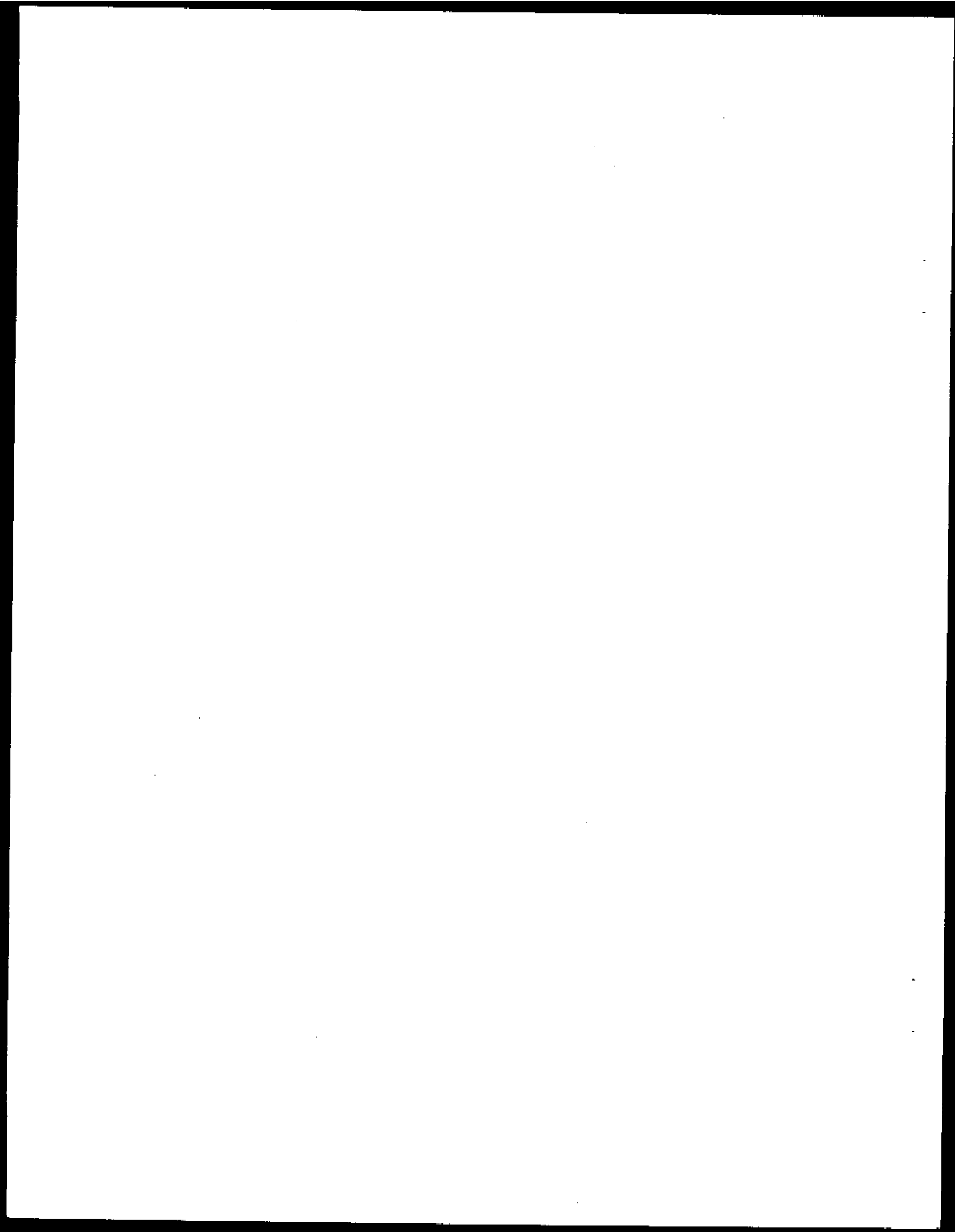


Appendix I

Ort, datum Place, date		Patient (efternamn, förnamn, födelsedag, födelseort) Patient, surname, Christian name, Date of birth, identity no.			
Läkarens namn Name of doctor					
Tjänsteställning Title					
Namnförtydligande Name in block letters					
Adress Address					
Telefon Telephone no.		<input type="checkbox"/> Male Man		<input type="checkbox"/> Female Kvinna	
Biverkning, art och kort beskrivning Adverse reaction, diagnosis and short description		Datum då biverkningen iaktogs: Date when the adverse reaction was observed			
Grundsjukdom Main disease					
	Dosage form	Route Administrationssätt	Dosage Doserings	Duration of medic. for use of drug Medikationens varaktighet FROM TO från o med till o med	Disorder or reason Patienten har fått medlet för behandling av
Misstänkt läkemedel Suspected drug					
Ovriga läkemedel Other drugs					

One copy should be sent to the Adverse Drug reaction Committee  
S 104 01 Stockholm 60

Insändes i ett ex. till Läkemedelsbiverkningsnämnden, Fack, 104 01 Stockholm 60



Appendix II

Information from the Swedish Adverse Drug Reaction Committee

Report No. 9

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 January 1st, 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 uncertainty about 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 specialities for less than three years and important or unexpected effects due to the use of old drugs. By this definition it was hoped to obtain a picture of the adverse reactions due to new drugs and limit the reporting concerning the old drugs. However, it has become evident that the above-mentioned definition lacked clarity and it has therefore been rewritten. In future for old drugs all probable or suspected adverse reactions which cause hospitalization, prolonged stay in hospital or sick leave should be reported. Some well known adverse effects will thereby be included, but it is of importance to the Committee to be informed about them if they have led to hospitalization or sick leave. As before, for new drugs all probable or suspected adverse reactions should be reported.

Among the adverse reactions which should be reported the following can be mentioned: organotoxic effects like blood, liver, kidney and eye damage, as well as neurotoxic effects and cases where systemic effects are suspected e.g. lupus erythematoses disseminatus. Furthermore, it is essential that allergic reactions like anaphylactic shock, asthma and severe skin reactions are reported. If it is suspected that a drug has caused tumours or teratogenic effects it should be reported, as well as addiction to drugs which are not already declared to be narcotics. It is also of interest to get reports on cases where it can be 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 with a dose which only slightly exceeds the recommended one it is of interest to get reports about it 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

Appendix II

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the drug earlier it should be reported as well as allergies towards food and other drugs and chemicals. The trade name, the 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, April 18th, 1969

Swedish Adverse Drug Reaction Committee

(Sgd.) BORJE UVNAS  
Chairman

(Sgd.) BARBRO WESTERHOLM  
Medical Officer in Charge

Appendix III

Evaluation of the Causal-Relationship between Drug and Adverse Reaction

- A Reports which 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 (the criteria under I are 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 should be followed (that is the well known drug reactions where only the frequency is of interest for instance sulphonamides and skin rashes, jaundice and oral contraceptives).
- C Reports which cannot be classified because of lack of data.

Table 1

No. of adverse reaction reports obtained by the drug monitoring centre in Sweden

1965	155 (Oct.-Dec.)
1966	576
1967	598
1968	657
1969	1103
1970	1303

Table 2

Origin of report 1970

University hospital	17	88
General hospital	71	
General practitioner		
Other		11

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Table 3

Proportion of doctors reporting adverse reactions.  
Figures given in per cent.

1965	1.7 (Oct-Dec.)
1966	6.0
1967	6.5
1968	6.5
1969	7.9
1970	8.5

Table 4

The most frequently reported adverse reactions  
October 1965 - December 1970 (4. x) reactions)

	% of all reactions
Skin	21 <sup>x</sup>
Liver	15 <sup>x</sup>
Thromboembolism	12 <sup>x</sup>

x) to be checked when computer list is available.

Table 5

The most frequently reported drugs:

Total number of reports	4.392
	% of all reports <sup>x)</sup>
Chemotherapeutics	26 <sup>x</sup>
Oral contraceptives	23 <sup>x</sup>
Cardiovascular drugs	14 <sup>x</sup>
Analgesics, anaesthetics	12 <sup>x</sup>

x) figures to be corrected when definite computer lists are obtained.

Table 6

Data stored in record linkage system

Hospital no.	Date of admission
Department no.	Date of discharge
Medical record no.	Discharge diagnosis (1-4)
Birth date and no.	Cause of death (1-4)
Age	Operations
Sex	Anaesthesia
Marital status	Patient's local insurance office

Table 7

Agranulocytosis in one hospital region (Uppsala) in Sweden.  
About 15 per cent of the Swedish population lives within  
this area (from Westerhelm and Reizenstein 1971)

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