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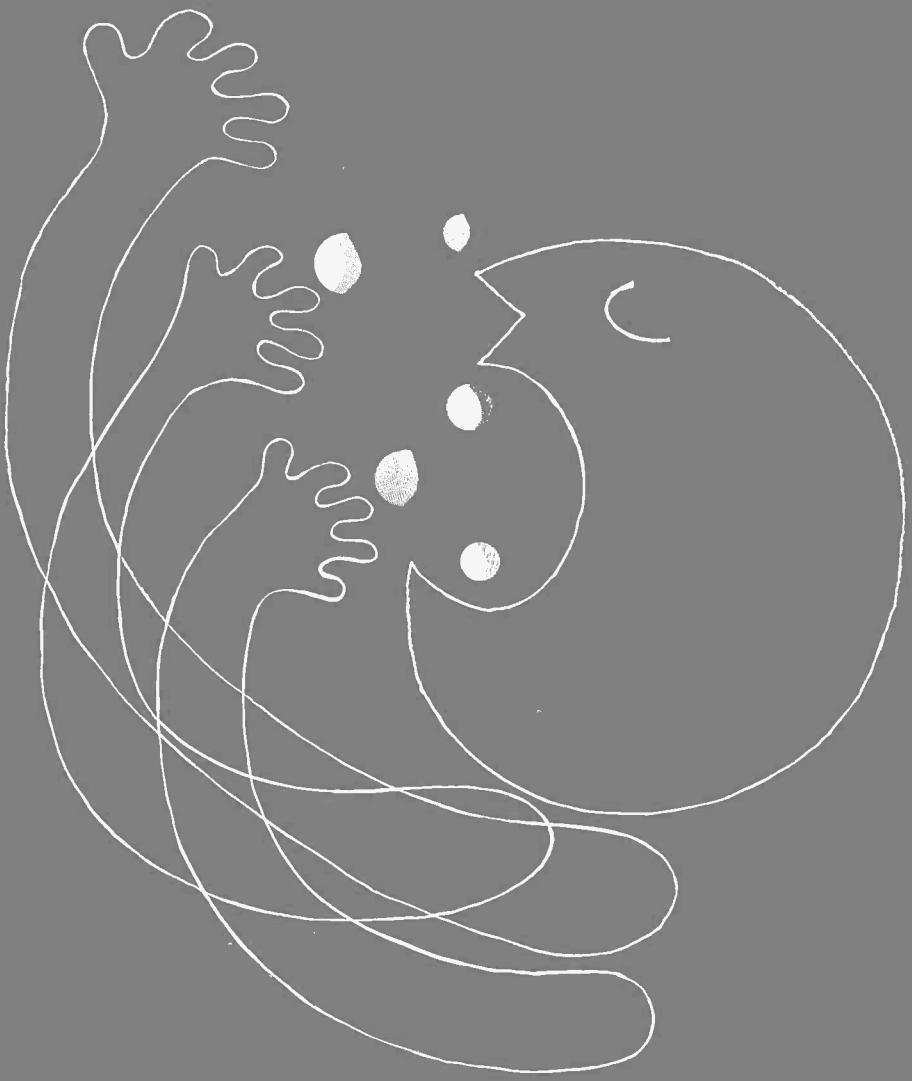
Studies in drug utilization



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STUDIES IN DRUG UTILIZATION
Methods and Applications

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INTRODUCTION

Drug utilization has recently been defined as follows: "The marketing, distribution, prescription and use of drugs in a society, with special emphasis on the resulting medical, social and economic consequences".[a]

During the last hundred years, the development of more efficient drugs has led to dramatic improvements in health care. On the other hand, the potent drugs available today must be used with great caution, because many of them, if given in too high a dosage or for too long a period, can produce dangerous adverse reactions. In order to ensure that patients will receive the right drug in the right dosage and for the right period of time, the prescribing physician has to have a thorough knowledge of pharmacology and therapeutics.

Modern drugs also tend to be very expensive and the large quantities in which they are prescribed add heavily to the cost of the health services. Economists and politicians, as well as the general public, have joined the medical profession and the pharmacists in expressing anxiety about such vast expenditure on drugs and have asked whether the extent of drug use is medically justified.

These doubts have been increased by research carried out in recent years, which has revealed remarkable differences in prescribing habits between physicians in neighbouring countries of Europe. As explained in chapter 1, the pioneer work was a study carried out in 1966–67 by Dr A. Engel of Sweden and Dr P. Siderius of the Netherlands. Their findings prompted the WHO Regional Office for Europe to arrange a Symposium on the Consumption of Drugs, which was held in Oslo in 1969. The most important result of this meeting was the formation of the Drug Utilization Research Group (DURG), in which scientists from at least 14 countries are now participating.

A development that has had a profound influence on subsequent work was the publication in 1975 by Norsk Medisinaldepot of a list of defined daily doses of drugs registered in Norway and classified according to the EPhMRA code (see chapter 2), with the addition of two chemical subgroups. This provided a most valuable basis for international comparisons on drug utilization.

[a] WHO Technical Report Series, No. 615, 1977 (*The selection of essential drugs:* Report of a WHO Expert Committee).

The obvious limitations were that drug markets in various countries differ greatly, even between countries with closely related health systems such as the Nordic countries.

During the 1976 meeting of DURG in Copenhagen, it was proposed that WHO should sponsor a publication on guidelines for performing basic drug utilization studies and at the 1977 meeting of the group, the WHO Regional Office for Europe reaffirmed its interest in publishing such guidelines. The meeting appointed an editorial board and in mid-1977 various authors were invited to contribute to the publication.

This book represents the outcome of the activities of the members of the Drug Utilization Research Group since its foundation. It deals with drug utilization studies mainly from the point of view of prescribing patterns and touches only briefly on questions of distribution and marketing. Its aim is to stimulate the gathering of information on drug utilization studies with particular emphasis on international comparisons.

The greater part of the book (chapters 3 to 12) is devoted to descriptions of the national sources of information that are available and the uses to which they have been put in the various countries that have participated in the project. Chapters 1 and 2 discuss the general background to drug utilization studies and the methodological problems in using a common drug classification system, as well as the establishment and use of the defined daily dose as a unit of comparison. Some practical applications of drug utilization studies are presented in chapters 13, 14 and 15, while the concluding chapter looks back at what has been accomplished and suggests ways in which such studies could be made more fruitful in future.

The addresses of institutions in the European Region of WHO where further information on drug utilization studies can be obtained are listed in an annex.

THE CONCEPT OF DRUG UTILIZATION STUDIES

O. Wade[a]

In the last 50 years there has been a remarkable increase in the use of drugs in medical practice. This has followed the introduction of the many effective and potent synthetic drugs produced by the pharmaceutical industries of the world and few physicians would wish to practise medicine without antibiotics, vaccines, or corticosteroids. There has, however, been increasing concern that much prescribing may be unnecessary, inappropriate, or irrational, and not without dangers.

In these circumstances it is increasingly important that we should learn more of what drugs are prescribed, who prescribes them, for which patients they are prescribed, for what reasons, and with what resulting benefits or possibly ill effects. We are as yet far from being able to carry out such a comprehensive "therapeutic audit". This chapter outlines the way in which, in the last 15 years, a small number of research workers have studied the prescribing of drugs by physicians in their various countries, explored the potential value of such studies, and generated novel and exciting concepts.

The first studies

Early in 1962 Speirs (*1*) tried to identify whether the mothers of babies born with limb deformities in Stirlingshire, Scotland, had taken thalidomide during their pregnancy. He found that statements by the mothers that they had taken no thalidomide and statements by their family physicians that they had not prescribed thalidomide for these women were unreliable. He made a long and arduous search through many thousands of prescriptions written by physicians in that area of Scotland during the relevant time and eventually retrieved prescriptions written for thalidomide for the majority of the mothers. Smithells (*2*), in a similar investigation in Liverpool in 1962, also found the memories of patients and physicians fallible.

It was provident that in March 1962 it was realized that a search for prescriptions for a particular drug could be more easily carried out in Northern Ireland than had been possible in Scotland. Unfortunately the cards on which

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the data for 1961 had been recorded had already been destroyed and it was not possible to carry out the intended investigation to determine the incidence of the birth of deformed children amongst the pregnant women to whom thalidomide had been prescribed. Instead the prescribing of chloramphenicol was examined. It was found that, in the month of December 1962, 10600 g of chloramphenicol were prescribed for a population of 1.4 million persons. Two hundred and sixty-three of the 736 general practitioners in the Province had written prescriptions for chloramphenicol during that month. Most of them had written between 1 and 4 prescriptions in the month, but there were 30 physicians who prescribed chloramphenicol frequently and between them accounted for more than one quarter of all the chloramphenicol prescribed. Many of the prescriptions were for chloramphenicol syrup and were probably for children with whooping cough.

These findings were completely unexpected. Reports of aplastic anaemia caused by chloramphenicol had received wide publicity since 1952 and it had been assumed that the use of this drug was negligible. The survey was repeated in February 1964. The findings were similar; a large proportion of the prescribing of chloramphenicol was by a small group of high prescribers of this drug and, moreover, the high prescribers in December 1962 were found to be still high prescribers in February 1964. When this work (*3*) was published in 1966 it was in part responsible for the issue by the Committee on Safety of Drugs of one of its first warning notices to physicians in the United Kingdom drawing their attention to the hazard of aplastic anaemia associated with the prescribing of chloramphenicol.

The computer and drug utilization studies in Northern Ireland

In 1966 a computer system was introduced to pay pharmacists for the drugs prescribed by physicians that were supplied to patients. This made it possible to undertake more extensive investigations. It was possible (Fig. 1) to monitor the prescribing of chloramphenicol month by month and to watch the effect on its prescribing of the warning that was issued by the Committee on Safety of Drugs in February 1967. Changes in the prescribing of individual hypnotic drugs were examined over a number of years (Fig. 2) and an increase in the prescribing of Mandrax, a proprietary preparation of methaqualone and diphenhydramine, was observed. The prescribing of this drug in individual practices could be followed (Fig. 3).

Because the number of patients registered with each physician was known it was possible to examine the prescribing of drugs in relation to the number of patients on each physician's list each month and thereby to start a series of investigations that constituted a study of the epidemiology of drug use in the Province. The prescribing of insulin was found to be remarkably uniform in all parts of the Province, but the prescribing of the oral hypoglycaemic drugs showed very marked regional variations. These differences might have been related to the differing quality of dietetic advice given in diabetic clinics (*4*).

Fig. 1. The prescribing of chloramphenicol in Northern Ireland in 1966 and 1967

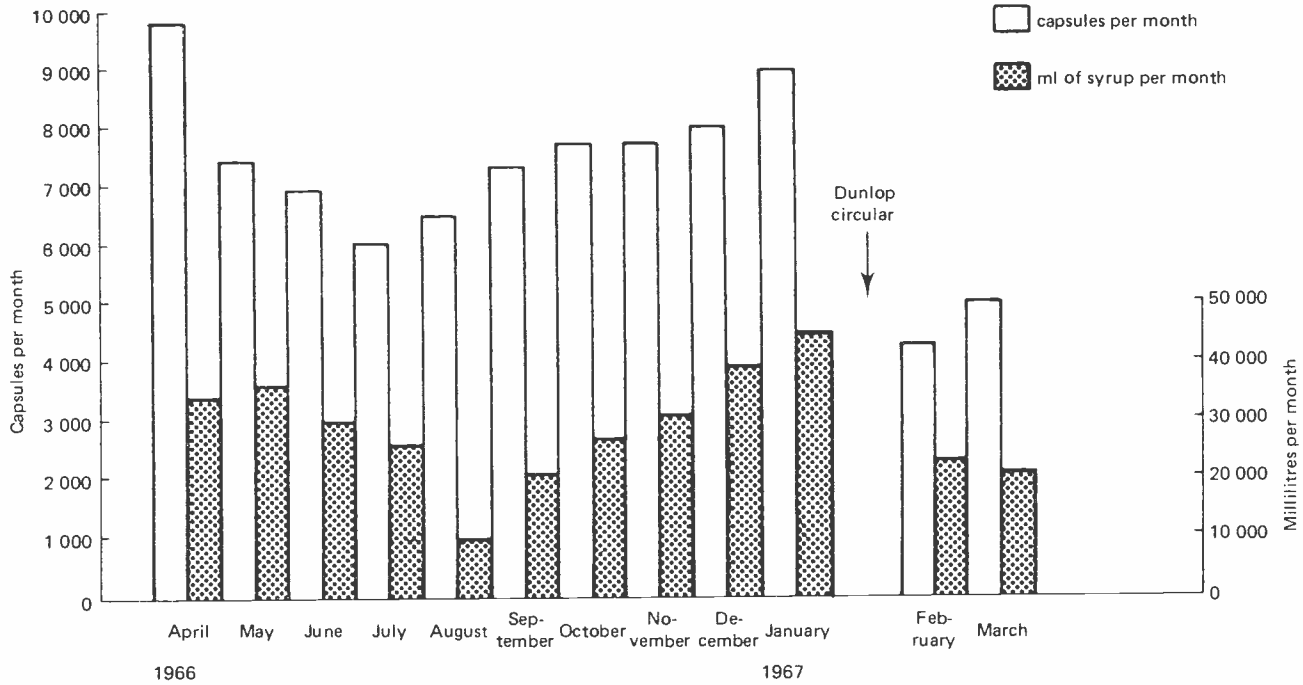
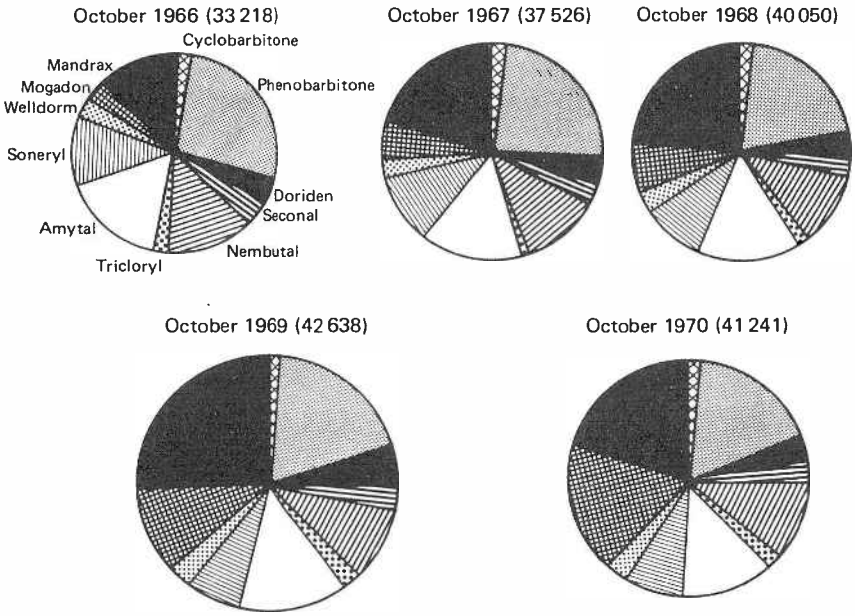


Fig. 2. Changes in the prescribing of Mandrax and 10 other hypnotic preparations in the month of October each year from 1966 to 1970[a]



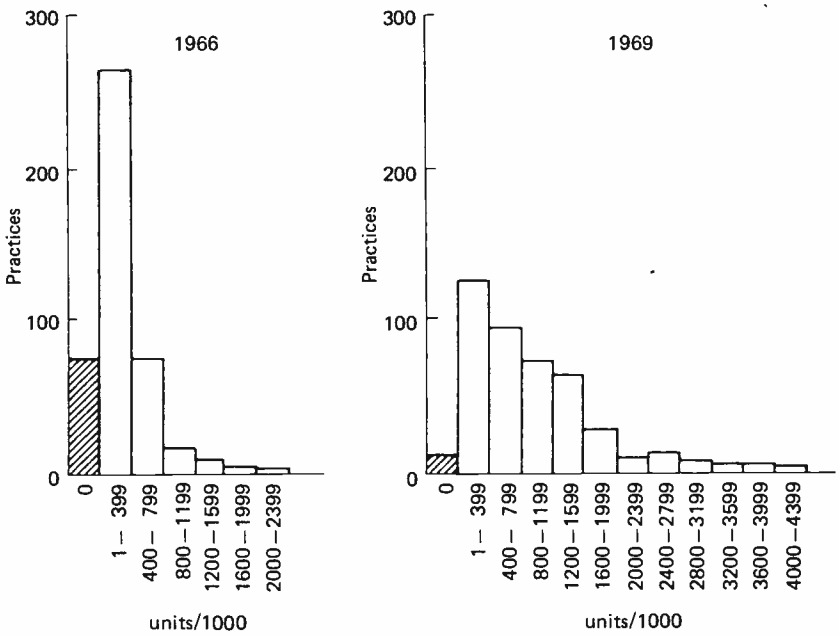
[a] Total prescriptions for hypnotics in parentheses. Mandrax was first marketed in the United Kingdom in 1965. Mandrax prescriptions were 12% of the total in 1966, 20% in 1967, 24% in 1968, 25% in 1969 and 20% in 1970. They subsequently decreased and it is seldom prescribed now.

International studies of drug utilization

The credit for the first international study on drug use belongs to Engel & Siderius (*5*) who visited six European countries in 1966–67 on behalf of the World Health Organization.

Following their findings, the Regional Office for Europe of the World Health Organization arranged a meeting in Oslo early in 1969 of people interested in this and similar problems. This occasion was crucial to the further development of this work for it led to the formation of a research group with members in Northern Ireland, Norway, and Sweden. The group, now called the WHO Drug Utilization Research Group, has since grown and been joined by workers from Czechoslovakia, Denmark, Finland, Iceland and the Netherlands. The work carried out by members of the Group is the basis of this book.

Fig. 3. Rate of Mandrax prescribing in all practices in Northern Ireland from July to September in 1966 and 1969



With the help of the World Health Organization it has been possible for members of the Group to meet every year to discuss problems of mutual interest and concern.

SOURCES OF INFORMATION ABOUT DRUG UTILIZATION

There are a number of sources of information about drug use, each of which has advantages and disadvantages.

Official sources

In countries that have national health services much information is available from official sources but usually only in a crude statistical form with little

information about the prescribing by individual physicians and none about the patients and the conditions for which the drugs are prescribed to them. Moreover, there is seldom any information about the use of drugs or preparations purchased by members of the public without prescription.

Records of manufacturers, importers or distributors

In countries where production or distribution of drugs is under governmental control, data about overall production, import, or distribution of drugs may be available. In countries where the pharmaceutical industry or the distribution of drugs is not controlled centrally, the completeness of data varies greatly but most firms keep meticulous and detailed records. This information is not usually available publicly because of the competitive nature of the pharmaceutical industry, but it is readily made available to governmental sources when serious problems of adverse reactions or defective production batches occur.

Sales sampling services

There are in western European countries, the USA, and Australasia privately owned companies that carry out surveys of the prescribing habits of physicians. The results of these surveys are available at a commercial price to pharmaceutical companies and in Australia the data are published. Such surveys are carried out with the assistance of a sample of physicians, who are paid to record the details of what they prescribe. These surveys are moderately representative of the prescribing of the whole medical profession and the data from different countries can be compared. The data are of limited value because the main purpose for which they are collected is commercial and not primarily for health research.

Records from pharmacists and retailers

The laws governing the sale or dispensing of drugs to the public differ greatly in different countries. In some countries all drugs are supplied or sold through pharmacies and good statistics may be available. In other countries, drugs may be sold outside pharmacies or in ways about which it is difficult to obtain good records. The only data available may be in the form of details of sales by wholesalers or invoices to retailers and may not reflect the quantities used accurately.

Physicians' records

Physicians' records can provide valuable information that relates the prescribing of drugs to the age, sex, employment, social status, or disease of patients.

Where such records have been made available, it has usually been on a modest scale and by specially motivated physicians whose prescribing may not be typical of all physicians in the community (*6, 7*).

Hospital records

Hospitals are responsible for only a small part of the total prescribing in a country, but studies of the influence of prescribing by hospital physicians on the prescribing of drugs by physicians in the community are badly needed.

Consumers

The user of drugs, whether the drugs are obtained by a physician's prescription or over-the-counter, is a source of information about drug consumption and the only source of information about drugs that are prescribed or purchased but are not consumed.

Surveys of the use of medicines by members of the public are difficult to carry out, need careful validation and are usually either of limited scope or of short duration.

Jefferys et al. (*8*) and Wadsworth et al. (*9*) in the United Kingdom and Rösch (*10*) in France have thrown considerable light on the relative use of prescribed and over-the-counter medicines. A number of surveys have shown that many patients do not take the medicines that physicians prescribe, or take them for a short time or in an inadequate manner, thus reducing the efficacy of the drugs (*11*).

Collection, analysis and interpretation

Even when adequate data are available, special techniques are required for their collection, validation, correct analysis, and interpretation. The skills of the physician, pharmacist, clinical pharmacologist, economist, statistician, and sociologist are needed. If sampling techniques are used it may be important to examine the age, sex, race, social status, cultural behaviour and habits of consumers, the age and training of medical practitioners and whether they are single-handed or work in a group, the size and nature of their practices, the production policies, and the influence of salesmen of the pharmaceutical industry and the fiscal policy and legislation of governments. All these factors may introduce bias.

Modern computer techniques have made work in this field easier – indeed some of the work might have been impossible without them – but require resources of equipment and trained personnel that are difficult to obtain in many countries.

The initial aim of our research has been to determine the use of individual drugs or groups of drugs per head of population. Whenever possible investigations have been carried out in such a way that changes that occur with time can be observed and the use of drugs in different countries compared. The information obtained in these studies already has or could throw light on the following.

The prescribers

It has been possible on a small scale to examine and compare the prescribing of individual physicians and relate their prescribing to such characteristics as their age, sex, medical school and postgraduate training, whether they work alone or in partnership, and whether they are in urban or rural practices. Most physicians claim that if they had more time to talk to their patients they would prescribe fewer drugs. Elmes et al. (*12*) found, however, that physicians with small practices prescribed more hypnotics per patient under their care than did physicians with large practices.

There is some evidence in the United Kingdom (*13, 14*) that an individual general practitioner prescribes from a limited number of preparations, usually between 150 and 180, and that as much as 80% of his prescribing is confined to some 20–30 preparations. Far more work needs to be done before firm conclusions can be drawn.

The improvement of prescribing

Several studies have demonstrated that the prescribing of drugs may be unsatisfactory. Doses, routes, or schedules may be inappropriate in the light of recent pharmacokinetic and pharmacological knowledge. Some drugs may be prescribed for a period of time that is too short to allow the patient to derive any benefit (*6*). Others are prescribed in large amounts or for long periods of time that are inappropriate. Drug utilization studies will be of great value for they will allow assessment of the prevalence and importance of such unsatisfactory prescribing and indicate whether guidance or advice to physicians is needed.

Misuse of drugs

One of the early studies in Northern Ireland was an examination of the prescribing of amphetamines and it was found that a few physicians were prescribing these drugs in amounts that seemed grossly excessive (*15*). In Norway, detailed studies of the prescribing of narcotic drugs have allowed the identification of individual patients who go from physician to physician

obtaining supplies of these drugs. It is likely that study of the prescribing of new psychotropic drugs would allow a more rapid ascertainment of their liability to cause dependence than has been possible up till now.

The choice of drugs by physicians

One of the most interesting outcomes of this research has been the discovery that it is possible to examine the pattern of prescribing of physicians in the community and watch its changes (Fig. 2). Which hypnotics, antibiotics, or analgesics do physicians prescribe? Why does their choice change over the years? Is it due to their experience in the use of the drugs and their assessments of effectiveness or ineffectiveness, is it because information of adverse reactions reaches them, or is it because new drugs are marketed and promoted? There are innumerable problems of this sort yet to be solved.

The prescribing of new drugs

Little is as yet known of the factors that influence the use by physicians of new drugs. The build-up in the prescribing of a drug like streptomycin, levodopa, or cimetedine, each of which was completely novel when it was first introduced, is likely to be very different from that of a drug that is merely a variant of one already in use, e.g., yet another antihistamine, tricyclic antidepressant, or hypnotic. It is possible that some physicians are "new drug prone" and others are so conservative that they continue for many years to use outdated therapy.

The adequacy and effectiveness of drug information

Not only can drug utilization studies indicate that physicians may not have adequate information about the pharmacology, uses and adverse reactions of a drug, but they may allow determination of the effectiveness of the steps taken to inform physicians. In the United Kingdom, the issue of the warning about chloramphenicol and aplastic anaemia by the Committee on Safety of Drugs (see p. 4) was shown to be promptly followed by a reduction in the prescribing of the drug (Fig. 1). Further experience may allow assessment of the most effective ways of delivering information to physicians and improving data sheets, package inserts, reference books, and drug information services.

The effectiveness of education

It is often claimed that the teaching of therapeutics to undergraduates and postgraduates is inadequate and ineffective. Educators could be helped in their planning of effective programmes of teaching of therapeutics by

studies of prescribing. Most teachers would welcome evidence to show whether their teaching was or was not effective, and it may be possible to monitor the effect of their teaching by monitoring subsequent changes in prescribing.

Drug promotion to physicians

It is widely believed that prescribing by physicians is greatly influenced by drug promotion and especially by the visits of the sales representatives of drug firms. It would be valuable to study this. A good case might be made not only for improving the calibre of men selected by firms as their representatives but also for developing more effective training schemes for them. Individual firms no doubt make a close study of the effectiveness of their representatives as salesmen, but health authorities might well examine the possibility of improving the quality of information given by them to physicians.

Drug promotion to the public

Publicity about a drug in newspapers or on television or radio, especially if unduly laudatory or controversial, may lead to great pressures from the public on physicians to prescribe or to stop prescribing a drug (*16*); in the case of an over-the-counter drug, favourable publicity may lead to its inappropriate use by the public. Further investigation of the effects of such promotion would be most valuable.

The prevalence of adverse reactions to drugs

In order to measure the burden of drug-induced disease in a community, it is not enough to characterize the nature, severity, and frequency of the adverse reactions to a drug. The use of the drug in the community must be known if the prevalence of the reactions is to be estimated. If steps are taken to identify all patients receiving a drug then this may well make the detection or validation of the presence of adverse reactions much more efficient and this may be an important consequence of developing methods of monitoring drug use.

The economics of prescribing

There is increasing concern in many countries about the cost of drugs to the community (*14*). In the United Kingdom, with a population of 50 million persons, the pharmaceutical services of the National Health Service cost more than £300 million per annum; most of this is the cost of prescribing by general practitioners. Wade & McDevitt (*16*) examined the prescribing of high cost and low cost prescribers. They were able to identify factors that influenced the cost of physicians' prescribing and suggested steps that might be taken to

reduce them. Improved methods of examining drug prescribing in a health service are a necessary prerequisite for planning measures intended to bring about financial economies in drug use with the least possible impairment of the quality of medical care.

Drug use and drug need

The observation that in some areas of a country a drug or a group of drugs is widely prescribed while elsewhere its use is small, raises a series of problems to which we can as yet give no very adequate answer. How can we assess whether drug use is congruous with drug need? How can we determine what is an appropriate or the optimum use of a drug? It may in some instances be possible to show that differences in drug use are related to differences in the incidence of disease, or the age-sex structure of the community. More often it will be found that differences in drug use are related to differences in the concept that physicians have of what constitutes a disease state requiring treatment or their concept of what is appropriate treatment. The reason for the greater use of oral hypoglycaemic drugs in Sweden than in Northern Ireland (*17*) is being investigated and data are discussed in chapter 14.

Policies of the pharmaceutical industry

Critical examination of drug use and especially of the behaviour of the consumer may have important consequences for the pharmaceutical industry. Not only may it become apparent that new methods of packaging and labelling of drugs are needed but it may become easier to ascertain whether industry is producing the drugs we need or is carrying out appropriate research and development programmes.

Pharmacy practice

It is increasingly apparent that there may be a considerable difference between what the physician prescribes and what the patient takes (*11*). Moreover, it is often extremely important if patients are to benefit from treatment that the correct dose of the drug is taken at the right time. This is an increasing problem for it is the elderly patient who is most likely to need medicines and is the least likely to be able to understand instructions or keep to a complicated regimen. Further research on patient compliance and use of drugs is needed, but it is already clear that the traditional role of the pharmacist as the dispenser of medicines needs to be expanded: new techniques of delivering drugs to patients are needed, and patients need more information about their medicines and more guidance on how to take them in the required fashion (*11, 18*). Drug utilization studies may play an important role in indicating how this can best be achieved.

Governmental legislation

There have been many instances in the past in which legislation has intentionally or unintentionally altered drug use. Changes in prescription charges, alterations in taxation, restrictions on imports, and changes in the licensing laws for the sale of alcohol may all affect the pattern of prescribing and have seldom been the subject of critical study.

Drug use in developing countries

Developing countries are often short of resources and frequently request advice from the World Health Organization on the drugs that they should import or purchase.[a] It would already be possible for WHO to give expert aid to Member States to enable them to produce their own national formularies. It might also be possible to create a small central unit with the appropriate expertise to advise on the wise use of their limited resources and on the quality, purity, effectiveness, and value of drugs available for purchase from the pharmaceutical industries of the world.

The aim of drug utilization studies is to be able to carry out a complete therapeutic audit: to see clearly what is prescribed, with what intention, and with what benefit or what ill effects and at what cost to the community. A beginning has been made, but a full picture has yet to emerge.

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CHAPTER 2

THE METHODOLOGY OF DRUG UTILIZATION STUDIES

P.K.M. Lunde,[a] *I. Baksaas,*[a] *M. Halse,*[b] *I.K. Halvorsen,*[c] *B. Strømnes,*[d] *& K. Øydvin*[e]

Cost and prescription figures have indicated that "consumption" of drugs in Europe, and probably in many other areas, has been increasing over the last two decades (*1–4*). It has also become increasingly evident that drugs are frequently not used to their full potential, nor according to generally accepted criteria (*5, 6*).

This has led to an enhanced interest among research workers, health administrators, and members of the health professions in surveying the drug utilization pattern and following its development with time. Major quantitative and qualitative differences in the prescribing pattern have been detected between countries and regions within individual countries (*2, 7–11*). This calls for a more systematic, precise, and comprehensive description and follow-up of drug utilization after the drugs have been marketed, in order to evaluate the clinical consequences of the sometimes widely different drug therapy traditions.

As outlined in Table 1, drug utilization can and should be studied at various levels, depending on the purpose and the facilities available. Certain elements in the strategy when planning and performing such studies are, however, of special importance. Generally, the value of such studies will be considerably enhanced if they are made comparable by applying uniform methods (a common drug classification system and unit of measurement) in investigations from different regions and countries. The common methods should provide data on all relevant drugs in a therapeutic class, given either in cost or quantity parameters, taking into consideration the differences in therapeutic practices. The methods could be designed to quantify the drug inventory only, or to evaluate drug utilization.

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[d] Institute of Pharmacotherapy, University of Oslo, Norway.

[e] Norwegian Medicinal Depot, Oslo, Norway.

Table 1. Levels of cost or quantity parameters[a] in drug utilization statistics

1	*Drug*	
	All drugs	
	Groups of drugs (anatomical/chemical/therapeutic classification)	
	Single drug(s)/product(s)	
2	*Area/sources*	
	Country/countries	Hospitals/wards/"beds"
	Region(s)	Physician(s)
	Pharmacy/pharmacies	Patient(s)
	Health insurance systems	
3	*Levels of therapy*	
	Wholesale/overall pattern	
	Prescriptions	
	Patients' drug intake (compliance/noncompliance)	
	Pharmacokinetics/dynamics ("plasma levels"/effects)	
4	*Unit of measurement*	
	Cost	*Quantity*
	Overall cost	Overall weight/volume
	Unit cost	Unit quantity
	per package, "tablet", DOSE, cure/regimen, etc.	No. of packages, "tablets", etc., prescriptions, DOSES (single dose, daily dose – initial/maintenance), etc.

[a] As related to time period (year, quarter, month, day) and unit of population/patient (morbidity) categories.

The objective of a drug utilization study is to quantify the present state, the developmental trends, and the time course profiles of drug usage. Such data can be used for the following purposes:

(1) to measure the effect of informational and regulatory efforts, price policy, etc.;

(2) to detect or identify problems and define areas for further investigation on the absolute and relative efficacy and safety of drug therapy;

(3) to aid in the determination of benefit-risk and cost-effectiveness;

(4) when properly interpreted, to suggest over-use, under-use, or misuse of single drug compounds or therapeutic classes of drugs.

The data are also of value in the planning of drug supply and distribution and for estimating drug need in a society, preferably after considering the overall morbidity pattern within the actual country or region. In any event, the data must be adjusted to their specific uses, i.e., whether medical/pharmaceutical or administrative/commercial purposes. Whenever conclusions are to be drawn and measures are to be taken, the limitation set when considering *drug* statistics alone must be faced (*12*).

DRUG CLASSIFICATION SYSTEM(S)

Drugs can be classified according to their chemical structure or on the basis of their pharmacological action and therapeutic use. This leads to a grouping of the drugs into chemical or therapeutic classes. So far no single and generally accepted drug classification system has been adopted on a worldwide scale. An entirely *chemical* classification system might be the most logical solution, but because of the widely different therapeutic application of quite similar chemical entities, such a system becomes medically irrelevant. Other difficulties are due to the fact that not all drugs have yet been chemically defined and some are mixtures.

With a strictly *therapeutic* classification system other problems may arise, such as those due to the use of one drug for widely different clinical indications. Thus most useful systems developed so far represent some kind of a compromise between the two types mentioned, i.e., they are "therapeutic/chemical".

The so-called anatomical classification system of the European Pharmaceutical Market Research Association (EPhMRA) which is also approved by the corresponding American organization, the International Pharmaceutical Market Research Group (IPMRG), is one of the systems most widely used. Here the drugs are distributed in 13 main classes, such as those related to the alimentary system and metabolism, the blood and blood-forming organs, the heart and vascular system, the central nervous system, etc. The basic EPhMRA system also includes two levels of therapeutic subgrouping of the drugs (down to the dotted line in the following example):

Example:	Morphine (N 02 AA 01)
N	– Central nervous system
N 02	– Analgesics
N 02 A	– Narcotics
. . . . .	
N 02 AA	– Morphine and its derivatives
N 02 AA 01	– Morphine

To improve the precision of this system it has been extended by the Norwegian Medicinal Depot (*13, 14*) to include two more levels, allowing complete

chemical and therapeutic identification of each compound, as shown below the dotted line in the example. Accordingly, it is possible to give statistics based on actual drug substance (or product), using the code as illustrated in the example. Unless this possibility exists, combined with sufficiently comprehensive information about alternative drugs, strictly comparable drug statistics cannot be obtained.

UNIT OF MEASUREMENT

Irrespective of the level of the actual drug statistics or the drug utilization study (Table 1), a design should be considered that allows comparisons with previous and future studies. Although relevant for the problem under focus, most cost and many quantity parameters are not at all suitable for making comparisons, at least not in a medical context.

At best, cost parameters are of value when absolute or relative expenses of drug treatment are to be compared. The indiscriminate use of drug costs as a parameter to describe developmental trends in the intensity of therapy within or between societies can be quite misleading. Obvious reasons for this are different drug or drug product prices for alternative preparations, price and currency differences, and their changes with time. In addition, there is a tendency for drug prices to follow more complicated rules than the prices of many other products. Patent protection, varying interests and strengths among the national or local regulatory agencies to influence price setting, and wide differences in the general level of cost in the country of product origin, as well as in those where marketing takes place, could be important factors.

Although the application of unit cost (Table 1) may result in improved precision, units of quantity should generally be preferred when illustrating tentatively absolute and relative therapy intensity with drugs. The number of prescriptions is quite often used and may reflect the physician/patient interrelationship. However, the number of drug units (or drugs) prescribed per prescription may vary widely and must be corrected for if interpreted in terms of therapy (*15, 16*). In general this cannot be done properly unless the investigation includes the diagnosis and other considerations that are involved in physician- and patient-oriented situations. Unfortunately, such an insight is often difficult to obtain for confidence reasons, because such analyses may interfere with the situation and the problem to be analysed, and also because such investigations are usually quite expensive.

On the basis of discussions and experience within the International Working Group on Drug Utilization, a defined daily dose (DDD) unit has been chosen for the sake of comparability. The only comprehensive national dose list published so far is the *Drug dose statistics* (*13, 14*) in which DDDs for all drugs for systemic use as registered on the Norwegian market in 1975 were given. The number of drugs registered in Norway is quite limited (some 750 chemical substances and 1850 products), however, and for international comparisons a more complete dose list is needed. Such a common list is at present developed

for Denmark, Finland, Iceland, Norway and Sweden. It should be recalled that the concept of the daily dose had already been adopted by Hood & Wade in some of their early studies on drug consumption profiles in Northern Ireland and its regions (for review, see references *17* and *18*).

The doses given in the dose list (*7, 13*), as well as those used for international comparisons (*5, 8–10, 19*), have been chosen according to what is recommended in the literature and thought to be the average maintenance dose when used routinely for the assumed major, or one of the major, indications for the actual drug. Additional advice was received from a number of experienced clinicians in the relevant fields. For practical reasons only one daily dose, usually the adult dose, is generally given. Whenever relevant and possible, the size of the parenteral doses is adjusted in relation to that of the oral doses, according to assumed therapeutic equivalence.

Despite all the efforts made to improve the medical relevance of our drug statistics, the DDD should be taken for nothing more than it is, i.e., *a technical unit of measurement and of comparison.* If properly defined and interpreted, the overall number of DDDs per 1000 inhabitants per unit time prescribed or sold may provide a rough estimate of the fraction of subjects/patients within a community that could receive a certain drug treatment. Thus when applying this methodology to the field of antidiabetics (Table 2) the results were found to be in reasonable harmony with previous morbidity figures and the local therapeutic practice in several countries (*5, 8, 10, 19*), although some dose adjustments might have been desirable. However, one single dose can never fit

Table 2. Defined daily doses (DDD) for antidiabetic therapy[a]

	DDD
Insulin	40 IU
Sulfonamides	
Glibenclamide	10 mg
Chlorpropamide	375 mg
Tolbutamide	1.5 g
Glibornuride	37.5 mg
Glymidine	1.0 g
Biguanides	
Phenformin	100 mg
Methformin	2.0 g

[a] See Baksaas Aasen et al. (*13*) and Norsk Medisinaldepot (*14*).

into all kinds of therapeutic practices, and in the interpretation of the various local situations the *real* dose must always be considered. If the precision in the therapeutic application of drugs were higher or more uniform within the various countries and regions, even product bioavailability differences – if sufficiently pronounced – might be predictable from this type of study. Although overall sales or prescription figures for a number of other drug groups (anticoagulants, cardiac glycosides and other cardiovascular drugs, antiepileptics, anti-infectives and psychotropics) have uncovered a number of pronounced intercountry differences in therapy profiles (*2, 5, 9–11, 19*), more detailed studies are necessary to evaluate their medical significance and consequences.

As regards the drug dose statistics, special problems arise when a drug is used in different doses for more than one major indication, or in combination with other drugs for the same disease. Hypertension and antihypertensive drugs represent such a constellation. However, in a broad prescription study on hypotensive drugs in four Norwegian counties made in October 1975 (*15, 20*), the antihypertensive drug prescription pattern detected corresponded quite well with that predicted from the overall sales figures based upon DDD methodology (Table 3). As seen from Table 4 there was a fair correspondence between

Table 3. The distribution in therapeutic subgroups of hypotensives as a result of the 4 095 prescriptions by 154 general practitioners from 4 Norwegian counties (October 1975) as related to sales figures obtained from the Norwegian Medicinal Depot, using defined daily dose (DDD) as the unit[a]

County		DDD (%)		
		Beta-blockers	Synthetic hypotensives	Diuretics
Østfold	1 388 prescriptions	19	25	57
	sales statistics	19	19	62
Telemark	874 prescriptions	14	24	61
	sales statistics	20	18	62
Møre & Romsdal	1 482 prescriptions	9	16	75
	sales statistics	12	14	74
Finnmark	351 prescriptions	20	23	57
	sales statistics	15	20	65
Total	4 095 prescriptions	13	20	67
	overall statistics	16	15	69

[a] From Baksaas (*15*).

Table 4. A comparison between the defined daily doses (DDD) and the prescribed doses for single hypotensives prescribed more than 50 times in the same prescription study as presented in Table 3[a]

Drug	No. of prescriptions	DDD	Mean prescribed dose
Synthetic hypotensives			
Hydralazine	162	0.1 g	0.09 g
Clonidine	55	0.45 mg	0.35 mg
Methyldopa	1 116	1 g	0.8 g
Diuretics			
Bendroflumethiazide	123	2.5 mg	3.2 mg
Hydrochlorthiazide	402	50 mg	31 mg
Polythiazide	265	1 mg	0.9 mg
Trichlormethiazide	327	4 mg	3 mg
Chlorthalidone	420	50 mg	33 mg
Mefruside	369	25 mg	24 mg
Spironolactone	92	75 mg	49 mg
Beta-blockers			
Alprenolol	138	0.3 g	0.4 g
Pindolol	103	15 mg	14 mg
Propranolol	286	0.16 g	0.19 g
Timolol	136	40 mg	20 mg

[a] From Baksaas (*15*).

defined and mean prescribed doses of synthetic hypotensives and beta-blockers (except for timolol). The DDDs for diuretics, however, were chosen for the situation when these drugs were given alone, and not for combination treatment. Thus, they are mostly higher than those prescribed in an antihypertensive regimen. The sales figures for antiepileptic drugs had earlier been found to correspond relatively well with epilepsy morbidity in northern Norway (*7*).

For drugs that are used intermittently (such as cytostatics and some vitamins) the DDD concept is medically meaningless, but it can still be used as a technical unit of comparison. Whenever possible, the daily dose should be given in *weight* of active substance. With regard to combination drugs or multiple ingredient preparations (in Norway, especially analgesics) it is necessary to choose daily number of tablets, capsules, etc. Similarly, liquid drug combinations must be given in daily volumes. If the relative exposure of a

population or a patient group to one or more active substances (phenacetin, paracetamol, etc.) included in such a mixed preparation is to be analysed, the calculations must, of course, be repeated on the basis of the exact amount of these substances within each preparation.

As already stated, special precautions must be taken when interpreting drug dose figures from those therapeutic groups for which the indication and the dosage vary widely. Such groups are corticosteroids, antibiotics, and psychotropic drugs such as the neuroleptics. As regards the last class, there may be a more than 10-fold difference between the dose level used for the treatment of neuroses and that necessary in psychoses. Because these drugs may sometimes be used as alternatives to minor tranquillizers, like the benzodiazepines, and to some extent instead of, or together with, antidepressants, the risk of misinterpretation is considerable, as pointed out by Hilden (*21, 22*), in relation to intercountry comparisons (*2, 9*). It might be better to redefine the DDDs according to the varying strengths of the actual products. In the case of chlorpromazine, a fixed daily number of 10-mg, 25-mg, or 100-mg tablets could represent the DDD, irrespective of the varying dose in milligrams. However, the gain, in terms of improved medical relevance, from the introduction of such a sophisticated procedure remains to be demonstrated.

POSTMARKETING SURVEILLANCE

With the methodology outlined above, it is possible to bring forward approximate drug therapeutic profiles at various levels (Table 1) within a reasonable time and at an acceptable cost. However, the medical relevance of the data must be thoroughly considered and preferably tested and evaluated through specific drug-, physician-, and patient-oriented studies, whenever necessary.

Fig. 1 gives a tentative overall example of "the relative therapy intensity" for some drug classes in Norway. As already indicated above, the figures for psychotropic and anti-infective drugs must be interpreted with caution. Not only are there wide variations in dose range and indications for the anti-infective drugs, but they are mostly used for short-term purposes, while most drugs in the other classes are used for long-term maintenance therapy.

Fig. 2 shows the overall sales figures for oral anticoagulants in Norway and Sweden from 1972 to 1976. Since the official information pamphlet on anticoagulants (*23*) was distributed to all Swedish (and Norwegian) physicians in 1973 a gradual change from dicoumarol to warfarin has been going on in Sweden. This has also been supported by local and regional Swedish drug committees (*5*).

It is not claimed that the present, relatively drug-oriented methodology can replace the sampling or intensive monitoring type of drug efficacy and safety evaluation. Such examples are the Boston Collaborative Drug Surveillance Program (*24*) and the continuous recording of prescriptions in the county of Jämtland, Sweden (*16*). However, because the resources for running continuous

Fig. 1. Overall therapy pattern in Norway (1974) for some important drugs

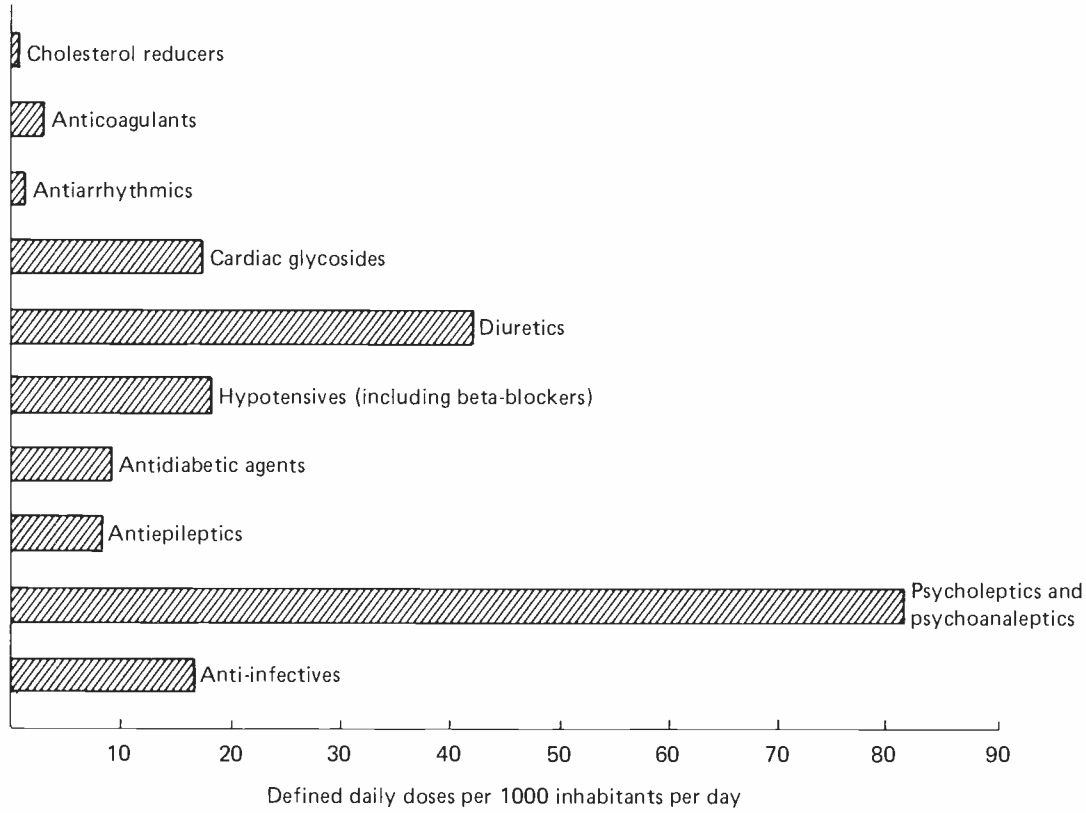
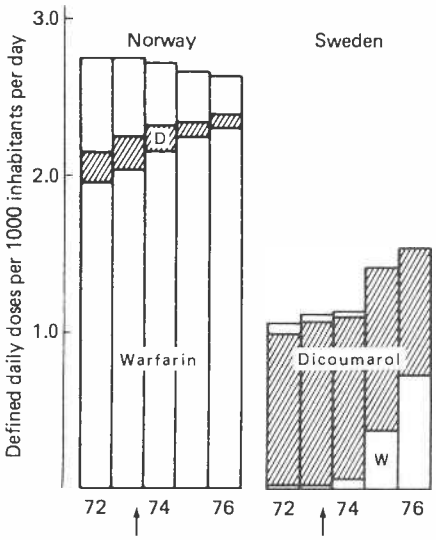


Fig. 2. Overall sales figures of oral anticoagulants in Norway and Sweden, 1972–1976[a]



[a] Defined daily doses for dicoumarol, phenindione, and warfarin were set at 100, 100, and 7.5 mg, respectively. The arrow indicates the date on which warfarin was recommended as the drug of choice (*23*). D = dicoumarol, W = warfarin. The upper white part of the columns for Norway represents phenindione.

intensive studies are limited in many countries, the adoption of common and relatively cheap methods on an overall base is necessary in order to improve the international exchange of knowledge and experiences in the field of drug utilization.

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CHAPTER 3

DATA COLLECTION IN DENMARK

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DISTRIBUTION OF DRUGS IN DENMARK: SPECIAL FEATURES

In order to understand the conditions under which drug statistics are collected in Denmark it is necessary to emphasize some special features relating to the distribution of drugs.

In Denmark the distribution of drugs at the consumer level is handled by privately owned pharmacies while the hospital pharmacies are managed either by the state or by the county. Manufacturers, importers and wholesalers must obtain a special licence from the National Health Service for their activities. Only the privately owned pharmacies are authorized to deliver drugs directly to the consumer. In principle a hospital pharmacy in Denmark cannot sell medicinal products directly to the public; as a rule it serves only the inpatients of the hospital in which it operates.

The privately and independently owned pharmacies, which, as stated above, possess the monopoly of delivering drugs to the consumers, are also manufacturers of drugs. For some commonly used drugs, production is centralized in a few pharmacies, which can supply all other pharmacies with these products. It should be pointed out that the Danish pharmacies therefore act as retail distributors both of the industry's products and of drugs manufactured by themselves.

The publicly owned hospital pharmacies may also manufacture their own drugs in addition to purchasing products from the industry.

A particular feature that influences the pattern of drug consumption in Denmark is the system of subsidizing the consumers' expenses for certain drugs by a reimbursement system managed by the National Health Insurance System and administered locally on the county level. Only about 50% of the drugs on the Danish market are subsidized in this way. All drugs are divided into 3 classes: one for which the reimbursement is 75%, one for which the reimbursement

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is 50%, and one for which no reimbursement is provided. A detailed description of the Danish system has recently been published.

There are reasons for believing that the prescribing doctors predominantly make use of subsidized drugs, when a choice is possible. This means that changes in the policy and spectrum of subsidized drugs probably influence the pattern of prescribing and thereby the pattern of drug utilization.

SOURCES OF DATA FOR DRUG STATISTICS

Centralized drug statistics

In general, the Danish medical and health statistics must be regarded as well organized. However, as far as the measurement of drug utilization is concerned, this is not the case. Complete information is not at present available on either the total utilization or on the utilization of individual medicinal products. No control-recording system that includes a data base for total utilization statistics is at present organized by the National Health Service. The authorities have either no possibility of obtaining the necessary data or no access to data in such a form that they can be utilized without a considerable demand for additional resources.

The official Danish statistics concerned with general trade and goods are not particularly suitable for collecting data for the purpose of studying drug statistics. They are, however, used by the Danish pharmaceutical industry in its annual report for statistical information on manufacture, import and export. Other sources are available, although only some of the data are published and they are not directly developed for the purpose of studying drug utilization.

The only central registration carried out by the official authorities is the continuous recording of prescriptions on narcotics made by the National Health Service on the basis of copies of all such prescriptions collected from the pharmacies. A computerized technique is applied to this material in such a way that the authorities can immediately recognize the use of narcotics by an individual patient and ordered by an individual physician.

Predominantly private registration of drug utilization is carried out continuously by the pharmaceutical industry (importers and domestic manufacturers), wholesale distributors, and the Association of Danish Pharmacy Proprietors (DA). The industry and the wholesale distributors jointly keep complete sales statistics for the members of their organizations, i.e., the individual firms. However, data generated from these statistics are only available for and open to members. A general survey is published yearly. A limitation is that these statistics cover only the drugs manufactured and sold by the pharmaceutical companies (to both the private pharmacies and to the hospital pharmacies) and not drugs manufactured within the pharmacies on a more or less industrialized basis (see previous section).

On several occasions the industry has – by special request – provided the National Health Service with information on sales statistics for special purposes

and for limited groups of drugs. A condition for this supply of data has been that the resulting information was not published in a form that would disclose the sales data of the individual preparations.

A yearly registration of the total utilization of drugs at the retail level, i.e., through the pharmacies, is done by the DA. These statistics (called the DAK statistics) give information on certain therapeutic groups and single preparations based on data collected from a panel of approximately 50 pharmacies, equal to about 15% of all Danish pharmacies. These are selected as being representative of the whole country. The advantage of this system is that it covers drugs sold in the privately owned pharmacies, whether these are produced by the industry or manufactured by the pharmacies. These statistics are at present handled by a manual system and are only available with a delay. They are put at the disposal of the National Health Service for administrative purposes, but are not worked up any further by the DA. The material, or parts of it, has occasionally been used as a data base for utilization studies carried out by various researchers during the last few years. These projects will be discussed in the next section.

A special kind of data generation has involved the collection of all prescriptions filled in all Danish pharmacies on one particular day. This kind of data collection has been used twice by the national health authorities in order to provide a rational basis for decision in matters concerning the policy on subsidized medicine.

Collection of prescriptions in local areas (e.g., one or a few pharmacies) has been possible for special studies (see below), but no attempt has yet been made to organize a more general data source on this basis.

PROJECTS CONCERNED DIRECTLY WITH DRUG UTILIZATION

Although, as discussed above, centralized systems for collection of data for drug statistics have not yet been established in Denmark, several projects concerning various aspects of drug utilization have been carried out or are in progress. These studies are usually characterized by their limitations with respect to the period covered, the size of the geographical area, the selection of groups of drugs, and the part of the population investigated. The Danish system for subsidizing drugs provides a possibility of collecting pharmacy sales data from the reimbursing agencies, but inasmuch as not all drugs are subsidized (not even always within the same group because of price differences) this kind of data collection has its obvious limitations. Nevertheless, interesting results have been produced on this basis. Hilden (*1*) examined all prescriptions on psychotropic drugs, subsidized at that time, in a small provincial town and found that 10% of the population consumed more than half the drugs in this group and, furthermore, that the consumption increased in the lower income groups. In a larger and more recent study (*2*) from the county of Aarhus, the data base was a random sample of all prescriptions for subsidized drugs in the county. The study confirmed much that was already known from other studies (for

example, about sex- and age-dependent patterns of prescribing) but also revealed some surprising facts, such as the use of phenacetin on an unexpectedly wide scale. Between the study by Hilden and the study in Aarhus a considerable change had taken place in the subsidy policy. This change affected both the amount reimbursed and the selection of drugs to be subsidized, for which reason direct comparisons between the results of the two studies might be impossible.

The previously mentioned "one day collection" of all prescriptions in all Danish pharmacies in the autumn of 1971 was initiated in connexion with changes in the reimbursement system. This study was repeated almost exactly 6 years later. The data have provided useful information on the total pattern of prescriptions and some of the results and consequences of the 1971 study have been published (*3*). The data from the latest "one day collection" were to be processed and compared with the previous one. The results were expected to be released towards the end of 1978.

Studies based on all prescriptions in limited areas have also been done (*4, 5*), resulting in useful descriptions of the pattern of the use of drugs, also with respect to the distribution among social and age classes. Another approach, with prescriptions as the data base, was made in a series of investigations by Kyneb et al. (*6–8*). Prescriptions for the total population of a small island (approx. 5500 inhabitants) were analysed during a 5-year period. In particular, the prescribing of psychotropic drugs was studied, together with psychiatric morbidity and other parameters. Such combined studies will probably prove to be very profitable in limited communities, although they may not necessarily reflect a national pattern of drug use, in view of the special demographic features of such more or less isolated societies.

The data source provided by DA from a panel of representative pharmacies (DAK statistics) has been used in several studies. Thus, Gram (*9*) looked at the development in the total use of psychopharmacological substances from 1960 to 1973 and showed, for example, that the consumption (in 1972) of both barbiturates and benzodiazepines was almost twice as high in Denmark as in Norway or Sweden, calculated on the basis of defined daily doses (DDD) per 1000 inhabitants. The consumption of antacids and anticholinergic agents has also been studied (*10*), using data from both DA and the Medif-Meda-statistikken (MMS). The authors took the opportunity of emphasizing how difficult it was to collect information concerning utilization of drugs from all Denmark, even for a limited group of therapeutic agents.

Attempts to examine the use of drugs by interviewing the consumer (the patient) have also been made (*11*). Some 70 households in the town of Elsinore were interviewed, providing a valuable insight into the drugs stored by the general public. In another study a group of general physicians are about to complete a joint study with the pharmacies of the same area about the pattern of drug utilization and consumer motivation in a provincial town in Denmark. The study is carried out in collaboration with DA and the DAK laboratories and the planning has recently been published (*12*). The data base includes both prescriptions and interviews.

Very recently the consumption of narcotic analgesics, based on the total number of prescriptions in this group, was analysed (*13*). The data base was

here, for the first time, the computerized collection of copies of narcotic prescriptions described in a previous section.

At several places in Denmark the initiative to collect drug utilization data has been taken locally. The purpose, as well as the methods, of data collection varies. In some places, local drug committees have expressed the need for information about utilization as a basis for their decisions. In other places, research of the type carried out in Jämtland, Sweden, is being tried. Several new studies are in progress.

In connexion with research on adverse reactions, some investigators have made an additional effort to compare their results with the utilization of the drugs in question. Such studies are described in the next section.

REGISTRATION OF ADVERSE REACTIONS TO DRUGS

The Board on Adverse Reactions to Drugs was appointed in 1968 and began collecting reports from May of the same year. The number of annual reports is now in the region of 1500. They are evaluated by the Board and classified into four groups with regard to the likelihood of a causal relationship: A – possible (13%); B – probable (60%); C – definite (24%); and D – unclassified (3%). Out of a total of about 2000 drugs on the market, approximately 500 different drugs are represented. Of these, nearly 30% are used as oral contraceptives, about 22% are anti-infective drugs, 7% are antirheumatics, and 7% are psychotropic drugs.

The use of drug utilization registration in connexion with studies on adverse reactions is important. Such combined studies will inevitably give the necessary quantitative dimension to the adverse reaction problem, but are not frequently carried out. A few Danish studies have recently emerged, one concerned with consumption and adverse reactions of analgesics and antirheumatics (*14*). This study gives a quantitative measure of the use of these drugs (including fixed combination preparations) in Denmark and a well founded recommendation for a more limited use of the phenylbutazones. A study on adverse reactions to and utilization of beta-blockers in Denmark (1968–76) (*15*) demonstrated an exponential increase in the use of these drugs, measured as DDD per year. The last two studies were based on data provided by the DAK statistics (see previous section).

CONCLUSION

Several sources of data have been exploited resulting in interesting information on various aspects of the utilization of drugs in Denmark. It is realized, however, that a centralized and readily available data source must be at hand for scientific projects before it will be possible to launch meaningful

nationwide studies, the results of which can match and be compared with those from other countries. In Denmark there are as yet no general and publicly released statistics on total consumption of drugs as a basis for drug utilization studies. It is probable, however, that such statistics will eventually emerge from collaboration between the manufacturers, importers, and distributors of drugs.

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DATA COLLECTION IN FINLAND

J. Idänpään-Heikkilä[a]

In a law enacted in 1964 the efficacy, safety, quality, and proper labelling of drugs were defined as criteria for the granting of a sales licence (registration, marketing permission) for therapeutic agents and products in Finland (*1*). An additional criterion, reasonable price, was added in 1969. This law introduced a new task for the governmental health regulatory agency (the National Board of Health – NBH) and its permanent advisory council, the Committee on Safety of Medicines (COSM), since it required them to evaluate, control, survey, monitor, and regulate the drugs and their use (*2, 3*). Once the NBH started this activity and the COSM was established in 1964 it very soon became apparent that the health authority urgently needed accurate data on the consumption and utilization of drugs in the country. The first attempts to collect gross sales statistics were made in the late 1960s (*4*).

DATA COLLECTION

The Health Care Law in Finland allows the health authority to request drug sales statistics from the drug manufacturers, wholesalers, pharmacies, or hospitals. In the past, this privilege has been exercised only occasionally, owing to the enormous work needed to achieve reliable data from these sources (*4–6*). At the request of the drug manufacturers, an independent market research institute, IMS, established a nationwide system of drug sales statistics in 1966 for commercial purposes. The delivery of these data to third parties, such as health authorities, was not possible. However, in 1973 the pharamaceutical industry agreed that governmental institutions could have access to these statistics provided that official publication or passing on of the information to third parties was not allowed.

The IMS surveys the prescriptions delivered in 62 pharmacies (a representative sample of the national drug market) and the quarterly printed reports contain the estimated sales of all registered pharmaceutical products (among

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other things number of tablets, packages, sales in Finnmarks, etc.). The data are given on all individual brands as well as on larger pharmacological groups of drugs and their subgroups. The veterinary forms of the drugs are not included in these statistics. The direct sales by manufacturers to hospitals and social institutions are included in the IMS data only if these purchase their drugs through the retail pharmacies (*7*). The NBH has obtained the missing hospital data separately from the wholesalers. Since January 1978 all hospitals have to report their consumption of drugs in detail directly to the NBH.

In numerous drug utilization studies other data sources have been used such as prescription data from pharmacies, drug wholesalers' shipment protocols for pharmacies and hospitals, prescriptions and other documents of the National Social Insurance Institution, patient interviews, etc. (*4–6, 8–14*).

GOVERNMENTAL INTEREST IN APPROPRIATE UTILIZATION OF DRUGS

The rational use of drugs and expenditure on drugs for preventive and curative medicine have been the subject of much discussion. The drug industry, wholesalers, and pharmacies are all private enterprises in Finland. The manufacturers compete with each other by using vigorous promotion of drugs and their information activity towards physicians goes far beyond the sporadic information activities of the health authority. Over 50% of health care has been nationalized and the Social Insurance Institute reimburses about 50% of the costs of drugs. The physicians' prescribing habits and criteria in selecting drugs are major factors influencing national drug consumption and drug expenses.

Antihypertensives

Finland has one of the highest levels of morbidity and mortality from cardiovascular diseases in the world. The reimbursement costs of the antihypertensives alone account for about 50% of the costs of the totally reimbursed drugs in Finland. In 1972 about 93 000 Finns had been granted the right to free drug treatment of their hypertension. In 1976 this number had more than doubled and 225 000 Finns received free drugs for hypertension (Olli, M. personal communication). The regulatory agency has closely monitored the trends in physicians' prescribing habits with regard to antihypertensives, how physicians select an antihypertensive for their patients, and what the costs of antihypertensive medication are to society.

Diuretics have traditionally been the most popular treatment for hypertension (Table 1). Up to 1974 the *Rauwolfia* preparations were in second place. Since then, methyldopa and more recently also clonidine have become almost as popular as *Rauwolfia* preparations (Fig. 1). In fact, the decline in the sales figures of reserpine has occurred since 1974 as a result of the preliminary reports on an association between breast cancer and *Rauwolfia* use (*15–17*).

Table 1. Use of diuretics and beta-blockers in Finland in 1968–1976[a]

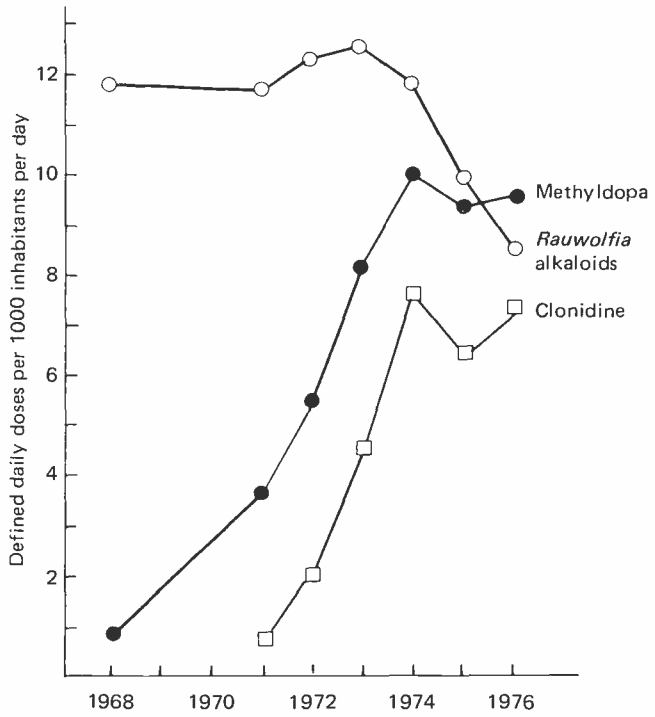
	Number of defined daily doses per 1 000 inhabitants per day						
	1968	1971	1972	1973	1974	1975	1976
Diuretics[b]	11.1	20.0	40.6	42.6	48.4	50.8	58.6
Beta-blockers[c]	0.2	1.5	2.9	4.9	10.4	16.0	17.6

[a] Excluding some hospital use.

[b] All indications.

[c] All indications, e.g., hypertension, angina pectoris, and cardiac dysrhythmias.

Fig. 1. The consumption of 3 leading antihypertensives in Finland in 1968–1976[a]



[a] Diuretics and beta-blockers are not included. Some hospital use is not included.

The validity of these proposals has been questioned in some more recent studies, among them a nationwide case-control study in Finland (*18*). Two nationwide registers, the Finnish Cancer Register and a register of persons entitled to free drugs for hypertension, were linked in a case-control study on the association between breast cancer and the use of *Rauwolfia*.

A striking, if not worrying, phenomenon has been the heavy commercial promotion of the beta-adrenergic blocking agents. Their sale has almost doubled annually (Table 1). At present there are no reliable data proving that their prescribing is excessive, but their use is so extensive that some reduction is desirable solely on this ground.

Overprescribing of hypnotics and sedatives

Claims that doctors overprescribe hypnotics and minor tranquillizers prompted the NBH to study the national prescribing pattern of all psychotropics (*4*). In 1966–1970, diazepam alone had increased from 6 to 18 DDD per 1000 inhabitants per day (Fig. 2). The use of neuroleptics and antidepressants had somewhat increased (Fig. 3), whereas chlordiazepoxide, meprobamate, and especially barbiturates showed a diminishing tendency (Fig. 2 and 4).

These findings were critically discussed by both physicians and sociologists in medical papers and in the lay press. This decreased the pressures on physicians from patients to prescribe sedatives for minor daily mental problems. In addition, in 1973 the NBH withdrew permission for telephone renewal of these prescriptions. Subsequently, the consumption of psychotropics and especially that of hypnotics and sedatives dropped in 1971–1975 (Fig. 2 and 4), and now shows a tendency to level off (*6, 7*). Concomitantly, the sales figures of neuroleptics and antidepressants increased, as they may have replaced some earlier use of hypnotics and sedatives (*6*) (Fig. 3).

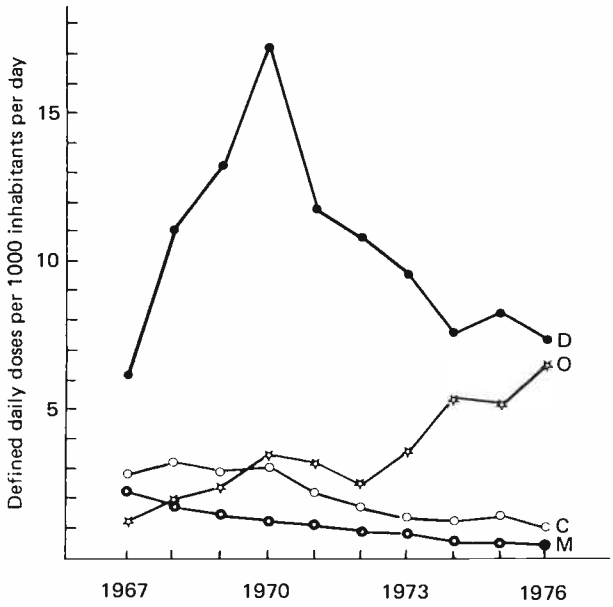
It may be of interest to note that the *per caput* consumption of alcoholic beverages (counted as 100% alcohol *per caput*) increased from 2.5 to 5.1 litres in 1966–1972 and rose further to 6.3 litres in 1976. The concomitant rise in the use of alcohol, sedatives, and hypnotics may be attributable to their having some background factors in common.

Over-use of over-the-counter hypnotics

Up to 1974, about 12 prescription-free hypnotics, most of them combinations of 2–4 active components (in all, 13 different active ingredients were available) were on sale in pharmacies (*6*). They were sold in packages of 3–100 tablets and more than 12 million tablets (4 tablets per inhabitant per year) were bought annually (Fig. 5). In January 1975, the NBH issued new regulations on over-the-counter hypnotics; only amobarbital 50 mg/tablet in packages of 3 tablets of *Valeriana* extracts were allowed to be purchased without prescription (*6*).

An enormous decrease in the sale of over-the-counter hypnotics occurred during the year 1975 (Fig. 5). Insomnia as such may not have been lessening

Fig. 2. Use of anxiolytics in Finland, 1967–1976[a]



[a] D = diazepam, C = chlordiazepoxide, O = derivatives of diazepam and chlordiazepoxide, M = meprobamate.

Note the rapid increase in diazepam use in 1967–1970 and the following decline in 1971–1974 as a result of an information campaign and limitations on prescribing.

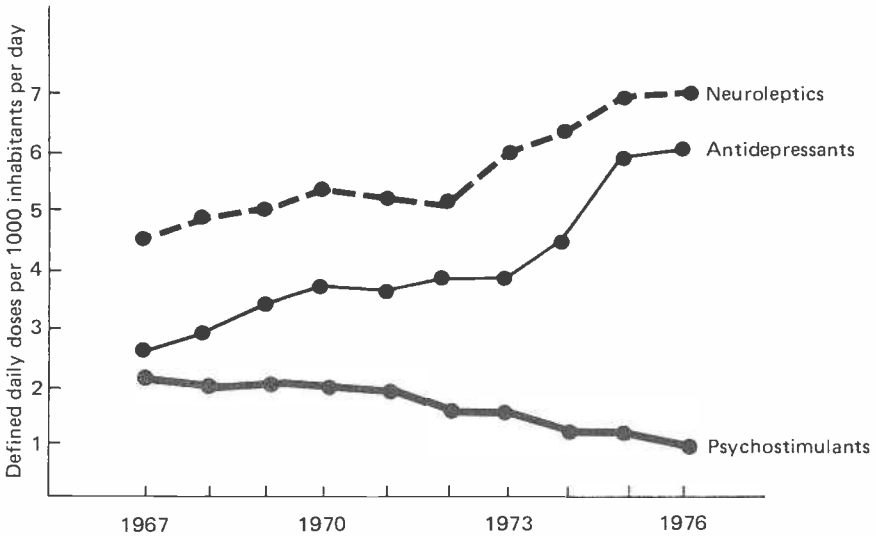
Hospital data included.

in Finland. Some of the patients turned to their physicians to get prescription hypnotics. This was, of course, desirable. Secondly, 3 tablets may be enough for the treatment of a temporary insomnia and some alternative treatments of mild insomnia may have been applied to avoid frequent visits to the pharmacy.

SIGNIFICANCE OF ADVERSE REACTIONS AND THE RELEVANCE AND OUTCOME OF GOVERNMENT ACTIONS

The adequate medical evaluation of adverse reactions is possible in most cases only if the number of patients exposed to the drug is known. Government actions to withdraw or to restrict the indications or prescribers of a drug on account of its adverse reactions should be based partly on the drug utilization data. This is necessary to make it possible to predict what consequences

Fig. 3. Use of neuroleptics, antidepressants and psychostimulants in Finland, 1967–1976[a]



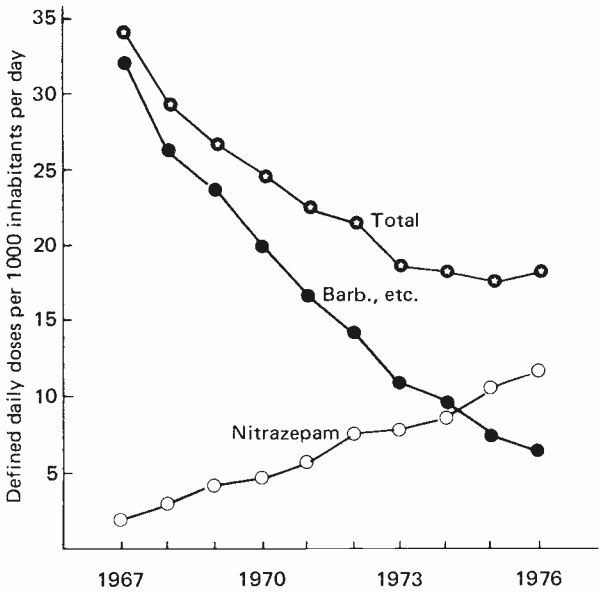
[a] Hospital figures included.

such a decision may have for routine therapy and whether a certain transition period is necessary. Drug utilization data are needed, too, to determine whether government actions to limit the use of a given drug or substitute another one have been satisfactory and relevant.

Biguanides and lactic acidosis

During the last few years an increasing number of biguanide-induced lactic acidosis cases have been reported in the medical literature (*19, 20*). In 1973, the NBH revised the indications for and contraindications to phenformin and metformin preparations in Finland (*21*). A more critical promotion and prescribing of biguanides was expected. However, the sales figures of biguanides almost doubled in 1973–1976 (Fig. 6). In all, 36 cases of lactic acidosis were reported to the NBH in 1973–1977 (November), 21 of which were fatal (*22*). Comparisons between the Nordic countries revealed that the Finns used biguanides 6 times more than the Icelanders or Norwegians and also significantly more than the Swedes (see chapter 14). In May 1977, COSM called a group of experts to examine the relevance of biguanides as antidiabetic medicines. It proposed strict limitations on the use of biguanides in August 1977 (*21*). Since then, phenformin has been reserved for a small number of diabetics who seem to avoid insulin by using sulfonylureas with biguanides.

Fig. 4. Consumption of hypnotics and sedatives in Finland, 1967–1976[a]



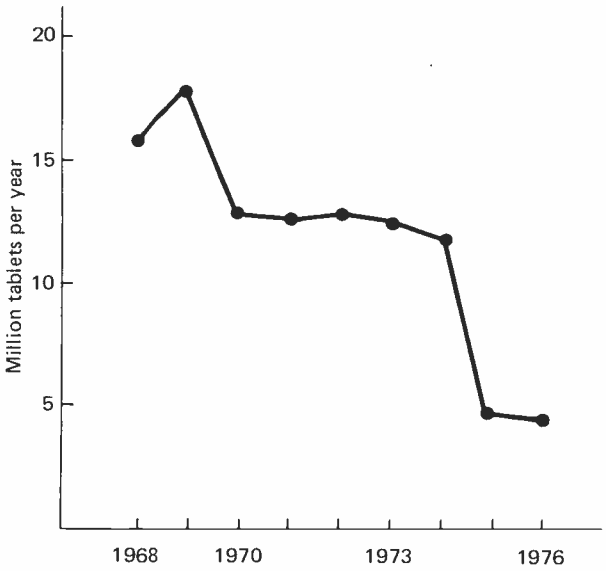
[a] Barb., etc. = barbiturates, methaqualone, glutethmide, chloral hydrate and clomethiazole.

Clozapine and agranulocytosis

Initial experiences in several European countries with clozapine (a piperazine derivative of the dibenzodiazepine group) were promising. It proved to be more effective than the earlier neuroleptic drugs (*23, 24*), and at least as safe haematologically as other widely used neuroleptic drugs such as chlorpromazine (*25, 26*).

Clozapine was introduced to Finland (Fig. 7) in January 1975 after clinical trials of about 200 patients in domestic hospitals and about 2900 abroad. In late June, after clozapine had been about 5 months on the market, a district hospital reported a fatal case of agranulocytosis among patients exposed to various drugs, which included clozapine. The same hospital and physician reported a similar case to the adverse reaction register 2 weeks later. In 1 week, in late July, 7 more fatal cases were reported, 3 of which had had clozapine alone (*27*) (Fig. 7). In the succeeding 2 weeks 11 recovered cases of blood dyscrasias were found. In summary, within 6 months of its introduction, 17 cases of neutropenia (7 cases) and agranulocytosis (10 cases) were found among some 3200 patients treated up to that time. Eight agranulocytosis patients died, 2 patients developed thrombocytopenia, and 1 patient died of leukaemia (Fig. 7). According to the consumption figures, the risk of agranulocytosis or severe

Fig. 5. Sales of prescription-free hypnotics (over-the-counter hypnotics) in Finland, 1968–1976, in million tablets per year[a]



[a] The new regulations were issued by the National Board of Health in 1975.

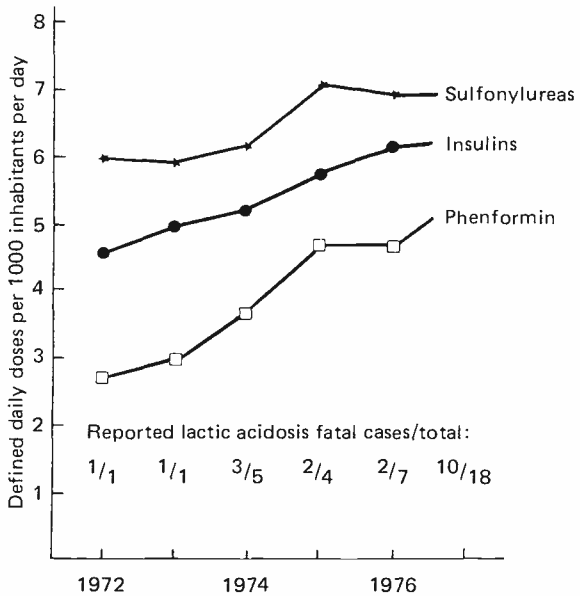
granulocytopenia during treatment was at least 0.5–0.7% (*28, 29*). This frequency has been estimated to be 21 times higher than in other countries (*23*).

These experiences show the importance of the close post-marketing monitoring of the safety of any new therapeutic agent, irrespective of how safe it has been in clinical trials (*29, 30*). They also demonstrate the important role of drug utilization statistics in finding the exact incidence of serious adverse reactions. This convinced the manufacturer, the physicians and the regulatory agency that immediate withdrawal of the drug from therapeutic use was needed.

PRICE CONTROL OF DRUGS

As stated in the introduction, the law of 1969 includes "reasonable price" as one criterion for drug registration (*1, 3*). The price evaluation documents of a new drug consist of the price in the manufacturing country, data on special manufacturing or developing costs, the price in other Nordic and European countries, and comparisons with synonymous preparations, related derivatives,

Fig. 6. Use of insulin, metformin, phenformin and sulfonylureas in Finland, 1972–1977[a]



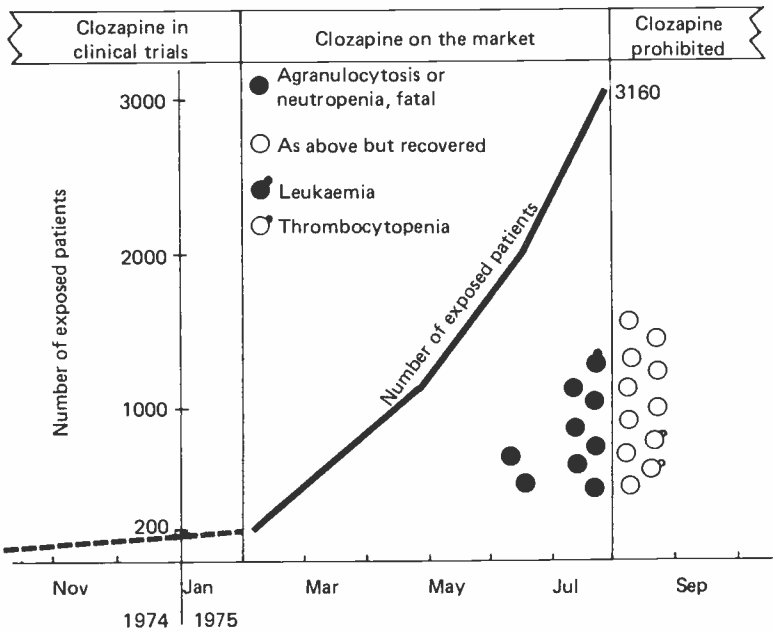
[a] The numbers refer to the reported lactic acidosis cases (fatal cases/total) during the same period of time.

or analogous drugs. When the manufacturers apply for price increases (usually once a year) the documents are completed with consumption statistics and with data on how the price increase will influence the yearly turnover of the firm. Here, the sales figures help the price control agency to regulate the costs of drug therapy as well as to accept relevant changes in prices (*31*).

Development of a price index of drugs and of a regulatory agency

In 1970–1976, the price index of drugs was studied by the Helsinki Research Institute for Business Economics (*32*). The 500 leading pharmaceutical products were selected from the utilization statistics. They covered 84% of the sale of drugs in the pharmacies. A total of 200 products, a representative sample of the 500 leading products, was further selected to monitor the price index of drugs in different categories (Fig. 8). The consumer price index increased much faster in 1970–1976 than the price index of the drugs. The most abrupt rises were in the price indices of the over-the-counter preparations (non-prescription drugs), drugs manufactured in Finland, and those totally reimbursed by the National Social Insurance Institute. On the other hand, the

Fig. 7. Reported cases of agranulocytosis or other blood dyscrasias associated with the introduction of a new neuroleptic, clozapine, in Finland and the concomitant governmental actions[a]



[a] Reproduced from Idänpään-Heikkilä & Palva (*30*).

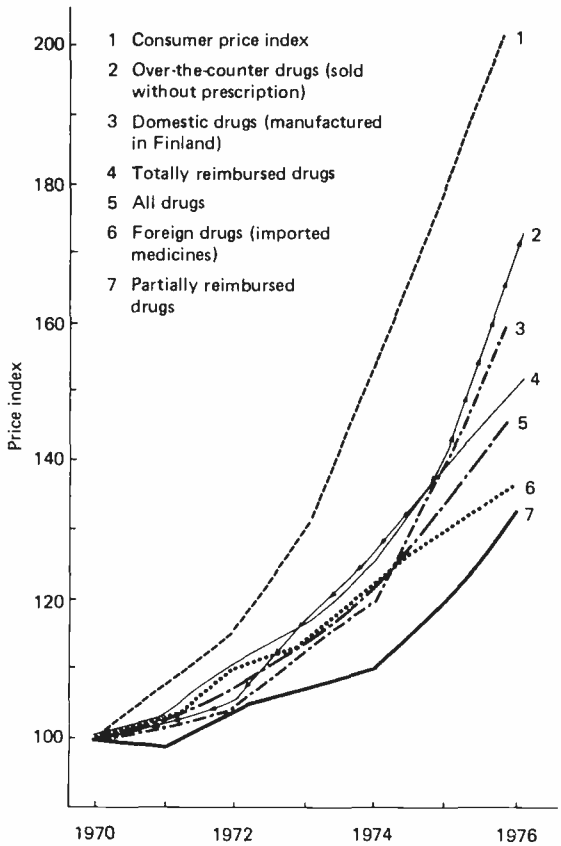
price levels of the over-the-counter and domestic drugs have been and still remain the lowest. Thus, as Fig. 8 shows, the prices of the cheapest drugs have risen the most, while the prices of drugs partly or totally reimbursed by the national health insurance system have increased less. This, in fact, reflects the general price policy carried out by the COSM in Finland.

Costs of antimicrobial therapy in 1968–1975

Infectious diseases are common in a climate such as that of Finland. They are one of the main causes of absenteeism and hospitalization, and the antimicrobials constitute about 14% of all drug sales in Finland. Antibiotics may well be medically needless in 80–90% of infection cases. Furthermore, new and more expensive antibiotics promoted in the 1970s have replaced the old, cheap, but still effective penicillin in the medical armamentarium of many physicians.

The cost of antibiotics increased from about 10% of the total expenditure on drugs in 1968 to 14% in 1975 (Table 2). The use of penicillin and tetracycline

Fig. 8. The development of price indices of different drugs in Finland, 1970–1976[a]



[a] The consumer price index and the price index of all drugs have been used as reference indices.

products and the amounts spent on them have markedly declined. For erythromycin and especially co-trimoxazole, azidocillin and cephalosporins both the costs and the use are increasing rapidly. The use of chloramphenicol in 1975 was very small, only 0.2% of the total use of antibiotics.

The use of cephalosporins (0.7%) and azidocillin (4%) is still low, but their costs among antibiotics (4% and 17%) were suprisingly high (Table 2). These findings have raised several suggestions as to how we could achieve a better utilization of antibiotics (*33*). However, the final actions and programmes are still under careful consideration. A stricter price policy and a better control of information on and the promotion of antibiotics have already been applied by the NBH (*33*).

Table 2. Consumption and cost of various antibiotics in Finland in 1968 and in 1975[a]

Antibiotic	Consumption of all antibiotics (%)		Cost of all antibiotics (%)	
	1968	1975	1968	1975
Penicillin V	56.5	42.0	40.0	29.0
Tetracyclines	25.0	20.0	33.0	29.0
— doxicycline	1.1	4.7	2.9	12.7
Erythromycin	0.6	3.0	1.6	8.2
Co-trimoxazole	not on the market	9.7	not on the market	19.0
Azidocillin	not on the market	4.0	not on the market	17.0
Cephalosporins	not on the market	0.7	not on the market	4.0
Chloramphenicol	6.2	0.2	4.2	0.1

[a] Excluding some hospital use.

CONCLUSIONS

Knowledge of sales figures for drugs throws light on prescribing patterns and the use of prescription-free products. The significance of a new and serious adverse reaction can be estimated only if the number of exposed patients is known.

Warnings in medical journals, revision of promotional information, and restrictions on the use of some drugs or even withdrawal from the market may become necessary. With drugs such as clozapine, practolol, biguanides and psychotropics the surveillance of utilization data may be of great value. Without these it is almost impossible to know how actions taken by the government have influenced prescribing and whether additional restrictions or other actions may be needed or not.

The costs of various drug therapies may be of interest to national health authorities. The Finnish National Board of Health is involved in the control of drug prices. Drug utilization figures are necessary for these purposes too.

In 1978 the hospital consumption of drugs will be included in the Finnish statistics. In-depth studies on local and individual differences in prescribing patterns are in progress. An investigation on the cost-benefit ratio of various therapies in rheumatoid arthritis and arthrosis has been initiated.

Comparable overall drug statistics are now to some extent available in the northern countries. Many of the problems touched on in this review indicate that more extensive comparable statistics from country to country are needed to monitor the efficacy, safety, and proper and adequate use and prescribing of drugs.

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DATA COLLECTION IN ICELAND

A. Grímsson[a]

BACKGROUND

Distribution of drugs

Organization of the distribution of drugs in Iceland is rather clear-cut. The manufacture of nonproprietary medicines, which accounts for approximately 20% of the total expenditure on drugs, is done by 3 firms and several pharmacies. Furthermore, there are 8 firms (including the 3 manufacturers) authorized to import and distribute drugs on a wholesale basis to pharmacies and hospitals. One of these manufacturing and wholesale firms is a state enterprise and its primary function is to serve hospitals.

The retail sale of drugs is operated through a network of 36 pharmacies throughout the country, but in some rural areas, where the services of a pharmacy have not been established for economic reasons, the local physician is the sales outlet for drugs.

The hospitals procure their drugs predominantly from the wholesalers and to a very small extent from pharmacies.

Marketing of drugs

The Icelandic drug market is not a complex one, the total number of registered pharmaceutical specialities being relatively small (approximately 1100). The number of standardized nonproprietary drugs on the market is uncertain, but a reasonable estimate is 450–500 different strengths and administration forms, which gives an approximate total of 1600 different strengths and administration forms of drugs on the Icelandic market.

The procedure for registration of pharmaceutical specialities is the following: an expert Committee on Pharmaceuticals, appointed by the Minister of Health, evaluates the applications for registration and recommends to the Minister whether the applications should be approved or refused and any

[a] Pharmaceutical Division, Ministry of Health, Reykjavik, Iceland.

special conditions for marketing. The Ministry of Health takes the formal decisions, but these decisions have hitherto been in full conformity with the recommendations of the Committee.

During the last two years the Committee has recommended the registration of 11 new drugs, to be subject to a monitored release, which means that their administration is permitted only in certain hospital clinics and under the supervision of an appropriate specialist.

Control of drugs

The governmental administration of affairs related to the manufacture and distribution of drugs was reorganized in late 1971 when a special Pharmaceutical Division was set up within the Ministry of Health and Social Security. This Ministry was constituted by law in 1970, but before then public health affairs were administered, at a ministerial level, in a health division in the Ministry of Justice and by the Chief Medical Officer of Health (CMOH) who acted as adviser to the Minister and the Government in all matters concerning health. At that time the inspectorate of pharmacies was attached to the Department of Medicine, University of Iceland, but from 1 January 1972 it became an integral part of the new Pharmaceutical Division, like the other entities of the previous drugs administration, such as the Committee on Pharmaceuticals, the Drug Pricing Committee, and the Committee on Toxic Substances.

Social security

Generally speaking, public health in Iceland is a public enterprise. The state budget finances 85% of the costs for the building and equipment of new health centres, while the relevant communities finance the remaining 15% and pay the daily costs of running the centres, apart from the salaries of physicians and nurses, who are appointed and paid by the state.

At present, however, only a part of general medical practice is operated through these health centres. While the centres play an essential role in health services in rural areas, only a fraction of the general practice in Reykjavik is operated in this way, namely, through one municipal health centre in a suburb. Otherwise, general practice in Reykjavik is on an individual basis, the general practitioners being contracted by the local health insurance fund. The general practitioner is thus granted a fixed monthly fee for each of his patients 16 years of age and older.

The social security scheme automatically covers every citizen and the social security reimburses almost every prescription. Certain drugs, e.g., antidiabetics and cytostatics, are considered vitally important and are furnished free of charge for the patient. For other drugs the patient pays a fixed sum (approximately US$1.50–3.00 per prescription) and the health insurance funds the rest. Thus it is estimated that the social security pays a total of about 65% of the value of prescribed medicines.

Hospitals are run from public health finance through the social security scheme. The average cost of a bed in each hospital is estimated by a committee and the social security reimburses the cost in full. Drugs used for treatment in the hospitals are included in these reimbursements.

DRUG UTILIZATION RESEARCH

General

One of the top priorities of the Pharmaceutical Division, since its inception in late 1971, has been the promotion of research on the use of drugs. As early as 1972 the CMOH, in cooperation with the Pharmaceutical Division and sponsored by the health insurance fund in Reykjavik, carried out an in-depth study on prescriptions of drugs in Reykjavik.

The role of the CMOH in drug control is medical supervision of drugs and the sale of drugs and supervision of physicians' prescriptions for dependence-producing drugs.

Other methods for research on the use of drugs have been developed in cooperation with colleagues in the WHO Drug Utilization Research Group (DURG). Special emphasis has been laid on the development of a system for periodic review of the wholesale distribution of drugs and on the use of drugs in hospitals.

Prescription surveys

As already mentioned, the first prescription survey was effected in Reykjavik in November 1972. A month's sample of prescriptions in certain therapeutic groups was collected and a computer program was elaborated and tested (*1, 2*).

The main objectives of this study were:

(1) to collect information on physicians' prescribing habits and on use or abuse of drugs by the recipient;

(2) to provide a tool for the health authorities so that prescriptions could be controlled and the use of drugs monitored;

(3) to provide statistics on the taking of drugs.

Because of the high costs, continuous data registration and analysis were not practicable. Instead, an *ad hoc* study was carried out. From the prescription form the following data were collected:

(*a*) patient's name and number;

(*b*) physician's code;

(*c*) name of drug, the type of preparation, and the quantity;

(*d*) price.

The Icelandic National Register was computerized in 1952 and is updated yearly. Two identification numbers are used. The main one gives the date of birth in 9 digits: the first 6 stand for date of birth (day, month, year), the next 2 identify the serial number during the day, and the last one is a check digit. The other identification number, which is used widely by various institutions, is a name number of 8 digits, which is issued at the age of 12. This indicates the person's name in an alphabetical order.

In this first *ad hoc* study, only the name code was used for identification because it was already in widespread use although it is inferior to the person number, especially in the case of prescriptions for children who are identified by the name number of one parent. The name code was used to link the prescriptions to the National Register to obtain data on age, sex, and marital status. The rate of successful linkage was 93%.

During the following years this program has been further developed and 3 similar surveys have been carried out, the last one in November 1976. In these surveys the name code has also been used but in future surveys the birthdate number will be used.

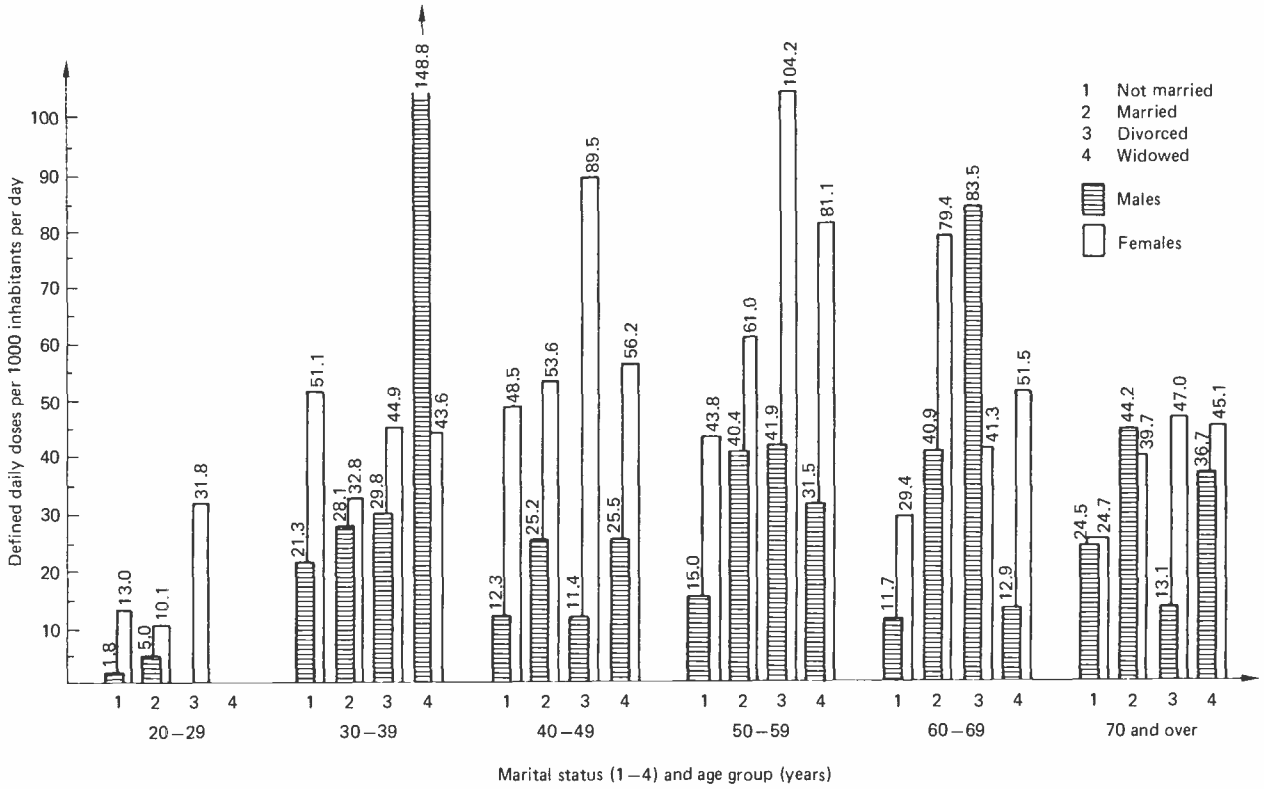
As an example from these surveys Table 1 shows, in terms of DDD per 1000 inhabitants per day, the prescriptions for antibiotics and chemotherapeutics in November 1972 and November 1974 (*2*). The increase in prescriptions for tetracyclines and sulfonamides is not balanced by a small decrease in those for penicillins. These increases are due to the growing number of prescriptions for the combination forms of trimethoprim and sulfamethoxazole and for minocycline.

Another example is given in Fig. 1. showing the distribution of prescriptions for diazepam preparations (5 mg) according to sex, age, and marital status (*3*). The columns are proportional to the number of DDDs (10 mg) (*4*)

Table 1. Prescriptions for antibiotics and chemotherapeutics in November 1972 and November 1974

Type of antibiotic or chemotherapeutic	Defined daily doses per 1 000 inhabitants per day			
	November 1972		November 1974	
	No.	%	No.	%
Penicillin V	3.77	24.5	3.59	20.5
Semisynthetic penicillins	3.99	25.8	3.81	21.7
Tetracyclines	3.92	25.4	5.29	30.2
Sulfonamides	2.35	15.2	3.70	21.1
Chloramphenicol	0.04	0.3	0.01	0.1
Others	1.37	8.8	1.13	6.4
Total	15.44	100.0	17.53	100.0

Fig. 1. Distribution of prescriptions for 5-mg diazepam preparations according to age, sex, and marital status



prescribed per 1000 inhabitants in each sex, age, and marital status group per day, thus providing a rough estimate of the number of people in every thousand using this drug in Reykjavik in November 1972.

The high figure for widowed males aged 30–39 years is due to two excessive consumers who had obtained prescriptions from various physicians on false pretenses. Such excessive consumers were also found in other groups but the number of individuals within each group certainly varied.

Wholesale data

Data have been collected from authorized wholesalers on yearly sales of drugs in certain therapeutic groups for 1970–76. These data have been transformed into DDDs per 1000 inhabitants per day according to the methodology elaborated and recommended by DURG.

The collection of wholesale data in Iceland was initiated after Icelandic members joined DURG in 1974. Data on sales of antidiabetic and psychotropic drugs were submitted to colleagues in DURG and jointly elaborated and published (*5, 6*).

Sales figures for other groups of drugs have been subject to periodic study, e.g., cardiovascular and dermatological drugs, with special emphasis on beta-blockers and corticosteroid preparations, respectively.

The collection of data on the wholesale distribution of drugs is now moving into a new stage as the wholesale drug distributors, in cooperation with the representatives of foreign pharmaceutical industries, are starting to operate a computerized joint statistical programme, which will provide data on the wholesale distribution of drugs on a quarterly basis. According to the operational plan for this programme, the first quarterly output is expected to cover January–March 1978.

The input code used will be the "Nordic product number", which is common to the 5 Nordic countries. This is a code number of 5 digits and 1 additional control digit. The code number identifies the package size, strength, and form of a given drug. Thus, Valium, 5 mg, in packs of 25 tablets, will have one code number while packs of 100 tablets of the same drug will have another. When the name, strength, administration form, package size, and manufacturer of a drug are the same in 2 or more countries, the code number will be the same in these countries.

The output will be arranged in accordance with the EPhMRA (European Pharmaceutical Marketing Association) therapeutic classification system. This originally comprised 3 levels but the Norwegian Medical Depot has added 2 more levels covering chemical composition and it is applied in this form to drugs registered in all 5 Nordic countries (see chapter 2).

Hospital data

Data collection in Icelandic hospitals has been quite limited. However, the use of antibiotics and chemotherapeutics and some psychotropics has been

under observation in the 3 major hospitals in the country. As yet there is no advanced system of data collection in any of the Icelandic hospitals, but special procedures enable data to be collected manually from the order forms of each hospital department. However, this produces an unnecessarily heavy workload which demands new techniques in the administration of drugs and in data collection in Icelandic hospitals.

Data on drug compliance

Generally speaking, the weakest link in the chain of drug prescribing and use is the consumer – the patient. Often this is due to incomplete instructions, together with a basic lack of knowledge as to how to handle drugs.

One pilot study has been carried out in Reykjavik (7). This covered the taking of drugs by 116 persons (33 males and 83 females) who were provided with home nursing services by a Central Municipal Clinic. Of these 116 persons, 102 were 70 years of age or older. The attending nurses checked whether the patients had been following the orders of the physicians by examining the home medicines cupboard and interviewing the patients or those responsible for them.

The results of the study were rather alarming (see Table 2), since most patients greatly exceeded the prescribed intake period. In each of the 5 groups of drugs studied, the average intake period was twice that prescribed.

Table 2. Drug use as compared with prescribed use

	Number of drugs	Taken as prescribed	Not taken as prescribed	Average duration of intake as ratio of prescribed duration
Antibiotics and chemotherapeutics	23	6	17	2.1
Digitalis glycosides	27	5	22	2.13
Antihypertensive drugs	44	14	30	2.28
Hypnotics and sedatives	87	24	63	2.48
Potassium chloride and other electrolytes	31	13	18	2.08

Adverse reactions data

There is no organized reporting of adverse reactions in Iceland, but naturally it is understood that severe or previously unknown reactions have to be reported

to the CMOH. Owing to the small population (220 000), the incidence of adverse reactions is relatively very small, so that a reporting system has not been considered a matter of priority. Reports of adverse reactions are, however, received from other countries (e.g., Sweden) and screened by the CMOH with special regard to the Icelandic market of drugs. An Icelandic system of reporting adverse reactions could therefore make only a small contribution to an international reporting system.

USE OF DATA

Wholesale data

International comparisons of wholesale data have proved to be very useful in evaluating drug use in a given country or area. A standardized classification system and a defined unit of measurement are the fundamental tools for the elaboration of such comparisons.

Comparisons of the use of antidiabetic and psychotropic drugs (*5, 6*)[a] have further stimulated in-depth research to elucidate the reasons for a relatively low use in Iceland of antidiabetic drugs and for a high consumption of benzodiazepines. The prevalence of diabetes and the actual daily intake of benzodiazepines are examples of parameters that might possibly answer some of the pending questions.

Prescription data

The data obtained from prescription surveys were broken down according to active substance, patient, and prescriber. The fact that several cases of severe misuse were revealed indicates the importance of such studies. In such cases, the CMOH issued information to the physicians who were involved in multiprescribing to one individual. In general, screening of prescriptions is an indispensable element in drug monitoring of every kind, e.g., as a follow-up to comparative overall studies.

Administrative measures

The overall data on wholesale supplies of drugs and on prescriptions, translated into DDDs (*4*), have been subjected to a thorough investigation by the central health authorities.

A comparative investigation on prescription frequency has been made in Reykjavik (population 84 000) and Akureyri (population 11 000), the largest

[a] See also chapters 14 and 15 of this book.

town in the northern part of Iceland. It revealed a distinct difference in the number of prescriptions per head: the number of DDDs per 1000 inhabitants per day for benzodiazepines (except nitrazepam) was more than twice as large in Reykjavik as in Akureyri, while the number of prescriptions for other hypnotics and sedatives was similar in the two towns (*8*). The results of a prescription survey in Reykjavik (*1*) showed that approximately 30% of prescriptions for diazepam preparations were for 10-mg tablets.

These findings motivated the Committee on Pharmaceuticals to recommend to the Ministry of Health and Social Security that preparations containing 10 mg of diazepam per tablet be omitted from the register of specialities. After consultation with the CMOH and the Icelandic Medical Association, who supported this recommendation, these drugs were withdrawn from the register from 1 June 1977. The effects of this action are now under observation.

Another example of the effects of administrative measures has a special relevance to hospital care. The number of outpatient prescriptions for topical corticosteroid preparations and especially the quantity per prescription increased steeply when these drugs were classified by social security in 1972 as highly important for the treatment of psoriasis and eczema and, when used for such purposes, were fully reimbursed. At the same time a dermatological polyclinic opened in the Reykjavik area and patients who had previously received free or practically free treatment only when hospitalized could thus receive this service outside a hospital. The effects of these administrative actions on prescribing of glucocorticoid preparations and on waiting lists in the dermatological department of the state hospital are shown in Tables 3 and 4 (Ólafsson, Ó., personal communication).

CONCLUSION

Drug utilization research in Iceland is still in its infancy, but several important results have already been obtained, both in national and in international studies and comparisons. The health authorities are giving priority to further work and development in this field of research and the outlook for the continuous collection of data on every aspect of drug distribution and use appears promising, especially taking into consideration the advantages of performing such research in a country with a small but relatively well defined population.

Table 3. Prescribing of glucocorticoid preparations (without antibiotics) in 1972 and 1976

	Number of prescriptions	Quantity prescribed (g)	Cost (Icelandic kronur)
November 1972	1461	44161	660016
November 1976	1434	80418	3016786

Table 4. Changes in the waiting list and average waiting time in the dermatological department of the state hospital between 1972 and 1976

	End of 1972	End of 1974	End of 1976
Waiting list	23 patients	6 patients	1–2 patients
Average waiting time	23.5 days	1 day	–

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DATA COLLECTION IN NORWAY

I.K. Halvorsen,[a] M. Halse,[b] P.K.M. Lunde,[c] I. Baksaas,[c] B. Strømnes,[d] & K. Øydvin[e]

Since 1956 the entire population of Norway (approximately 4 million) has been included under the obligatory national health insurance scheme. Under this scheme hospital treatment is completely free and drugs supplied to out-patients are fully reimbursable when used in the treatment of 36 long-lasting or chronic diseases. The amount reimbursed in 1976 was 385 million Norwegian kroner or 37.5% of the total drug bill. In addition, most of the municipalities reimburse other drug expenses for old people, disabled persons, etc. In other respects, patients must pay drug expenses themselves. Altogether 55–60% of the total drug bill is reimbursed from public funds.

Drugs manufactured by the pharmaceutical industry must be approved by the Specialities Board before being registered and marketed. At present about 1850 drugs involving about 700 chemical substances are registered, a relatively low number compared with other countries. Some nonproprietary drugs are traditionally made in the pharmacies, but the number has declined during the last few years (it is now about 5–10% of the total turnover).

The sale of registered drugs (packaged for the consumer) and raw materials is restricted to the 288 licenced pharmacies of which 6 are hospital pharmacies. All pharmacies are supplied by a monopoly, the state-owned firm Norsk Medisinaldepot (NMD). Hospitals are supplied from the pharmacies, except in the case of large-volume parenteral preparations, which are delivered directly from Norsk Medisinaldepot.

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[b] National Centre for Medicinal Products Control, Oslo, Norway.

[c] Division of Clinical Pharmacology and Toxicology, The Central Laboratory, Ullevål Hospital, University of Oslo, Norway.

[d] Institute of Pharmacotherapy, University of Oslo, Norway.

[e] Norwegian Medicinal Depot, Oslo, Norway.

The source

By reason of its position as the sole wholesaler, Norsk Medisinaldepot is in a unique position to collect overall data on drug sales. The company has a well developed computer and data-processing system. Detailed sales figures are recorded by the computer simultaneously with the order-taking from the pharmacies. These data are organized in such a way that sales statistics can easily be extracted at various levels, with the following limitations.

(1) Geographical distribution. Sales figures can be provided for the country as a whole as well as for the 19 counties.

(2) Statistical period. The shortest statistical period is a month, but a quarter or a year is mostly used.

(3) Grouping of drugs. Sales data can be given for the single consumer-package or preparation grouped according to the 5 levels of the EPhMRA classification system (see chapter 2). Additionally, totals for subgroups and main groups are calculated.

(4) Units of measurement. For the purpose of drug utilization studies, the defined daily dose (see chapter 2 and reference *1*) is the unit of measurement mostly used, often in the form of defined daily doses per 1000 inhabitants per day. Additionally, data can be expressed in terms of value, number of packages of each preparation or, in special cases, weight of active substances (*2*).

However, the dose statistics mentioned so far do not include the sale of raw materials for production in pharmacies. As regards a few EPhMRA-groups, it might be necessary to consider this and possibly to calculate the pharmacies' share of the production.

It is also necessary to consider how accurately the sales figures at the wholesale level reflect the actual usage of drugs. The pharmacies' accounts indicate that their stocks are maintained on a short-term refill basis (*3*). Accordingly, the record of 3 months' supplies provides a good estimate of the drugs used in filling prescriptions. How much of the prescribed quantity is really consumed is a more difficult question. There are probably different patterns for different groups of drugs. But even if the relation between sales figures and the real consumption is unknown, the wholesale data, taken over a period of time, give a rough estimate of drug consumption.

Presentation of data

Norsk Medisinaldepot can provide sales statistics a few days after the preceding statistical period. Overall drug statistics have been made available to the pharmaceutical industry as well as to health authorities in Norway for several

years. For purposes of research and investigation, detailed statistical data, including retrospective data, have been made available on request.

A statistical yearbook on drug utilization (*4*), published by Norsk Medisinaldepot, gives statistical data for all drugs registered in Norway. Examples of how data appear in this publication are shown in Table 1 and Fig. 1. The examples cover the main group, antibiotics for systemic use, and one subgroup, tetracyclines. From the figures it can be calculated that approximately one-third of the population can be given a treatment for 10 days annually with systemic antibiotics.

Table 1. Antibiotics for systemic use (EPhMRA-group J 01). Overall statistics given as defined daily doses per 1 000 inhabitants per day.[a]

		1974	1975	1976
J 01 A	Tetracyclines and combinations	2.46	2.48	2.42
J 01 B	Chloramphenicols and combinations	0.02	0.01	0.01
J 01 C	Ampicillins and penicillins with enhanced effect upon Gram-positive microorganisms	0.63	0.70	0.81
J 01 D	Cephalosporins	0.03	0.04	0.05
J 01 F	Macrolides	0.08	0.11	0.17
J 01 G	Streptomycins	0.03	0.02	0.01
J 01 H	Penicillins	6.19	6.66	6.51
J 01 K	Other antibiotics	0.07	0.07	0.08
		9.51	10.09	10.06

[a] From Norsk Medisinaldepot (*4*).

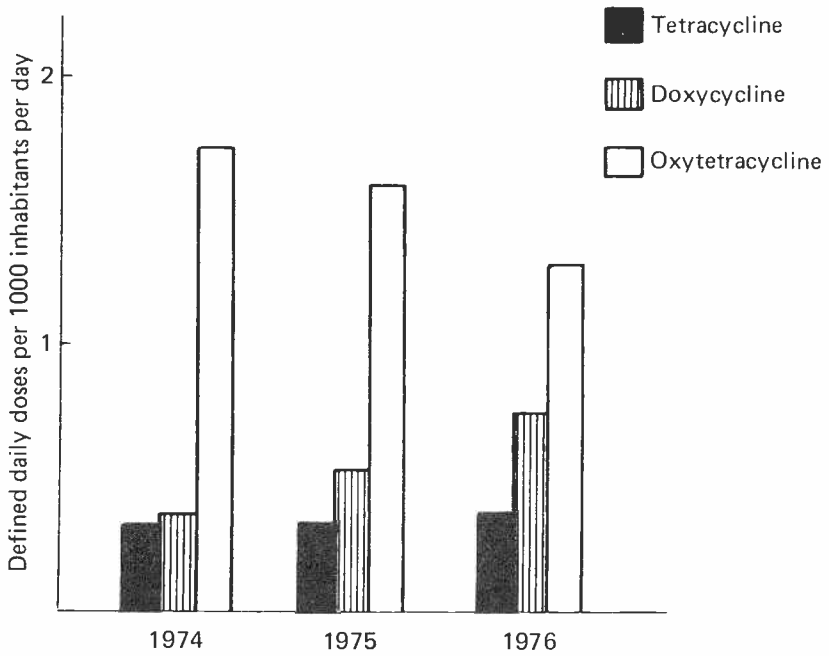
Use of the data

Rationality of drug utilization

The data shown in Table 1 and Fig. 1 might be held to indicate an overconsumption of antibiotics. However, the total amount used has been fairly constant for the last 3 years, even if changes have been recorded in the particular antibiotics used. The rationality of using certain antibiotics, or groups of antibiotics in preference to others might be discussed.

Trends such as those seen in the tetracycline groups will normally be apparent from the data and give rise to discussion. Efforts may eventually be

Fig. 1. Overall sales figures of tetracyclines in Norway, 1974–1976[a]



[a] From Jøldal & Halvorsen (5).

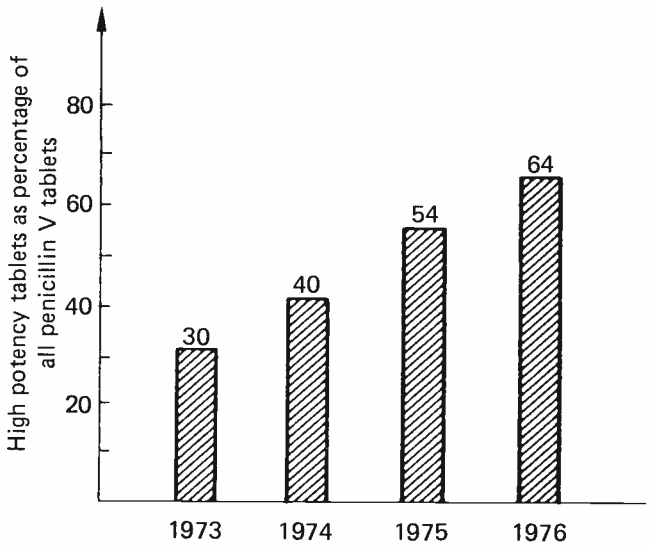
made to strengthen, arrest, or reverse the observed development. The effect of such efforts can be estimated by following the drug utilization statistics. An example is given in Fig. 2. The increased use of high potency penicillin V tablets (1 million units) might be the result of a recommendation published in a Norwegian compendium on the use of penicillins.

Adverse drug reactions

An organized reporting of adverse drug reactions (ADR) has been established in Norway. The number of ADR reports for a given drug can be related to the extent of its use and thus give a rough estimate of the risk ratio.

The practolol case illustrates some aspects of the usefulness of drug statistics (Fig. 3). From the available drug sales data it was calculated that approximately 12 000 patients were on practolol therapy in 1974 when the first reports of serious eye and skin complications appeared. A warning letter sent from the health authorities to all Norwegian physicians resulted in some 80 ADR reports. As seen in Fig. 3, sales figures for practolol dropped 30–40%

Fig. 2. Overall sales figures of high potency (1 million units) penicillin V tablets in Norway, 1973–1976



in a short time. The simultaneous increase in sales of other beta-blockers supports the view that the decrease in use of practolol was due to the information on its severe side effects.

When the peritoneal complications were reported, the Specialities Board decided to withdraw the drug from the market. The decision was published in good time before it came into force. This was done in order to give the physicians time to adapt the rather large number of practolol patients (approximately 8000) to an alternative therapy.

Need as a criterion for registration

One of the criteria for approval of drugs in Norway is need, as judged by the Specialities Board. For that purpose, sales data for equivalent drugs and for drugs in the same therapeutic group are taken into consideration.

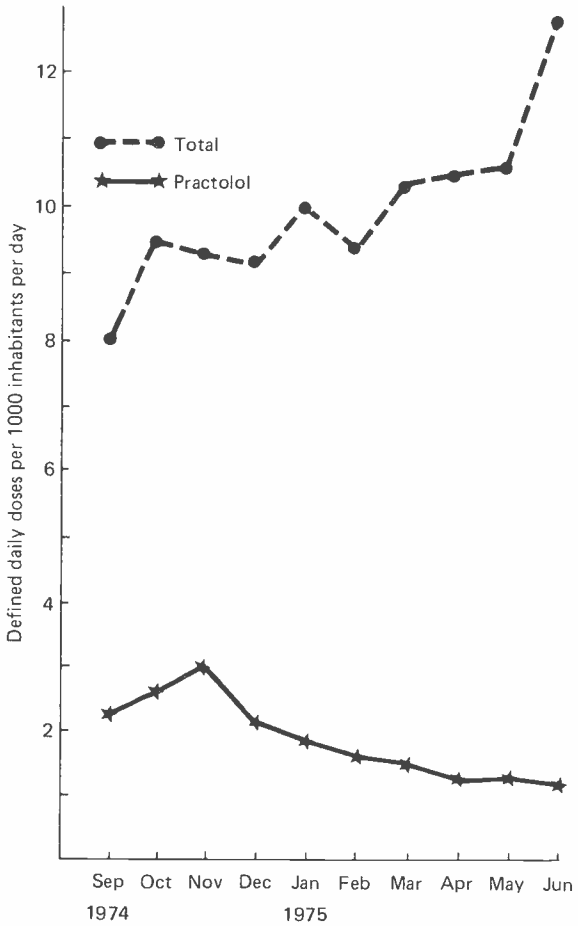
Plans for quality control

By planning how to make the most of limited resources in governmental drug quality control laboratories, priorities might be given to the most extensively used drugs.

Approval of price

Drug prices have to be officially approved in Norway. The total cost of a proposed price increase can easily be calculated from sales figures and is normally one of the factors taken into consideration.

Fig. 3. Overall sales figures of beta-blockers in Norway, September 1974 – June 1975



The source

To maintain short-time stocks of drugs in the hospital ward, pharmaceuticals are ordered from the pharmacy on special order sheets. These sheets are the source of basic data and serve as input for a computer system. This system is meant to serve two main purposes, the administrative (invoicing, etc.) and the medical aspects of drug utilization. From a modest start in 1971 with

5 major hospitals, the computer system has, after an overhaul in 1977, achieved a solid position, now covering around 60% of the nonpsychiatric beds in Norwegian hospitals.

Presentation of data

By this sytem, quarterly, half-yearly, or yearly information on drug supplies are obtained at different levels within the hospital (the ward, the clinic, or the hospital as a whole). The data are grouped according to the EPhMRA classification, and the defined daily doses and cost are the units of measurement used. The individual hospital can choose survey reports giving totals for all or selected groups at various levels and/or detailed information down to the individual preparation in the individual ward. The survey report on EPhMRA groups also presents the subgroup data as a percentage of the main EPhMRA group and as defined daily doses per patient-day for the period covered.

Use of the data

Drug committees

During the last few years, several hospitals have established drug committees. One of their tasks is to make recommendations on the use of selected drugs as the standard therapy in the hospital (*6–8*). For its preliminary work the drug committee needs, among other things, detailed information on the present use of drugs and traditional therapy, as well as more general surveys. Later it will be necessary to follow up the prescribing and check that the recommendations are being followed. Fig. 4 shows the effect of a recommendation concerning analgesics distributed at Rikshospitalet, Oslo, in January 1972 (*7*).

The clinicians

A comparison of drug utilization by different groups within a hospital (departments and wards) might reveal various therapy patterns that could be of interest to clinicians. Still more interesting would be comparisons between hospitals or even between corresponding departments in different hospitals. Such comparisons are not, however, done routinely, partly because the data from individual hospitals are not at present made available for that type of data processing. Some *ad hoc* studies of that kind have, however, been done (*9*). An example is given in Table 2, where the supplies of antibiotics in 2 hospitals are compared. When hospital B was informed of these comparative figures, the therapy pattern was immediately reviewed. The drug committee claimed that there had been an overconsumption of ampicillin. An information campaign among clinicians, accompanied by a suitable recommendation, led to a decline in use of ampicillin from 51.5% of the total number of penicillin

Fig. 4. Use of analgesics in Rikshospitalet, Oslo, in August 1971 and the second quarter of 1973

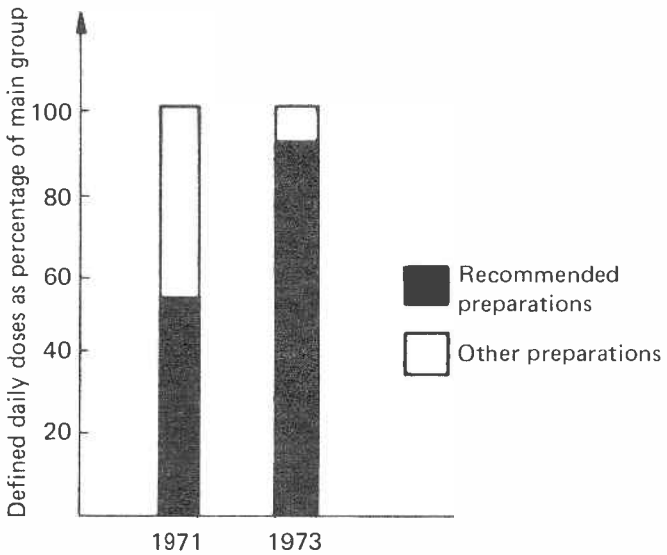


Table 2. The utilization of antibiotics in 2 hospitals in the first half of 1971[a]

	Hospital A	Hospital B
Broad spectrum antibiotics[b]	6.3%	14.5%
Penicillins[b]	93.7%	85.5%
	100.0%	100.0%
Ampicillin[c]	29.8%	51.5%
Sodium benzylpenicillin[c]	34.6%	57.5%
Number of penicillin doses per bed	28	125

[a] After Halse & Samseth (*9*).

[b] The figures are in defined daily doses as a percentage of the total for all antibiotics.

[c] The figures are in defined daily doses as a percentage of the total for all penicillins.

doses in 1971 to 26% in 1972, stabilizing at about 15% in the following years. Additionally, the change of therapy led to a marked decrease in the cost of treatment (*10*).

PRESCRIPTION DATA

The systematic handling of drug data at the prescription level is limited to narcotic drugs. The prescriptions reimbursed by the health insurance are not registered in such a way that meaningful statistics could be provided. Some *ad hoc* studies have been performed in the last few years.

Narcotic drugs

A computer monitoring system, based on data from all the prescriptions for narcotic drugs collected in the pharmacies, was introduced in 1970 (*5*). The purpose of the system was to give the health authorities an opportunity to follow and control the use of narcotics and to take action when consumption or prescribing patterns seemed unjustified. For that purpose, reports giving a rapid, detailed, and complete picture of prescribing and consumption patterns were needed. Such information has routinely been taken out of the computer system over successive quarterly periods.

The reports are investigated by the health authorities. As a consequence, 15–20 addicts a year have been referred for medical treatment for their dependence, and during the period 1970 to 1977, 38 doctors have relinquished their right to prescribe narcotic drugs (*11*).

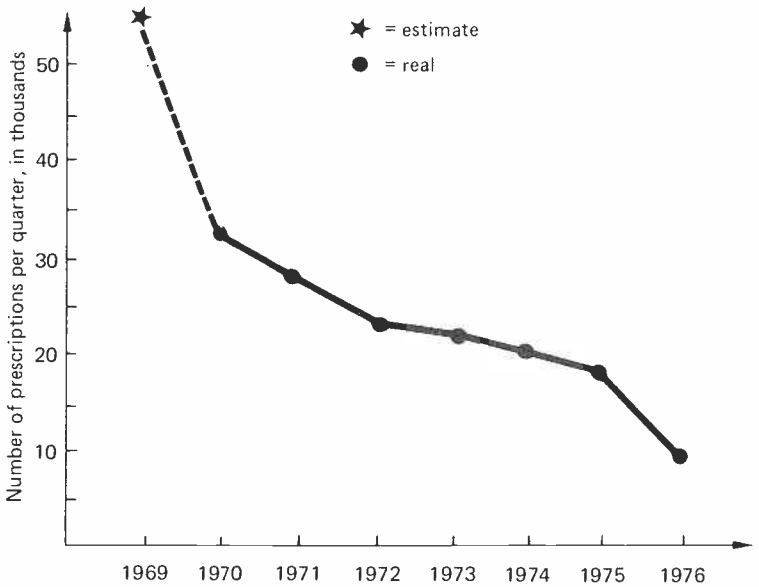
Additionally, comparative studies have been performed to follow the changes that have taken place as regards age, sex, geographical distribution, and drug preference (*12*). As expected, both the number of prescriptions and the quantity of drugs declined, especially after the monitoring system was introduced in July 1970 (Fig. 5). Further, it was found (Fig. 6) that elderly physicians were more frequently represented among the high prescribers than their younger colleagues, and a drug preference study demonstrates a marked transfer from ketobemidone to methadone from 1970 to 1975.

Ad hoc studies

Minor tranquillizers

To chart the utilization of minor tranquillizers in relation to geographic, cost, and individual factors, a prescription study was performed in 1970–71 (*13*). The study involved all prescriptions handled in 4 pharmacies in Oslo, together with the prescriptions reimbursed by the health insurance in Oslo, and in 4 sparsely populated municipalities and 2 smaller towns in Telemark county.

Fig. 5. Number of prescriptions for narcotic drugs delivered to outpatients in the fourth quarter, 1970–1976



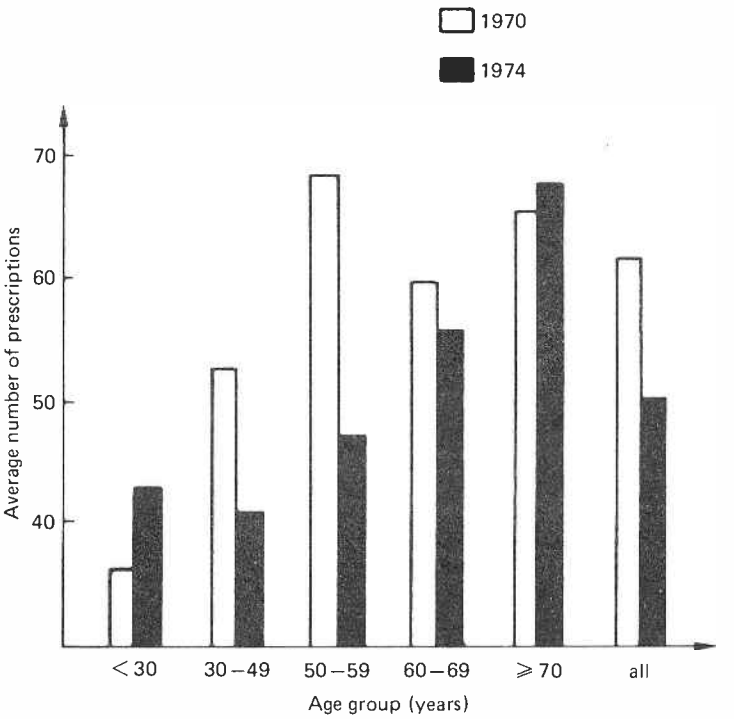
Up to July 1972, minor tranquillizers were reimbursable when used for special indications. The study indicated that about 50% of the minor tranquillizers used were reimbursed and that there was a very small difference in utilization between rural and urban municipalities in Telemark. In Oslo, however, the use per patient was somewhat higher. Further, the overall sales figures indicated that refusal of reimbursement did not significantly influence the utilization.

Total drug use in a small community

A comprehensive study (*14*) involved the collection of data on all prescriptions and two-thirds of the over-the-counter drugs for one year in a population of 1726 persons living in two isolated islands in the north of Norway, with only one physician.

Information was collected on the composition of the population (sex, age, and social factors), the diagnoses, whether drugs were supplied over the counter or on prescription, cost, and time of year. The data were collated and evaluated. In addition, the study demonstrated drug compliance, drug interaction, and adverse drug reactions, especially when self-medication was combined with prescribed drugs.

Fig. 6. Frequency of prescriptions for narcotic drugs for physicians with more than 30 prescriptions in the fourth quarter in 1970 and 1974



Hypotensives

On the basis of the overall statistics for the region, two counties with "high" and two with "low" overall data were selected for a study covering one month's prescriptions in 1975 (*15*), followed by a questionnaire to the participating general practitioners. The study involved 4095 prescriptions from 154 general practitioners, corresponding to 54% of those questioned. The results were used not only to analyse the utilization in relation to age, sex, blood pressure levels, and complicating diseases, but also to evaluate the therapeutic efficacy in terms of reduction in blood pressure following drug treatment.

The prescription pattern in the 4 counties corresponds very closely to the wholesale figures for hypotensives. This indicates that the wholesale statistics provide a fairly good picture, at least for hypotensives. The study has also given a basis for a tentative analysis of health economy in relation to the use of antihypertensive drugs and other expenses as regards diagnosis and monitoring of treatment.

CONCLUSION

The provision and publishing of overall drug statistics for the purpose of drug utilization studies has been made possible, first and foremost, by the governmental management of the wholesale trade in drugs. Norsk Medisinaldepot's knowledge about and interest in this field has resulted in this firm also becoming involved in developing and operating hospital drug statistics and the system for monitoring narcotic drugs.

However, drug statistics are useless if no one pays attention to them. During the last few years – particularly after the development of dose methodology – drug statistics have attracted wider interest and have proved to be a good tool for the health authorities and drug committees, and for the planning of research and the education of health personnel.

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DATA COLLECTION IN SWEDEN

B. Westerholm[a]

INTRODUCTION

All Swedish citizens (8.3 million inhabitants) belong to the National Health Service system. In 1954 the Swedish Parliament decided that certain drugs should be free of cost when prescribed for certain chronic diseases, e.g., insulin for diabetes and vitamin B_{12} for pernicious anaemia, while other drugs should be sold at a reduced rate when prescribed by a physician for treatment of a disease. In principle, this system has remained unchanged although the number of diseases for which certain drugs can be prescribed free of charge has increased and the proportion of the drug costs that the patient pays has changed.

In Sweden a drug has to be approved by the Board of Drugs before marketing. In 1977 there were about 2500 drugs (pharmaceutical specialities) on the market.

The number of physicians working with patient care amounts to about 12 000, of whom the majority hold positions within the National Health Care System.

There are about 750 pharmacies in Sweden. All, except 28 hospital pharmacies in the county of Stockholm, belong to Apoteksbolaget (the National Corporation of Pharmacies), a company in which the Government has the majority of the shares. It is responsible for ensuring an adequate supply of drugs, at a justifiable cost, for the general public and medical services throughout Sweden and, among other things, for making available statistics on drug consumption.

SOURCES OF INFORMATION ON DRUG UTILIZATION

Sales statistics

Since 1965, the total sales of drugs (combined sales to hospital and outpatient pharmacies) have been recorded by Läkemedelsstatistik AB (Swedish

[a] National Corporation of Pharmacies, Stockholm, Sweden.

Pharmaceutical Data, LSAB). The sales statistics are published quarterly in *Swedish drug market* (SDM) and are made available to governmental agencies and for specific research purposes. SDM contains information on the number of packages sold per package size of individual pharmaceutical specialities, the sales in monetary value during the quarter and percentage change from the previous year, and the running annual total and percentage change.

Since 1975, the National Corporation of Pharmacies also produces yearly sales statistics containing the number of packages and defined daily doses (DDD) sold per pharmaceutical speciality, and the cost for the country as a whole and for each of the 24 counties in Sweden.

In 1966, data processing of drug deliveries to individual hospitals and hospital departments was started (*1*). The system now covers almost all hospitals in Sweden (*2*). The data recorded are, among other things, hospital and department, drug, date of delivery and amount in packages, cost, and defined daily doses, and they are sent to the hospitals every 3 or 4 months and yearly. The National Corporation of Pharmacies and the main hospital pharmacy in Stockholm county are responsible for the data handling. The material is also summarized as total sales to hospitals in *Hospital SDM,* which has been published quarterly and yearly by LSAB since 1975.

Prescriptions

Since 1974, the use of drugs in outpatient care has been followed in a prescription survey run by the National Corporation of Pharmacies. It comprises a sample of 135 000 prescriptions per year (1 : 288 of all prescriptions) issued in Sweden (*3*). In this sample the drugs, amount, cost, dosage, age, and sex of the patient are recorded.

The individual drug purchases have been followed for 1 out of 7 of the population, or 17 000 inhabitants, in the county of Jämtland since 1970 (*4*). In this study, the identity number of the patient (which denotes, among other things, age and sex), the drug, with amount and dosage, dispensing pharmacy, type of prescription, and week of purchase are recorded.

There is as yet no continuous registration of the indications for drug prescribing or of the actual intake. Information on these questions is confined to data from studies conducted for limited periods of time (*5, 6*).

Unit of comparison

The defined daily doses (DDD) used have been worked out for the majority of drugs intended for systemic use in the Nordic countries on the initiative of Nordiska Läkemedelsnämnden (Nordic Council on Medicines) (*7*), which will regularly publish data on drug utilization in the Nordic countries, starting in 1978.

EXAMPLES OF HOW DATA HAVE BEEN USED

Access to data on drug utilization is a recent accomplishment and therefore the information has not been used to the full extent. The most important users of such data are the National Health Service, the Department of Drugs, local drug committees, the drug industry, politicians, research workers, and health planners. A few examples will be given here in order to show how the data have been utilized.

Cost analysis

The National Health Service has to pay for part of the costs of prescribed drugs in outpatient care. It is therefore important to follow the changes in prescribing. This is done continuously by means of the prescription survey described above. Kristoferson & Wessling (*3*) have shown that the mean cost per prescription has risen from 55 Swedish kronor in 1974 to 72 Swedish kronor in 1976. Psychotropic drugs and cardiovascular drugs dominate, with 15% of the prescriptions each, followed by analgesics with 10%.

Certain changes in the prescribing of individual drug groups have been observed during the period 1974–1976. Thus, the largest change is seen in drugs used for allergic diseases, especially in 1975, when there was a 50% increase. Also drugs for eye diseases and dermatologicals, as well as hormones and drugs used in metabolic disorders, show an increase, while drugs used for blood diseases and neoplasms have decreased.

The use of drugs in hospitals is paid by the local counties out of taxes. Even if the drug bill is a small part of the total expenditure of the hospital ($\triangleq 5-6\%$), it is important to follow the use of drugs. Analyses of the drug delivery statistics showed that albumin headed the drug bill in most hospitals. An analysis of the use of albumin was therefore undertaken (*8*). It was found that the total use of colloids (albumin, dextran, haemacel, plasma) had been rather stable during the period 1971–1975. There were, however, differences in the choice of colloids between hospitals of similar type. Thus, albumin constituted 10–50% of the colloids used while dextrans varied from less than 10% to close to 75%. This indicates that there is uncertainty as to which colloids to use. An estimate of the costs showed that if one university hospital with high albumin use changed to the pattern of another with low use, about 900 000 Swedish kronor could be saved per year. The findings led to a symposium in 1976 where guidelines for the choice of various colloids were discussed. It is too early as yet to say what effect these recommendations have had on the use of blood and blood components.

Regulatory agencies (Department of Drugs)

Drug utilization data are essential for the regulatory agency when it comes to the evaluation of marketed drugs, with regard to both therapeutic efficacy and adverse reactions. A few examples of how data have been used are given here.

Psychotropic drugs

Around 1970, a debate started in Sweden about the overprescribing, overuse and abuse of psychotropic drugs, mainly hypnotics, sedatives, and minor tranquillizers. Mostly, case reports were presented and very little was known about how the drugs were actually used. Later the various sources of information became available and an analysis of the use was made (*9*).

From the overall sales statistics it is obvious that the sales of psychotropic drugs have been rather stable during 1971–1976 if one measures the sales in number of DDDs per 1000 inhabitants per day (Fig. 1). Within Sweden there are differences between counties (Fig. 2–4), which should be interpreted with caution and motivate further investigation, since factors such as age distribution, disease pattern, and nearness to health care could have affected the figures.

From these figures it is also possible to produce a drug profile for each county. It was noticed that the ratio between benzodiazepines and barbiturates plus combined hypnotics in the most northern county was 2.9 while in the most southern county the ratio was 2.0.

Figures for deliveries of psychotropic drugs to departments of internal medicine (Table 1), for example, reveal considerable differences between hospitals (*10*). It is necessary to analyse the disease pattern and routines for handling the drugs in the wards in order to obtain an explanation of these findings.

The drug profile can also vary between departments of the same kind. Thus, the benzodiazepine deliveries varied from 20% to 58% of the total amount of hypnotics, sedatives and minor tranquillizers distributed to 5 psychiatric hospitals. Again it must be stressed that the indications for the choice of drugs have to be studied before any conclusions can be drawn concerning the therapy.

Fig. 1. Sales of psychotropic drugs in Sweden

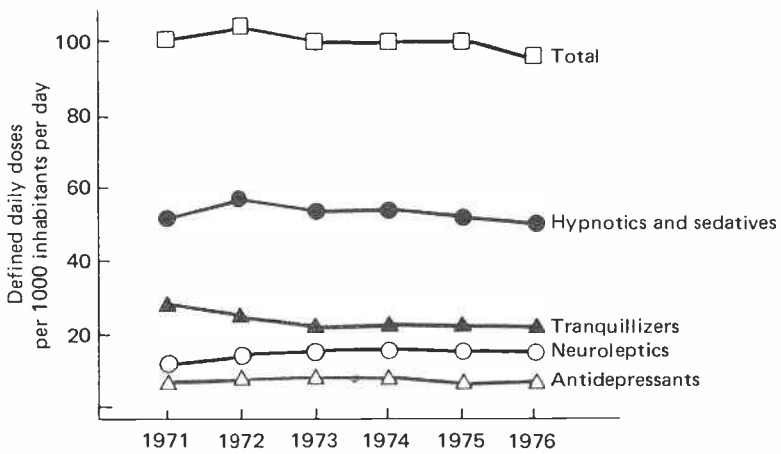
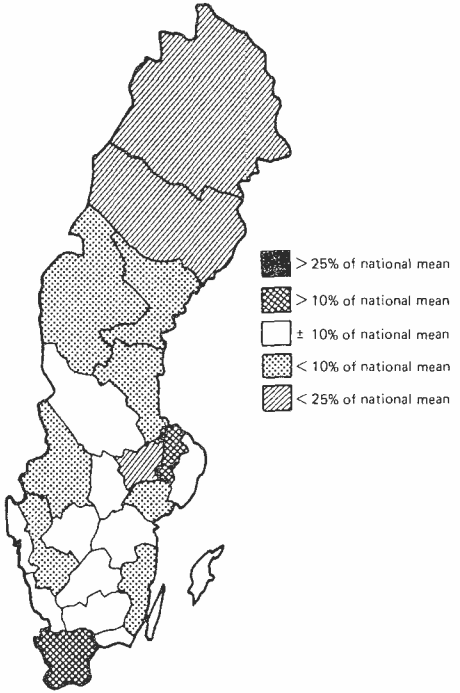
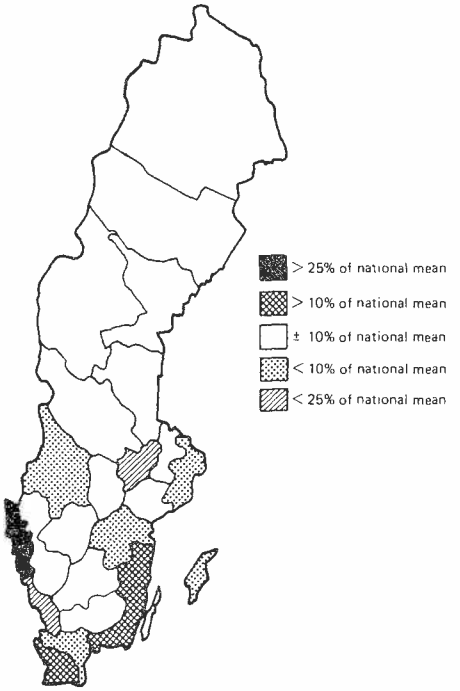


Fig. 2. Sales of hypnotics, sedatives, and minor tranquillizers in Sweden, 1976[a]



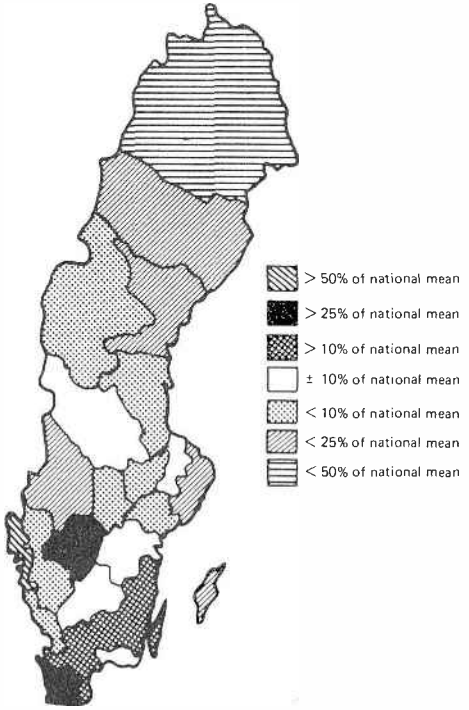
[a] National mean, 73.6 DDDs per 1000 inhabitants per day.

Fig. 3. Sales of neuroleptics in Sweden, 1976[a]



[a] National mean, 15.6 DDDs per 1000 inhabitants per day.

Fig. 4. Sales of antidepressants in Sweden, 1976[a]



[a] National mean, 6.6 DDDs per 1000 inhabitants per day.

Table 1. Deliveries of psychotropic drugs to departments of internal medicine in 8 regional and 8 district hospitals in 1975[a]

	Defined daily doses per bed-day[b]		
	Hypnotics, sedatives minor tranquillizers	Neuroleptics	Antidepressants
Regional hospitals	0.57 *0.20–0.65*	0.04 *0.02–0.06*	0.01 *0.008–0.02*
District hospitals	0.55 *0.32–0.95*	0.04 *0.02–0.06*	0.02 *0.009–0.04*

[a] See Westerholm (*10*).

[b] The mean figure is given first in Roman type, with the range below in italics.

From the prescription survey it is obvious that women receive more prescriptions than men. There is an increase with age, a finding that has also been made in a number of other investigations (e.g., *11, 12*). Information on the extent to which drugs are used sporadically or regularly by a patient is available from the Jämtland study (*4, 11*).

Among the 16 600 inhabitants recorded in this study, 2 566 (15.5%) obtained prescriptions for hypnotics, sedatives, and minor tranquillizers in 1970 (*11*). Occasional use (one purchase only) was seen in 7.4% of the population, whereas 1.2% were regular users (7 purchases or more). A new survey made 5 years later showed a highly significant reduction in individual purchases of these drugs as well as of other psychotropic drugs. Among those who had increased their purchases the increase was usually very slight. Signs of over-use or abuse were seen in only 4 patients. It should be remembered, however, that without knowing why and how the patients used the drugs one cannot judge when a justified and regular use of a drug turns into over-use and abuse.

From the Jämtland study it is also possible to obtain information on which doses are prescribed. Thus, it was found (Boéthius, G. & Sjöqvist, F., unpublished findings) that the mean doses of amitriptyline and nortriptyline prescribed were remarkably low, about 50 mg/day, as compared with a daily dose of 150 mg recommended for use by depressive patients. This indicates that patients might have been undertreated or that antidepressants were used for indications other than endogenous depression.

Our information on why psychotropic drugs are prescribed is very limited. An investigation conducted in 1973 at a district health centre (*5*) revealed that 11% of the patients visiting the centre obtained psychotropic drugs and that psychotropic drugs were prescribed for 14% of the problems/symptoms the patients came for. Insomnia, psychoneurosis, and mental depression were the main reasons for prescribing hypnotics, sedatives, and minor tranquillizers,

while neuroleptics were mainly prescribed for psychoneurosis and insomnia. Support was obtained for the suspicion that antidepressants are used for other indications than endogenous depression. It could be shown that 32% of the prescriptions were issued for psychoneurosis and 10% for various disorders.

Oestrogens

When the reports on oestrogens and endometrial cancer appeared in the medical press the question arose of how many Swedish women might be at risk. Sales data showed that the number of DDDs per 1000 inhabitants per day had risen from 3.65 in 1974 to 9.86 in 1976 (*13*). From data in the prescription survey (Table 2) it could be estimated that about 80% of the drugs sold were taken by women aged 45 years or older. On the assumption that each woman takes the drug for at least a year, the number of women exposed to the drugs in 1975 was estimated at 62 000 or 3.7% of the population. This figure is considerably lower than in the USA, where almost 50% of women in the menopause use oestrogens.

Table 2. Prescription survey 1974–1976: oestrogens for systemic use (sample 1 : 288)[a]

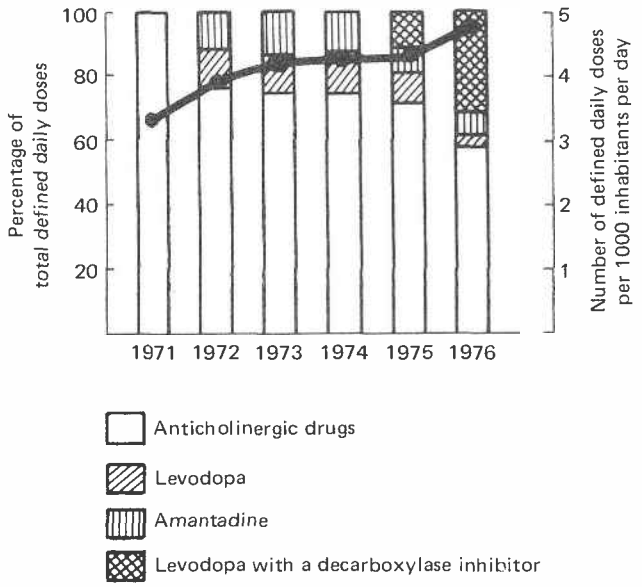
Age (years)	No. of prescriptions					
	1974		1975		1976	
	men	women	men	women	men	women
15–44	1	43	3	50	4	54
45–54	8	235	14	368	9	355
55–64	13	106	17	202	12	239
65–74	52	9	53	37	47	45
75–84	45	13	39	10	43	17
85 and over	14	2	11	1	3	4
Total	133	408	137	668	118	714

[a] See Westerholm (*10*) and Halse & Westerholm (*13*).

Influence of new drugs

During the period 1971–1976, the sales of drugs used for parkinsonism increased from 3.25 to 4.75 DDDs per 1000 inhabitants per day (Fig. 5).

Fig. 5. Sales of antiparkinson drugs



Levodopa was introduced in 1972 and represented a new advance in the treatment of parkinsonism. Levodopa had 15% of the market until 1974 when a combination of levodopa with decarboxylase inhibitor was introduced. The combination took about 30% of the market, while the sales of levodopa alone sank to 5%. It should be noted that anticholinergic drugs still have 50% of the market.

Information to local drug committees

In Sweden most hospitals have a local drug committee, the duties of which include the development of a drug formulary to be used in inpatient and outpatient care in the hospital area and analysis of drug utilization.

Besides the drug delivery statistics to hospitals, data on the drug sales in the whole area are being made available to the committees in the form of tables or maps (Fig. 2–4). It is quite clear that the use of therapeutic groups varies from county to county and a study is now being undertaken to elucidate why, for example, antidepressants are sold to a much higher extent in parts of southern Sweden than in the north.

EFFECT OF DRUG INFORMATION

Sales and prescription data can also serve as instruments for checking on the use of drugs that, because of the risk of adverse reactions, are contraindicated in certain age groups or that should be restricted to inpatients.

Because of the risk of enamel hypoplasia, tooth discoloration, and storage in skeletal tissue, tetracyclines should not be used by children below 8–12 years of age unless there is a special reason. The prescription survey (*10*) shows that such drugs are rarely used in young children (Table 3).

Because of the risk of aplastic anaemia, chloramphenicol should be used as a first choice only in typhoid and paratyphoid fever; otherwise it should be used only when other types of treatment are not acceptable. Thus, in practice, the use of chloramphenicol is restricted to hospitals and this was shown to be the case. The total sales in 1966 amounted to 0.13 DDDs per 1000 inhabitants per day, while in 1976 the figure was 0.013 DDDs per 1000 inhabitants per day. In the prescription survey, only 9 prescriptions were found during 1974–1976. It should be stressed, however, that with these small numbers the prescription survey does not give statistically significant figures.

Table 3. Prescription survey 1976: tetracyclines (sample 1 : 288)[a]

Age (years)	Number of prescriptions		
	men	women	total
0– 3	0	0	0
4– 8	1	0	1
9–12	4	10	14
13 and over	668	855	1 523
Total	674	865	1 539

[a] See Westerholm (*10*).

CONCLUSIONS

The data that are available today can give information on the extent of drug use, where drugs are used, local differences in the choice of drugs, the use in various age groups, and the changes with time, both on a general and on an individual basis. More information is needed about the indications for prescribing,

the real drug intake, and the results of treatment. Such in-depth studies require considerable resources and the cruder data that are available today should be used as indicators of what to look for.

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CHAPTER 8

DATA COLLECTION IN ENGLAND

F.J. Darby[a] *& G. Greenberg*[a]

In the United Kingdom the vast majority of prescriptions for drugs and appliances are written by general medical practitioners and it is on the basis of these prescriptions that a system of monitoring drug utilization has been established. There is no system of monitoring drug usage in the fringe areas of medicine, such as herbalism or naturopathy. Substances prescribed in those areas escape monitoring either of sales or prescriptions or adverse reactions. Similarly, there is no system of monitoring the usage of those drugs that are permitted to be sold over the pharmacist's counter without a prescription.

NATIONAL HEALTH SERVICE PRESCRIBING

After a general practitioner has written a National Health Service (NHS) prescription the patient takes the form to a pharmacist for dispensing. Normally 20p is payable for each item on the form, whether a drug or an appliance, but the patient may be exempted if he comes within certain categories. These include persons suffering from certain specified medical conditions, elderly people and children, persons with low incomes, and war service pensioners. About 62% of prescriptions are dispensed without charge to patients (*1*).

A prescription form carries the following information:

(*a*) the patient's name, address, and sex;

(*b*) the patient's age, if under 12;

(*c*) the exemption category, e.g., a patient under 16 years of age, a woman aged 60 or over, a man aged 65 or over;

(*d*) the prescribing physician's name and address;

(*e*) the dispensing pharmacist's name and address;

(*f*) the drug prescribed and date of prescription;

(*g*) the quantity dispensed, including formulation, pack size, etc., if appropriate.

[a] Department of Health and Social Security, London, England.

PRESCRIPTION PRICING AUTHORITY

Each month in England the pharmacist sends bundles of the NHS prescriptions he has dispensed to the particular processing division of the Prescription Pricing Authority (PPA) that is responsible for pricing in his part of the country. There are several divisions in Newcastle-upon-Tyne where the headquarters of the PPA is located and where there is also the one Investigation Division; there are seven other small pricing divisions located elsewhere in the country. When the month's prescriptions arrive, they are priced and arrangements made for the pharmacist to be reimbursed the sum due. In England in 1976 PPA processed about 182 million forms bearing nearly 293 million prescriptions. The total cost was about £451 million (*1*).

PRESCRIPTION MONITORING

After pricing has been completed, statistical information is extracted from the prescription forms. The prime purposes are to monitor the NHS drug bill and promote cost-effective prescribing by individual general practitioners. The first investigation routinely conducted by PPA concerns area prescribing. Its aim is to supply all family practitioner committees (the NHS authorities with which general practitioners are under contract) with statistical data on the number and cost of prescriptions dispensed in their individual areas. Each Family Practitioner Committee (FPC) is given information for its own area each month on:

(*a*) the total number of prescription forms;

(*b*) the total number of prescriptions on those forms;

(*c*) the average number of prescriptions per form;

(*d*) the basic and total costs;

(*e*) the average total cost per prescription;

(*f*) the total number of persons on physicians' NHS prescribing lists;

(*g*) the average number of prescriptions per person on lists;

(*h*) the average total cost per person on lists.

An annual tabulation is also prepared; that for 1976 for England showed an average total cost per prescription of £1.54 and an average total cost per person of £9.88. Many of the statistics issued by the Department of Health and Social Security (DHSS) are extracted from the information provided by the investigation and on it other statistical data are based. The information is also made available to organizations on request and much of it appears in the annual report published by PPA.

PPA's second set of statistics concerns individual general practitioners. The general practitioners are not employees of the NHS but are self-employed independent contractors. Although a general practitioner is required by his terms of service to prescribe any drugs or approved appliances that are needed for the patient's treatment, he may have to justify his prescribing decisions if the cost appears to be in excess of what was reasonably necessary. The procedure is dependent upon effective monitoring of physicians' prescribing patterns. Although originally designed with the disciplinary role in mind, the procedure has been extended to provide information of an educational character that will promote effective appropriate prescribing.

The experience of medical staff in the DHSS, which goes back many years and is probably unequalled in this field, is that the better informed the prescriber is, the more efficient and economical his prescribing.

In each month of 11 months of the year, the prescribing patterns of general practitioners in certain FPC areas are selected for special monitoring, so that in the course of the year the prescribing costs of all the general practitioners in England (20 500 in 1976) are estimated. The FPCs are sent lists for the month in question, which bear the following information:

(*a*) the name of every physician in the area;

(*b*) the average number of persons on each physician's NHS prescribing list;

(*c*) the number of prescriptions issued by each physician;

(*d*) the total cost of prescriptions issued by each physician;

(*e*) the average number of prescriptions issued per person on each practice's NHS prescribing list;

(*f*) the average cost per prescription for each physician;

(*g*) the average cost per person on each practice's NHS prescribing list;

(*h*) the ratio of each practice's cost per person to the FPC area's cost per person for the month in question and for the month monitored in the previous year;

(*i*) the averages for the FPC area for (*e*), (*f*), and (*g*).

Physicians are given extracts from the lists by their FPCs. The statement relates only to the prescribing of their own practice but enables them to compare their costs with those of their colleagues in the same area. The information includes the following:

(1) the number of prescriptions issued by the practice;

(2) the ratio of the practice's figures to the average for the FPC area of:

(*a*) the number of prescriptions issued per person on NHS prescribing lists;

(*b*) the cost per prescription;

(*c*) the cost per person on NHS prescribing lists.

If the practice's average cost per patient is 1.25 or more of the area average, the Investigation Division at PPA is asked to prepare detailed statements. These

give a complete breakdown for one month of the cost and frequency of prescribing of each physician in the practice. Examples are given of patients who received a large number of prescriptions, and the preparations and quantities involved are stated. The number of patients over the age of 65 – their costs are inevitably higher – and the proportion to the total of the physician's NHS list are shown. The physicians are sent copies of these detailed statements and are then usually visited by one of the DHSS's Regional Medical Officers (RMOs) to discuss the pattern of prescribing revealed by the analyses. The RMO is not concerned with disciplinary procedures – they are conducted from headquarters – but with enlarging on the information provided and promoting an informal exchange on therapeutics for the educational purposes previously mentioned. In 1976 there were 1144 contacts with general practitioners based on the investigation. In 65% of contacts over a 10-year period, two detailed statements at the most were required for prescribing costs to fall below the 1.25 level. Of all the physicians for whom statements were prepared, a reduction in costs followed in 87% of cases.

Drugs frequently give concern because of their doubtful therapeutic value or undesirable effects. The DHSS may ask PPA to prepare statistics on the prescribing of a number of drugs of that type during the same month as the monitoring previously described and for the same area. A sampling technique is used and the investigation, particularly suited for frequently prescribed drugs, usually runs for the whole of the yearly cycle, i.e., until all FPCs have been covered. The monitoring level having been determined statistically, reports are prepared for those physicians who have issued numbers of prescriptions exceeding that level, for instance of more than twice the national average. The DHSS then arranges for the RMO, provided with a statement detailing the prescribing frequency, to visit the physician to discuss the particular field giving rise to anxiety.

A similar investigation may be made to screen prescriptions issued throughout the country in any given month for certain listed drugs in which the DHSS is particularly interested at the time. These are often the habit-forming and/or "controlled" drugs. Because of PPA requirements the investigation is more suited to the scarcely used drugs and to only a limited number. Physicians frequently prescribing them are identified as explained in the previous paragraph and statements prepared. However, in contrast to the investigations previously described, there is usually a different selection of drugs each month but statements are prepared and visits made by the RMO in much the same way. There were 1182 contacts based on these two types of investigation in 1976.

PPA also sends to the DHSS individual prescriptions that appear to merit enquiry. This may be because the combinations on the prescription form appear to be dangerous, the quantities seem unjustifiably large, or the prescription is unusual in some way. The investigation may also concern new drugs, and trends and deviations may be identified. It is intended to isolate unreasonable or unwise prescribing in those physicians whose overall costs are not necessarily excessive. The RMO does not usually contact the general practitioner until a particular pattern of prescribing has been identified. In 1976 there were 702 contacts on that count.

BORDERLINE SUBSTANCES

A further field of prescription monitoring concerns the substances that lie on the borderline between drugs and such items as food and toilet preparations. General practitioners in the National Health Service may prescribe any drug they consider necessary for their patients, though they may be called upon to justify their prescribing decision. However, there are no powers whereby the NHS can pay for substances that are not drugs for patients who are being treated out of hospital in their own homes. General practitioners may, however, prescribe these "borderline substances" when, in the particular circumstances of the case, they may be considered to have the characteristics of drugs. Certain patent foods with a high protein content may, for example, be considered drugs when prescribed for hypoproteinaemia and gluten-free wheat starch for coeliac disease. If a physician prescribes a food or a toilet preparation and cannot show that his decision was justified, he must pay the cost of the prescription out of his own pocket. PPA screens prescriptions for "borderline substances" at the pricing stage. Unless it is appropriately endorsed the prescription is referred to the FPC so that enquiries may be made. PPA referred several thousand prescriptions in 1976.

SPECIAL INVESTIGATIONS

Finally PPA is constantly engaged in a number of small-scale investigations on behalf of the DHSS. These usually involve the extraction of prescriptions issued by certain physicians for particular drugs. For instance, the Home Office may be concerned about the unusual pattern of a physician's prescribing of "controlled" drugs of addiction. There were 280 visits made by RMOs to general practitioners in 1976 for discussions in that connexion.

RESEARCH

Sometimes a research unit will ask for all prescriptions written by a particular group of physicians to be monitored. Although these requests are met wherever possible, PPA's resources are limited. In any case, the use of the prescription statistics suffers from the handicap that the prescription form contains no information on the characteristics of patients or the conditions for which the drugs were prescribed. In special studies one way of overcoming this difficulty is for general practitioners to provide carbon copies of prescriptions with additional data added. This is also the method used by commercial market research organizations to provide data to manufacturers. PPA can provide no data on hospital prescribing except in connexion with prescriptions issued in outpatient departments for dispensing outside hospital; these prescriptions are not analysed in detail.

An especially important piece of research, dependent upon the investigations previously described, involves a continuing study of the characteristics and prescribing of a group of about 700 physicians who entered general practice in England and Wales in 1969–70. A selection of the prescriptions written by these physicians is forwarded to the Unit for Research in Drug Use at the Department of Pharmacy, Heriot-Watt University, at which data are put on magnetic tape and sent to the Medical Sociology Research Centre, University College of Swansea. There the information is analysed and is correlated with demographic, sociological, and medical data obtained from the physicians. A number of papers have been published on this unique study of the changes and trends that occur over time in general practice prescribing (*2, 3*).

Examples of the topics covered include prescribing repertoires, the influence of medical training and experience on prescribing, paediatric and geriatric prescribing, prescriptions written by ancillary staff, high-cost prescribing physicians, sources of drug information, and prescriber accountability. According to an editorial in *Update* (*4*), the study showed that "the new general practitioners' prescribing patterns tended to be highly individualistic and idiosyncratic and unrelated to their training". An editorial in the *British journal of clinical pharmacology* (*5*) mentioned that 47% of these general practitioners had "felt unable to form an unbiased assessment of a new drug", most of them claiming that "drug company activities" had contributed to the bias. Another editorial, in *The Lancet* (*6*), drew attention to 90% of the physicians having stated that drug company representatives were important in making known the existence of a drug "but the most helpful information about usefulness seemed to come from within the profession". It also mentioned the finding that overseas-trained physicians prescribed a higher proportion of proprietary preparations and were excessively represented among high-cost prescribers.

More data were obtained from the cohort physicians in 1976 and, after analysis, it should be possible to compare the results with the data obtained from them in 1971 and 1972.

Departmental surveys have been made recently by PPA in connexion with the prescribing of barbiturates and with a pilot scheme for providing physicians in 4 FPC areas with detailed information about their prescribing of selected drugs (*7, 8*). The results are awaited.

All pricing and investigative work carried out by PPA is manually based. Under active consideration at the moment is a proposal to introduce automatic data-processing (*8*). This would undoubtedly introduce a more flexible system that could give a greater variety of information. In the meantime PPA already uses a small number of staff in preparing data for the production of DHSS prescription analyses, an investigation separate from those involved in prescription monitoring.

Prescription analyses, based on a 0.5% sample, are not concerned with influencing in any direct sense the prescribing costs of individual general practitioners; they provide information to various interested divisions in DHSS on the number and cost of general practitioner prescriptions and indicate trends. PPA selects a 1 in 200 sample of prescription forms by taking 1 in 20 forms from a 1 in 10 sample of pharmacists in each FPC area. After the prescriptions have been priced, PPA codes prescription information including a drug number,

the total quantity paid for, the net ingredient cost and an identification of the prescriber (e.g., general practitioner, hospital physician, or dentist). The coding system covers about 14 000 different drugs and also provides information on the therapeutic group, whether a nonproprietary or a proprietary drug, the manufacturer, the year of introduction, the type of prescription (i.e., exempt from prescription charge or liable), the region, quantities, and net ingredient cost. The system identifies not only the name of the drug but also its strength and formulation; about 130 000 items are coded monthly (*8*).

After coding, the information is sent to the DHSS computer at Fleetwood for processing and the production of monthly, quarterly, and annual tabulations. It was from these data that concern arose about the continued large-scale prescribing of barbiturates; as a consequence a campaign, only recently concluded, to reduce their use was mounted by the profession and funded by the DHSS. Similarly information was provided about the level of prescribing of high-oestrogen oral contraceptives and this led indirectly to drug companies either ceasing the manufacture of drugs containing more than 50 μg of oestrogen or of ceasing their promotion for contraceptive use.

Another prescription analysis concerns the monthly provision of advance information. This is done by taking 1 in 4 of the sample pharmacists' prescription bundles and sending, by the 10th of each month, details to DHSS of the numbers of prescriptions, the numbers of those exempt from prescription charges and of those liable, and the numbers of contraceptive prescriptions. These bundles are then priced before the others; by the 20th of the month details can be sent of the total number of prescriptions and costs. These advance indicators of the cost of general practitioner prescribing are crude in character and fluctuate from month to month, but they are found useful within the DHSS. For instance they provide data that may initiate the preparation of supplementary estimates and can help in forecasting the sums required for remunerating pharmacists. In all they amount to about 3700 forms each year (*5*).

Monthly tabulations are produced that give details of prescriptions (both exempt and nonexempt from charge) by class of preparation, the type of formulation, and therapeutic group. Some information is also provided about certain individual drugs, but the main analyses on these are prepared quarterly and annually. PPA itself circulates each month details of all prescriptions that have been priced. The details consist of the number of prescriptions, the total net ingredient cost, details of fees, etc., paid to pharmacists for dispensing the prescriptions, and prescription charges.

Prescription data are published each year by the DHSS (*9*). Actual figures are given for the total numbers of prescriptions, the total cost, the net ingredient cost, the average cost per prescription, and the average cost per person on NHS prescribing lists. These figures come from PPA's pricing records. The 0.5% sampling gives the number and cost of proprietary and nonproprietary preparations; it also gives the number of prescriptions, the total net ingredient cost of prescriptions, and the average net ingredient cost per prescription for each Regional Health Authority and by therapeutic groups. The DHSS will provide, on request, a table that shows the monthly number and cost of prescriptions for England in a particular year. Individual drug information is at present not released outside the DHSS as it is regarded as "commercial-in-confidence".

Information is, however, made available to manufacturers about their own products. Also, unpublished information may be given on written request to persons outside the DHSS provided individual drugs cannot be identified.

ADVERSE DRUG REACTIONS

Any account of data relating to drug utilization in the United Kingdom would be incomplete without reference to the work of the Committee on Safety of Medicines (CSM) in the study of adverse drug reactions. In 1964 the Committee on Safety of Drugs, the precursor of the CSM, set up its "yellow card" system. All physicians and dentists in the United Kingdom were invited to use these cards to report unexpected toxicity and side effects. The wording of the card has since been revised and the phraseology currently employed requests reports of all reactions to recently introduced drugs and serious or unusual reactions to other drugs.

For several years the CSM received reports at a fairly steady rate of approximately 3600 annually; 54% of these were sent in by general practitioners, 17% by consultants, and 17% from hospital residents. Other sources included the pharmaceutical companies, from whom came about 5% of reports. Recently the rate of reporting has increased markedly, so that the current annual total is approximately 10 000. The reason or reasons for this increase are not known for certain, but it probably reflects to a large extent the greatly increased awareness on the part of the medical profession of the hazards that may be associated with the use of modern drugs. Further, a notice reminding prescribers to report has recently been introduced into each prescription pad.

The yellow card system is voluntary, but despite the consequent inevitable incompleteness of reporting it has proved to be a valuable indicator of some serious problems and has shown the necessity for the CSM to issue warnings of toxicity. Fifteen such warnings have been sent out in the *Adverse reactions series,* which is restricted to notifications of serious hazards. In cases where the risk is less serious or the evidence less conclusive, possible hazards are brought to the attention of the profession in the Committee's occasional publication *Current problems.*

Pharmaceutical companies are required to keep records of adverse reactions reported to them and to furnish the Licensing Authority with a copy of such records should the Licensing Authority so direct. It is also possible for the Licensing Authority to issue a special directive under the terms of which a company must report to the CSM all adverse reactions of which it is aware.

In addition to the voluntary yellow card system, and to the reports received from industry, the secretariat of the CSM, often in collaboration with workers from academic departments, has carried out epidemiological studies of special problems. Probably the best known of these have been the work of Dr W.H.W. Inman (*10, 11*) assessing the risks associated with oral contraceptives.

The CSM and its secretariat within the DHSS are assessing other possible methods of collecting information about adverse reactions and it is hoped that the CSM will shortly embark on a pilot study of one of the methods that have been extensively discussed.

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CHAPTER 9

DATA COLLECTION IN SCOTTISH HOSPITALS

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The vast number of drugs which have become available in the last 25 years have produced a revolution in the practice of medicine. Indeed there are between 30 000 and 40 000 medicinal products available on prescription or directly to the public in the United Kingdom and in 1976 over 34 million prescriptions were dispensed by pharmacists in Scotland. Despite, however, the use of many potent pharmacological agents it would appear that serious adverse reactions are a relatively rare occurrence. To detect these and assess their importance it is necessary to study large numbers of patients before valid conclusions can be drawn and to have information about their drug therapy recorded in a manner that will facilitate rapid and meaningful analyses.

Two approaches have been used in the routine collection of information about drugs prescribed in hospital in Scotland. The first, intensive surveillance, entails the collection of detailed information, usually relating to a small group of patients, while the second involves the collection of basic information about a usually larger population exposed to drug therapy.

INTENSIVE IN-HOSPITAL DRUG SURVEILLANCE IN GLASGOW

The techniques and problems associated with intensive surveillance of drug use and adverse effects are probably best exemplified by the Boston Collaborative Drug Surveillance Program and have been documented elsewhere (*1*). In 1973, medical wards in the Western Infirmary and the Stobhill General Hospital in Glasgow first participated in this programme and information was collected on 2580 consecutive admissions to 4 medical wards. The aims were:

(*a*) to obtain and analyse data on clinical drug usage in these wards in Scotland for comparison with participating centres in other countries;

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(*b*) to record details of medication taken prior to hospitalization in the same population;

(*c*) to compare the frequency of adverse effects of commonly used drugs in the Scottish setting with those found elsewhere by the Boston group.

Prescribing patterns and adverse drug reactions

The patients in the medical wards of the two Glasgow hospitals studied proved remarkably similar. Their average age was 56 years and the duration of hospital stay was 14 days. One half of those studied were male and the main causes for admission were cardiovascular disorders (35%), gastrointestinal disorders (11%), respiratory tract problems (11%), malignant growths (8%) and endocrinal disorders (7%). On average, patients received 4.6 drugs per admission; the range of drugs used in these hospitals was similar and the commonest indications for drug therapy were cardiac failure, pain, infection, arrhythmia, prophylaxis, and insomnia.

Intravenous fluids

While the range of drugs used in both hospitals was similar, intravenous fluids were prescribed twice as often in one of the hospitals as in the other. This difference could not be accounted for by differences in observed patient characteristics nor by selection bias or observational differences between the two hospitals, and it was unlikely to have arisen by chance. It seemed most likely to be due to the existence of different policies in the hospitals studied. Although it was not possible to estimate the beneficial effects gained by the greater use of intravenous fluids, it was clear that adverse effects were common, occurring in 15% of recipients, and that they could readily be reduced by more circumspect prescribing. Such data collection facilities allow for regular review of drug prescribing habits both within and between hospitals.

Antibacterial therapy

Of all prescriptions for antibacterial therapy, 70% were for only 3 drugs (ampicillin-amoxycillin, co-trimoxazole and tetracycline), and 65% of antibacterials in the medical wards were for the management of respiratory infections, usually in patients with pre-existing chronic obstructive airways disease (*2*). In two-thirds of such patients there was no good bacteriological evidence that an antibiotic was required. Since 11% of all antibiotic exposures were associated with undesirable side effects, it was concluded that the risks of therapy were greater than the benefits to be expected, at least in a substantial proportion of the patients studied.

Digoxin

The use of digoxin also proved of some interest. A total of 438 (17%) patients received digoxin, of whom a large proportion (22%) developed one or

more adverse effects. Of the 438 recipients, 263 were in sinus rhythm at the time of receiving the drug and 175 were in atrial fibrillation. The risks of adverse effects attributed to digoxin were independent of the basic cardiac rhythm at the time of starting therapy.

Drugs prior to admission

All patients were questioned about their use of medication prior to hospitalization. Only 372 (14%) stated that they did not take a drug in the month prior to admission. The most common reasons for taking drugs prior to hospitalization were headaches (18%), cardiac failure (16%), pain (15%), and anxiety (14%). Of the 2580 admissions to medical wards, 85 (3.3%) were attributed to the adverse effects of drugs taken in normal doses and a further 66 (2.6%) were admitted because of intentional or accidental overdoses. These findings are similar to those reported from other centres contributing to the Boston Program (*3*). The drugs most commonly implicated as causing adverse effects were aspirin, digoxin, warfarin, phenylbutazone, and insulin. By contrast the drugs most frequently taken in overdose were benzodiazepines and tricyclic antidepressants.

International comparisons

The subject of international comparisons of drug utilization is dealt with in chapter 14 and we shall not, therefore, discuss it further. It may be mentioned, however, that centres affiliated to the Boston group use the same data collection system and central computer facilities so that international comparisons of drug use and adverse effects are possible and often yield worthwhile results (*4*).

THE DEVELOPMENT OF THE ABERDEEN-DUNDEE PATIENT DRUG FILE

A standard form of prescribing and recording drug administration was introduced in Aberdeen in the mid-sixties (*5, 6*). Although the primary aim was to increase the efficiency and safety of drug handling procedures in the hospital situation, the routine availability of standardized records made the development of a simple drug information system feasible (*7*). It soon became apparent, however, that this would be a considerable task for a hospital group with 40 000 patient discharges per annum as it would have to cope with 150 000–200 000 prescriptions. Such a system would, however, have great potential in the study of many aspects of drug usage, including their effects (desirable or otherwise) in clinical practice; the ready availability of computer support made it worth while investigating the feasibility of collecting the information. Pilot studies in one medical ward in 1967 showed that it was possible to process and retrieve information about prescriptions. The value of this information was greatly enhanced by linking it with (*a*) patient identification

data (hospital registration numbers, age and sex), which were entered in the case record folder, and (*b*) diagnostic data recorded on a diagnostic summary sheet used for hospital morbidity statistics.

As the system developed it was necessary to construct a drug index. This contains the names of all drugs (including synonyms) used in the system and their corresponding 5-digit codes, and both are held in a computer dictionary (*8*). The drugs were processed by name only with automatic coding by the computer. The workload was shared; the drug names were entered by drug research staff and the patient identity and discharge diagnoses by the medical records staff. Computer programs were then written to allow linkage of the data and information retrieval depending on the drug problem being tackled.

By 1972, all major hospitals in the Aberdeen and Dundee area (4300 beds) were included, the discharge rate being approximately 70 000 per annum. At present, the file comprises 350 000 patient discharges and over 1 250 000 prescriptions.

Quality control and the patient drug file

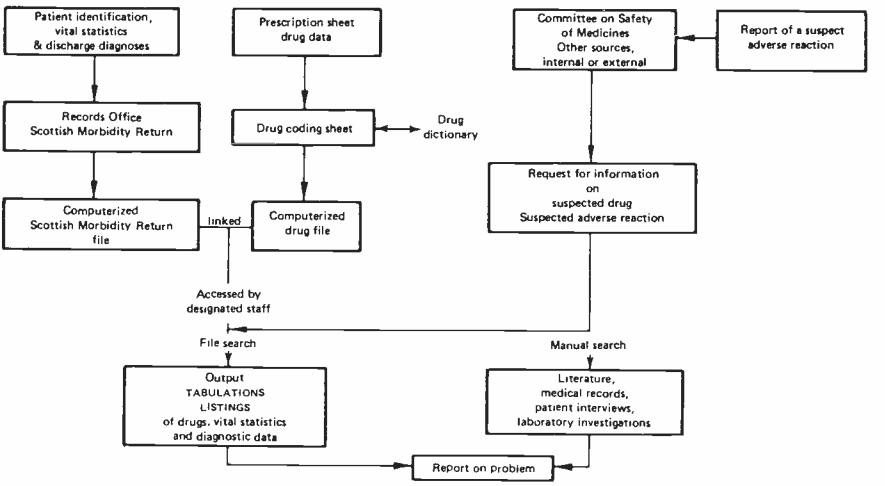
The value of any information system depends on the quality of the input, i.e., prescribing data, and this is checked from time to time. Raw data are entered onto coding forms and although there is no actual manual check on the quality of the data transcribed all punched cards are verified and subjected to a quality control programme that rejects cards bearing data not complying with certain criteria. The overall quality of the data is good (*9*) and is enhanced by the continuity of coding staff at both the Aberdeen and Dundee centres.

Uses of the patient drug file

Follow-up of suspected adverse reactions

In the main, the file has been used to aid *ad hoc* investigations of suspected adverse reactions – for example, in response to queries raised by the Committee on Safety of Medicines. The file permits rapid identification of all patients who have received a suspect drug in hospital and it is thereafter possible to follow up such patients by examination of their case records, by interview, or by carrying out appropriate investigations to determine the incidence of a suspected adverse drug effect (Fig. 1). Before any conclusion can be drawn, it is usually necessary to determine the frequency with which similar effects occur in a suitably matched population not receiving the drug. Controlled studies are necessary to confirm or refute suspicions and since the file includes parameters such as age, sex, diagnosis, and length of hospital stay, it may be used to obtain matching populations according to any of the above parameters but differing in respect of the drugs they have taken. Several studies have been undertaken using the file in this way, such as the investigation of a suspected association between the administration of tricyclic antidepressants and paralytic

Fig. 1. The Aberdeen-Dundee drug evaluation scheme



ileus. The matter was raised by the Committee on Safety of Medicines and a small study was initiated to ascertain whether such an association could be confirmed.

The hospital case notes of 213 patients who had been admitted to 4 general surgical wards during the period 1968–1974 and for whom amitriptyline had been prescribed during that period were scrutinized. Of the 213 patients identified, 21 were rejected for a variety of reasons leaving 191 patients for further study. Of these, 119 had had either no surgical intervention or an operation that did not involve the abdomen. In only 1 of the 72 patients who had had an abdominal operation was there a diagnosis of paralytic ileus. This occurred in a patient whose amitriptyline had been discontinued prior to surgery and for whom it had not been prescribed again until after the paralytic ileus had resolved. This preliminary study did not provide any recorded evidence to support the suspected association and no further action was taken.

Investigations have been carried out on other suspected associations, for example, between the following: (*a*) amitriptyline and sudden death (*10*); (*b*) frusemide and thrombocytopenia (*8*); (*c*) levodopa and direct antiglobulin tests (*11*); (*d*) *rauwolfia* derivatives and breast cancer (*12*); (*e*) beta-blockers and cold extremities (*13*).

Although the system was not designed for such a purpose, the diagnostic information it contains can also be examined over a period of time and it may be possible to detect changes in the frequency of certain pathological conditions pointing to drug-induced adverse reactions, e.g., blood dyscrasias or jaundice. In this way, previously unsuspected adverse reactions to drugs may be identified.

Drug-drug interactions and drug-disease interactions

The system also permits the identification of patients receiving two or more drugs in combination, thus facilitating studies of drug-drug interactions. These interactions may on occasion be beneficial, but not infrequently they are undesirable and the system has been used to study:

(*a*) the antagonism, as regards hypotensive effect, between adrenergic blocking agents and tricyclic antidepressants (*14*);

(*b*) the clinical outcome of an infective process in patients receiving oral tetracycline and iron simultaneously (*15*).

Again, matched populations are obtained as described above, the controls receiving only one of the suspect drugs. It is also possible to study drug-disease interactions, which may, of course, be of great importance, as in liver and kidney disease, where drug metabolism may be altered often leading to an increase in pharmacological and toxic effects.

Adverse reactions to long-term drug treatment

Patients receiving specific forms of therapy on a recurrent or long-term basis may be particularly at risk of developing adverse drug effects that were not detected at the clinical trial stage or in the first years of general use, since these may become manifest only after a long latent period. The ability of the system to identify patients on long-term treatment is, therefore, particularly advantageous and may be used in screening for possible carcinogenic, mutagenic, and teratogenic effects, e.g., in the case of reserpine and breast cancer (*12*).

Adverse reactions to new drugs

Monitoring of new preparations also becomes feasible. It can be done either retrospectively by reviewing the case records of patients receiving drugs such as beta-blockers or prospectively by the planned investigation of patients receiving new drugs. The file indicates which units within a hospital group are using a new drug so that patients may be followed up during and after their hospital stay for the purpose of identifying adverse reactions.

Drug efficacy

The facility to identify large numbers of patients receiving specific medication can also be used to investigate drug efficacy and this is likely to be particularly valuable in patients on long-term therapy. Indeed, such studies may produce different results from the artificially controlled conditions of the conventional clinical trial, because of the heterogeneity of patients' behaviour and in particular their compliance.

"At risk" groups

The system can also be used to study "at risk" groups, such as the elderly who may present special problems in respect of both efficacy and toxicity.

Studies are currently in progress to determine how drugs are prescribed for elderly patients admitted to acute medical and geriatric wards.

Information for medical and nursing staff

While the drug information system was initially developed to facilitate the investigation of adverse reactions, an attempt has also been made to use the information in the file to help medical and nursing staff in their practical management of wards and assessment of drug therapy. Bulletins giving information about recording procedures are circulated from time to time and because the system is an ongoing one it is possible to repeat analyses at a later date to ascertain if there has been any change in the prescribing practices of those to whom the information was circulated. While one cannot immediately assume a cause-and-effect relationship, it does not seem unreasonable to assume that, after exclusion of possible confounding factors, the feedback has been in some way responsible. Information regarding the prescribing practices of the various clinical teams has also been circulated and the pattern of use of new medicines is of particular interest. Initially, we avoided including information about costs in our bulletins in case the intention should be misunderstood, but subsequently, after several clinicians had expressed the opinion that such information would increase the value of the bulletins, it was included where appropriate. While it is important not to overplay this technique it is possible that it may have a further role in continuing education and may go some way towards encouraging more rational and economic prescribing; it may also have an application in general practice.

To be of optimal value it is essential that the information should be available as quickly as possible and as the data bank grows its scope as useful feedback will increase, thus enhancing its contribution towards improving patient care.

IMPROVEMENTS AND DEVELOPMENTS

By 1976, the Glasgow study had achieved its major aims and the data collection was discontinued in the medical wards, but a similar study was initiated in late 1977 in the surgical wards of two Glasgow hospitals.

In the Aberdeen-Dundee system, current concern is with what improvements can be made to the data collection and how the feedback of information should be developed. Although the present system undoubtedly has its limitations, these must be set against the cost of enhancement and, while it may be desirable to expand its scope, it is also important to strike a balance between what the file can immediately offer or be made to offer and what would have to be held on file for a full investigation of specific therapeutic problems. In practice so far, in each study it has been necessary to review original case records for information not on file; upgrading the system to include many

items on every case would be expensive and would not necessarily eliminate the need to refer to case records. Indeed, the current system may not be justified for any single purpose but the wide variety of problems related to drug usage that can be investigated makes it viable.

Since approximately 80% of all prescribed drugs are taken by patients in the community, attention is now being given to establishing accurate records of drugs recommended on discharge from hospital and in outpatient clinics. Studies are also in progress to assess the usefulness of obtaining data on drugs prescribed in general practice linked with patient morbidity data.

The two types of monitoring procedures described here have the common characteristic of availability of "denominator" data that are necessary to arrive at the frequency with which adverse reactions occur in relation to patient exposure to a given drug. In the Boston type system, such estimations may be made in the course of routine operations, while in the Aberdeen-Dundee system a special project must be mounted. The Boston system may also function as a hypothesis-producing source, since all prescribed medication as well as over 100 other items of data are routinely collected for each patient; the application of computing and statistical techniques makes rapid analyses of these data possible and facilitates the identification of unsuspected reactions. However, because adverse effects are often rare phenomena and because of the limited period of hospitalization, there are practical difficulties in studying adverse reactions that may not occur in the relatively small population studied or that may not be manifest for a long time after the initial exposure.

The Aberdeen-Dundee system is primarily a hypothesis-testing base. Because of the simple nature of its input and the accessibility of data on patients' vital statistics it is relatively cheap to run and, owing to the structure of the National Health Service and general practitioner cooperation, patient follow-up, even after discharge from hospital, may be carried out as required. The feedback of drug information locally has an educational role and various methods for increasing the efficiency of feedback are being explored. Indeed, the provision of information to those who prescribe aimed at enabling them to improve their use of drugs and care of patients might well be one of the most useful functions that can be fulfilled by a monitoring centre.

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CHAPTER 10

DATA COLLECTION IN NORTHERN IRELAND

D.G. McDevitt[a] *& C. McMeekin*[a]

METHODOLOGY

Northern Ireland, as part of the United Kingdom, participates in the National Health Service under which provision is made for the supply of drugs to patients who are under the care of their family physician. Every prescription written by a physician on an official form is taken by the patient to the pharmacist for dispensing. This form should bear the name and address of the patient, the name, address and serial number of the prescribing physician, and the name, strength and quantity of the drug or dressing to be supplied. At the end of each month the pharmacist codes these prescriptions and sends them to the Central Services Agency so that the cost of the drugs and service he has supplied can be paid.

Originally the examination and costing of each prescription was done by hand by specially trained staff, who, because of the amount of work involved, were only able to cost a 1 in 10 sample of forms from each pharmacy. In 1952, the system was replaced by the use of Hollerith punch cards with sorting and tabulating machinery, which increased the speed and efficiency of the pricing bureau, and since 1966, electronic data processing equipment has been used by the Agency. The information contained on each prescription is put on to computer tape to facilitate prompt payment of pharmacists, to assess the overall costs of prescribing in Northern Ireland, and to estimate the prescribing costs incurred by individual physicians.

From 1962, the information has been made available to the Department of Therapeutics and Pharmacology on a confidential basis. Data obtained from the Hollerith cards made it possible to trace and extract the original prescription forms written by general practitioners. This was, however, an extremely slow and tedious task, but gave access to the names and addresses of patients.

The information currently available to the Department comes in the form of a monthly computer printout presented in several different ways.

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(*a*) A "frequency table". In this a printout lists drugs by code number in numerical order with details of the number of prescription forms and the number of tablets issued in each month. This is regionalized geographically by showing the data separately for the 5 areas into which Northern Ireland is divided for administrative purposes in the Health Service.

(*b*) A second printout is available containing details of the prescribing of individual drugs for each prescribing physician and general practice in the Province.

In order to give the prescribing figures meaning and to allow comparison with other countries, the amount of each drug prescribed is related to population size. To compare the prescribing of different drugs used for the same purpose, the amount is expressed in "defined daily doses" rather than in grams or milligrams because the dosage within a group of similar drugs can differ widely. A list of defined daily doses is available in *Drug dose statistics* published by the Norsk Medisinaldepot (*1*).

From these two printouts, analysed in this fashion, it is possible in Northern Ireland to monitor the levels of prescribing of many drugs and thus to follow trends in prescribing, the usage of newly marketed preparations, and the influences of pharmaceutical advertising and government warnings on the prescribing of drugs or groups of drugs. Some of the uses to which this system has been put are described briefly in the next section.

Several limitations of the Northern Ireland data retrieval system must be mentioned. The figures supplied refer only to drugs requested by general medical practitioners for patients on National Health Service prescriptions. They do not include data for drugs paid for by private patients or dispensed by hospital pharmacies for inpatients or outpatients, though, in fact very little outpatient hospital prescribing is done in Northern Ireland. In addition, individual prescription retrieval is now difficult both for technical reasons and because of the need to preserve patient confidentiality. Information about patients' age and sex cannot, therefore, be readily obtained and patterns of prescribing related to these factors cannot be ascertained. The nature of the illness for which treatment was required is also unknown.

APPLICATION

Monitoring drug costs

A random sample of prescriptions written in an urban area in June 1965 was taken and all the prescriptions written by two physicians in a rural town during the same period were traced (*2*). The two practices were similar in size and composition but one of the physicians had prescribing costs above the average for Northern Ireland and the other had costs persistently lower than average. Every prescription was scrutinized to assess whether it was for:

(1) a preparation in the current edition of the British National Formulary (BNF);

(2) a proprietary preparation for which either an exact equivalent in the BNF could have been prescribed or, if this was not possible, for which a BNF preparation could have been substituted without substantially altering the expected effects for the patient;

(3) a proprietary preparation for which there was no suitable equivalent or alternative in the BNF.

The results are shown in Table 1. It was concluded that the BNF could have met most requirements of prescribers in general practice without detriment to the patients. Prescribing from the BNF, where a suitable equivalent or alternative existed, would have reduced drug-prescribing costs by about one-third, which, at that time, would have amounted to a saving of more than £1 million per annum in Northern Ireland. Neither the physician with high prescribing costs nor the physician with low prescribing costs wrote many prescriptions from the BNF (13% and 24% respectively) and they both prescribed for approximately the same number of patients during the month. The major difference between the two physicians appeared to be the quantities of drugs ordered on a single occasion, but the reasons for this could not be ascertained.

Table 1. Prescribing of preparations from the British National Formulary by doctors in urban and rural areas of Northern Ireland[a]

	Urban sample	Rural sample	
		High cost	Low cost
Total number of forms	455	968	969
Total number of prescriptions	695	1 558	1 300
Preparations from the BNF	110 (16%)	195 (13%)	313 (24%)
Proprietary preparations with an alternative in the BNF	526 (76%)	1 265 (81%)	866 (67%)
All other preparations and dressings having no alternative in the BNF	59 (8%)	98 (6%)	121 (9%)

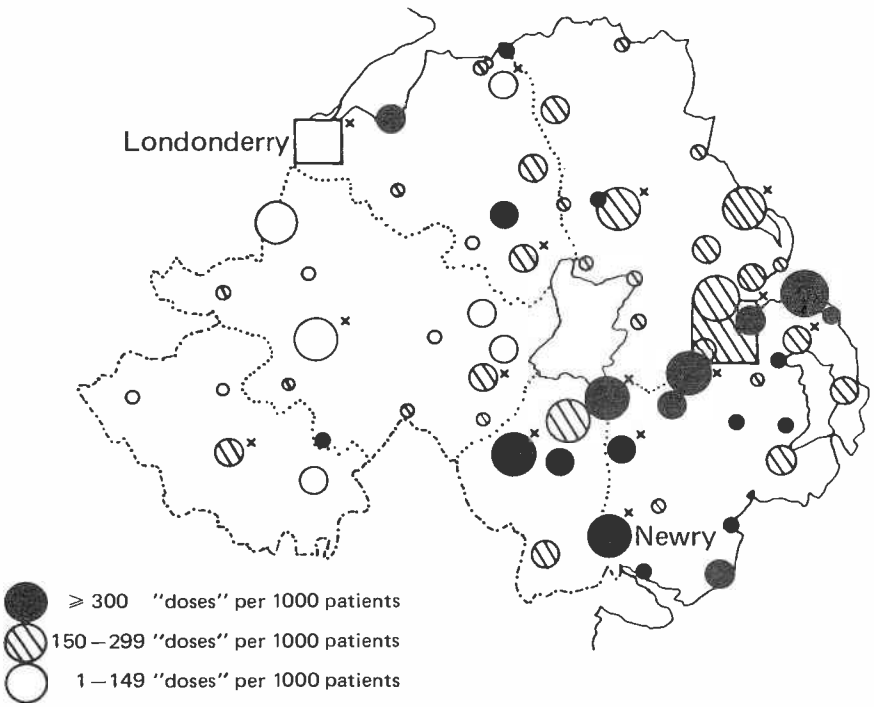
[a] From Wade & McDevitt (*2*).

Monitoring drug use

Geographical variation in prescribing in Northern Ireland

As already indicated, the data obtained in Northern Ireland allow regional variations in prescribing patterns to be estimated. Wade et al. (*3*) reported large differences in the amount of oral hypoglycaemic drugs prescribed in various areas of the Province (Fig. 1). Prescribing was high in the south-east, moderate

Fig. 1. Geographical distribution of prescribing of oral hypoglycaemic drugs in Northern Ireland, April–June 1966[a]



[a] Crosses indicate towns in which diabetic clinics are situated.

in the north-east and central areas, and low in the west. The towns of Londonderry and Newry were selected for further investigation. In both, the use of insulin was similar but Londonderry was a low prescribing area and Newry a high prescribing area for oral hypoglycaemics. All prescriptions for these drugs in both towns issued in one month were traced. It was found that the same number of prescriptions were written in the two towns but that, in Newry, much higher daily doses were prescribed. Further investigation revealed that, whereas in Londonderry a dietician could be consulted, none was available in Newry and physicians had resorted to using larger doses of oral hypoglycaemic drugs to control blood glucose levels in their patients.

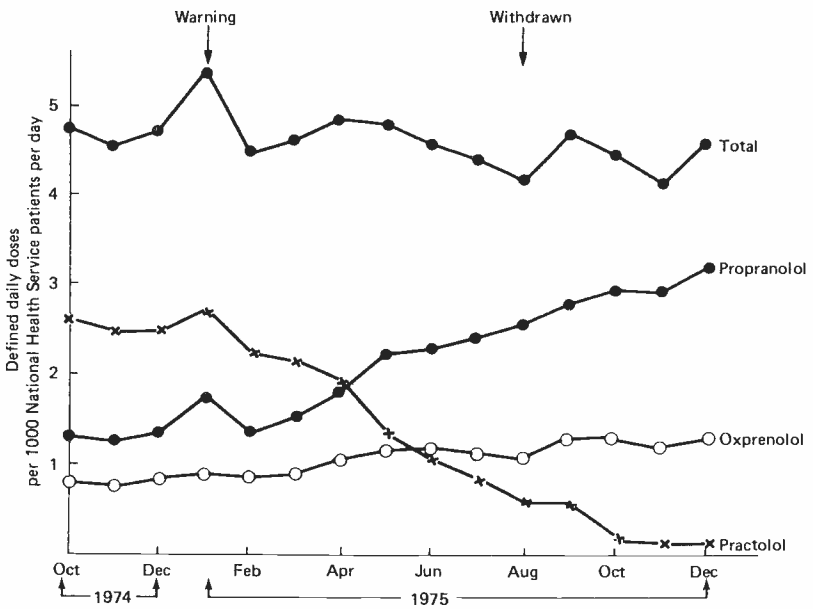
Large regional variations in the prescribing of antihypertensive agents have also been noted, but so far follow-up techniques have been inadequate to allow any investigation of possible regional differences in morbidity and mortality of patients with this disease.

The effects of reported adverse reactions

Wade & Hood (*4*) investigated the prescribing of chloramphenicol, amphetamines, and pressurized aerosols of bronchodilator drugs, which had all recently been associated with serious adverse reactions – aplastic anaemia, addiction, and sudden death. Despite warnings to physicians by the Committee on Safety of Drugs (now renamed Committee on Safety of Medicines) and widespread publicity of the dangers associated with the prescribing of these drugs, it was found that the frequency of prescribing changed only slowly over the years of the investigation. The adverse publicity produced no immediate effect. Indeed, it was felt that the decline in the use of isoprenaline-containing aerosols related more to the introduction and promotion of aerosols containing salbutamol.

More recently, however, concern about the adverse effects arising from the prolonged use of practolol, a beta-adrenoceptor blocking agent, resulted in a warning to the medical profession from the Committee on Safety of Medicines in January 1975. At that time it was the most commonly prescribed beta-adrenoceptor blocking drug in Northern Ireland but, by August 1975, when practolol was withdrawn from the market, the prescribing rate was well below that for other drugs in this group (Fig. 2).

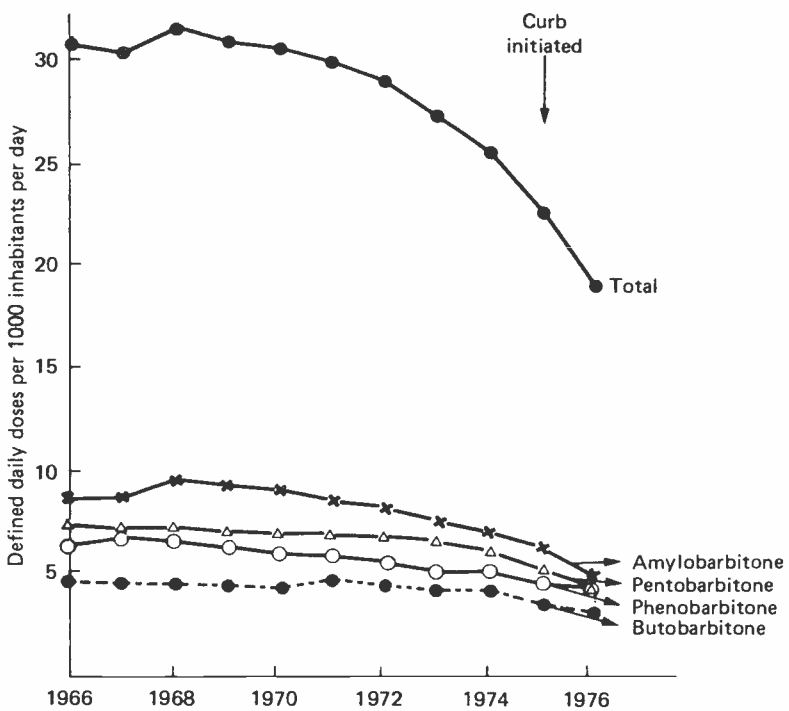
Fig. 2. Changes in the frequency of the prescribing of beta-adrenoceptor blocking drugs in Northern Ireland, October 1974 – December 1975



Several studies have also indicated that the frequency of prescribing of drugs with serious side effects may be substantially contributed to by a few physicians using the drug widely – 25% of the chloramphenicol prescribed in Northern Ireland in one month in 1962 was ordered by only 10 of 756 prescribing physicians (*5*) and 4% of general practices accounted for 20% of the total prescribing of amphetamines (*6*).

The campaign for the use and restriction of barbiturates (CURB) is an independent professional committee that acquaints physicians, dentists, and others with the hazards of prescribing barbiturates. Its success in Northern Ireland can be judged from Fig. 3, which shows the frequency of prescribing of barbiturate-containing drugs from 1966 to 1976. It is obvious that barbiturate prescribing was declining substantially before the campaign was initiated. The increasing availability of benzodiazepines may have been more significant (see Fig. 5).

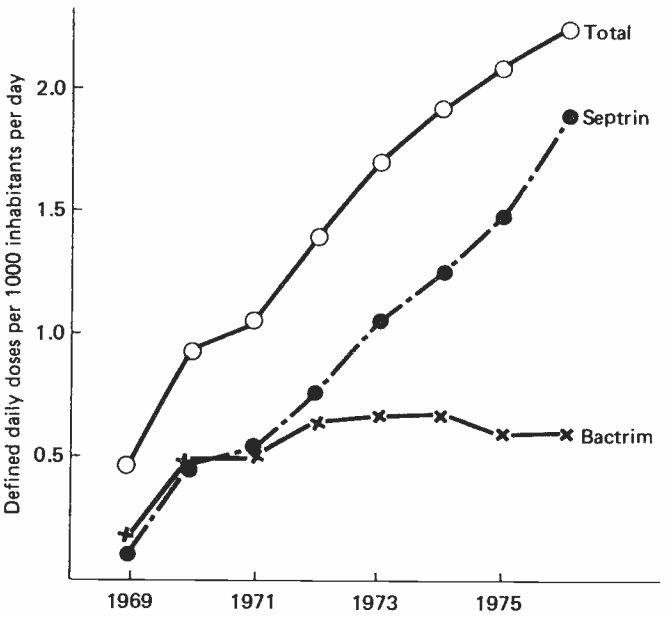
Fig. 3. Prescribing of barbiturates in Northern Ireland during the period 1966–1976



Monitoring the use of new drugs

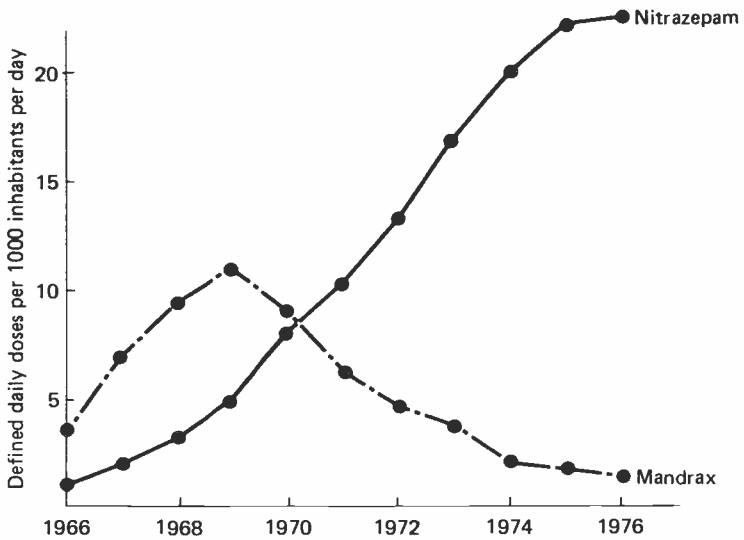
Co-trimoxazole is a broad-spectrum antibiotic containing trimethoprim, 80 mg, and sulfamethoxazole, 400 mg, in each tablet. It was marketed in 1969 simultaneously by two different pharmaceutical companies with identical preparations known as Septrin (Burrowes Wellcome) and Bactrim (Roche). In Northern Ireland, the prescribing of the two drugs was very similar in the first two years (Fig. 4) but, since 1971, a marked increase in the prescribing of Septrin has occurred while Bactrim continues to be prescribed at a constant level. Differences in promotional efforts between the two companies is a possible explanation.

Fig. 4. General practice prescribing of co-trimoxazole in Northern Ireland, 1969–1976



Mandrax, an hypnotic containing methaqualone, 250 mg, and diphenhydramine, 25 mg, was introduced just before the computer information became available in 1966. Between 1966 and 1969, there was evidence of increasing use but, thereafter, its decline coincided with the introduction and subsequent rapid rise in the prescribing of nitrazepam (Fig. 5). Wade & Hood (*7*) thought that the popularity of Mandrax indicated either physicians' dissatisfaction with the drugs already available or the need to try out a new

Fig. 5. General practice prescribing of Mandrax and nitrazepam in Northern Ireland, 1966–1976



drug. Either explanation could account for the initial prescribing of nitrazepam, which has, however, continued to be widely used.

Assessing disease incidence

If the drugs used for the treatment of a particular disease are not prescribed in any other circumstance, and if drug therapy is the principal or exclusive therapy for that disease, then the prevalence of the disease can be ascertained by estimating the amount of drug or drugs prescribed for it, making allowance for the defined daily dosage.

Such a system was used by Hadden & McDevitt (*8*) to assess the effects of the civil unrest (or environmental stress) in Northern Ireland on the incidence of hyperthyroidism. Patients treated in Northern Ireland with antithyroid drugs are almost all given carbimazole and it was assumed that 45 mg was a daily dose. Independent assessments of patients treated with radioiodine therapy and surgery were made and the number of patients in each treatment category in the 3 years before the civil unrest began (1966–1968) were compared with those in the first 3 years of the disturbances (1969–1971). Overall there appeared to be no alteration in the incidence of hyperthyroidism before and during the civil unrest, suggesting that environmental stress was not important in the pathogenesis of the disease. Assuming that the therapeutic dose ranges did not alter, the number of patients receiving a year's supply of carbimazole tablets in the control (1556.2) and study periods (1571.6) were almost identical.

CONCLUSIONS

As illustrated, the relatively simple system for collecting data on drug prescribing in Northern Ireland has allowed information to be obtained on important topics – namely, cost, patterns of prescribing, influences on drug prescribing and even the prevalence of disease. So far it has been an instrument for assessing what has happened already, but there is no evidence that the results have altered materially the future prescribing habits of the medical profession. Progress in this direction is more difficult to achieve but of ultimate importance.

ACKNOWLEDGEMENTS

This work was conceived and instigated by Professor O.L. Wade. Many others have made a major contribution to its progress – these include Dr Helen Hood, Dr P.C. Elmes, the staffs of the Northern Ireland General Health Services Board, now the Central Services Agency, and the Computer Branch of the Research and Intelligence Branch of the Department of Health and Social Services, Northern Ireland. Financial support has been gratefully received from the Nuffield Provincial Hospitals Trust, the Department of Health and Social Services, Northern Ireland, and the World Health Organization.

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CHAPTER 11

DATA COLLECTION IN THE NETHERLANDS

F.Samuels Brusse,[a] F.M. Bertens,[a] & D.D. Breimer[a]

GENERAL INFORMATION CONCERNING THE HEALTH CARE SYSTEM AND DRUGS

In order to provide a framework for better understanding of the drug utilization data some general information concerning the health care system is presented in Table 1. It shows the number of general practitioners

Table 1. Number of physicians, pharmacies and hospital beds per 100 000 inhabitants (January 1977)[a]

	Number per 100 000 inhabitants
General practitioners	35.7
— 3 669 nondispensing	
— 1 257 dispensing	
Specialists	54.7
Pharmacies	6.7
Hospital beds (general and university hospitals only)	493.1

[a] Sources: Chief Medical Inspector of Public Health, Chief Pharmaceutical Inspector of Public Health, and Central Bureau of Statistics.

[a] Department of Pharmacology, Subfaculty of Pharmacy, University of Leyden, Netherlands.

(dispensing and nondispensing), specialists, pharmacies and hospital beds (of general and university hospitals) per 100 000 inhabitants. Note the very low density of pharmacies. Besides pharmacists there are over 1200 drug-dispensing general practitioners serving approximately 25% of the population.

The Dutch health insurance system covers approximately 70% of the Dutch population. Everyone with an income below a certain level, which is revised periodically, is insured with an insurance association called a sick fund. The insurance provides free medical, hospital, and dental care and free drugs for the insured person and his dependants. The remaining 30% of the population is privately insured. At present there are about 70 sick funds in the Netherlands but this number is on the decline because of amalgamations. The sick funds are supervised by the Health Insurance Fund Council, an advisory board of the Government. In 1976, drugs accounted for approximately 13% of total health care costs. Since October 1963, when the "board for evaluation of drugs" was set up, the number of pharmaceutical specialities decreased from 4931 to 3480 in 1976.

It should be borne in mind that each form of presentation and each drug strength represents a different pharmaceutical speciality. The total number of trade names is only approximately 2000. Apart from the specialities there are around 3000 "generics"[a] on the market, mainly manufactured by wholesalers. Of the total amount of drugs prescribed, some 10–15% are prepared by the pharmacist and rather less by the dispensing general practitioner. One of the most important committees, established by the Health Insurance Fund Council, is the Central Medical Pharmaceutical Committee. Its main task is to compile – and subsequently to supplement and revise – a list of drugs and dressings that can be prescribed by physicians to sick fund members. Up till now pharmacotherapeutic recommendations have been given for most of the drugs on the Dutch market. These guidelines, known as "Regeling en Klapper", are not legally binding, but are considered to carry great weight. Criteria used are, of course, efficacy and relative safety, but comparisons are also made with drugs already on the Dutch market. Only if two drugs are equivalent in therapeutic respects can their price be taken into consideration.

DRUG SALES DATA

In the Netherlands, no detailed data on production and distribution of drugs are available. The Central Bureau of Statistics, which is a government agency, only provides figures on sales, exports, and imports of medical and pharmaceutical products, and on wholesale turnover in pharmaceutical commodities. This merely gives an impression of the size of the Dutch pharmaceutical market. The only other source of information is the pharmaceutical

[a] "Generics" are drugs produced and sold under their generic name, i.e., the international nonproprietary name proposed by WHO. They do not, therefore, bear a trade name and do not have special packaging.

industry itself. The Information Centre of the Pharmaceutical Industry periodically publishes a table containing the sales figures of the main therapeutic groups, according to the EPhMRA classification (Table 2).

Table 2. Drug sales on the Dutch market[a]

Therapeutic group	Wholesale sales to pharmacies in millions of guilders		% change
	1975	1976	
Alimentary canal and metabolism	105.4	112.9	7.1
Blood and blood-forming organs	19.8	21.1	6.5
Heart and circulation	147.0	170.0	15.6
Skin preparations	45.5	50.5	11.0
Urinogenital system (including sex hormones)	63.5	68.7	8.2
Hormones for general administration	8.8	10.2	15.9
Preparations for general infectious diseases	101.7	108.4	6.6
Muscular and skeletal system	51.9	57.2	10.2
Central nervous system	135.2	145.8	7.8
Preparations for parasitic diseases	1.0	1.3	30.0
Respiratory organs	54.6	61.5	12.6
Sensory organs	6.8	8.1	19.1
Others	11.9	16.6	39.5

[a] Source: Nefarma.

As for the over-the-counter drug sales, they are estimated at 15–20% of total drug sales. About two-thirds of these sales take place in nondispensing pharmacies (in 1976 there were approximately 3300 nondispensing pharmacies), representing only a very small portion of their overall sales. The number of over-the-counter drugs, as far as the pharmaceutical specialities are concerned, is less than 800 out of a total of 3480 packaged remedies.

DRUG CONSUMPTION IN HOSPITALS

In most hospitals, the cost of drugs is included in the charge per treatment-day, and therefore no central account is kept of drug use. This makes it hard to trace overall drug consumption. Large-scale collection of hospital data on drug

utilization is also difficult because of differences between the hospitals. Hospitals with more than 300 beds have their own pharmacy, while smaller hospitals have to obtain their drugs from a retail pharmacist or another hospital pharmacy, very often from several sources.

The National Hospital Institute conducts an annual inquiry among all Dutch hospitals in order to compile data for financial statistics (*1*). One of the findings has been that in general hospitals drugs account for approximately 2.5% of the charge per treatment-day. These data refer to total costs and do not allow a further breakdown into, for instance, pharmacotherapeutic classes.

A general feeling that a decrease in the total number of drugs was desirable led to the introduction of a formulary in several hospitals. Such a formulary is the result of a joint effort of physicians and hospital pharmacists. Its main objective is to cut down the number of different drugs prescribed. Another development aimed at improving hospital drug utilization is the introduction of a unit dose distribution system. The tendency towards data collection in hospitals by pharmacists is clearly shown by several authors (*2–4*). Controlled drug distribution and drug management systems may provide for large-scale data collection and future in-depth studies, which will enable comparisons of drug use to be made between corresponding departments of various hospitals.

OUTPATIENT DATA

Outpatient data on drug utilization can be obtained from various sources, such as the prescriber, the dispenser, or the patient.

The prescriber

Data collection at the prescriber level in the Netherlands is done very extensively by Intercontinental Medical Statistics (IMS) and to a far lesser degree by the Ministry of Public Health and the Environment.

The IMS collects data especially for the pharmaceutical industry. One of the activities of this marketing bureau is the Medical Index. A large number of general practitioners and specialists cooperate with the IMS by collecting prescription data. When a prescription is written, a copy is also produced on a special form. After the patient has left, some additional data are filled in, such as age and sex of the patient, diagnosis, and the desired effect of a prescribed drug. During one week every patient-physician contact is registered on such a form whether a prescription has been written or not. In this way, insight is acquired into drug treatment in relation to the morbidity pattern as seen by general practitioners and specialists. The major advantage of these data is that differences in prescribing even for one and the same diagnosis can be studied. However, as yet these data are only available to the pharmaceutical industry but attempts are being made to obtain access to the material, even if trade

names are not specified. For that purpose, the authors have approached the IMS, and their response gave rise to some optimism.

The Ministry of Public Health and the Environment, in conjunction with organizations in health care, has set up a network of sentinel stations with the purpose of gaining a better insight into the epidemiology of a number of illnesses and conditions, as they present themselves to the general practitioners (annual reports 1970–1975). Starting from 1970, each year data were collected on a limited list of items by about 50 general practitioners. Although the sentinel stations were primarily set up for continuous morbidity registration, they seem to provide a good opportunity to investigate certain features of drug utilization. The items of interest in this connexion are at present:

(*a*) consultation for family planning, prescribing of the "pill" and prescribing of the "morning-after pill";

(*b*) prescribing of tranquillizers.

A weekly account is kept of the number of patients seen, with reference to one of the selected items. Each year the list of items to be registered is determined by the programme committee, composed of members appointed by the Ministry of Public Health and the Netherlands Institute for General Practice. The number of patients to whom a tranquillizer was prescribed for the first time decreased over the period 1972–1974. Only patients with prescriptions for chlordiazepoxide, diazepam, medazepam, meprobamate, and oxazepam were registered.

It was suggested that the registration itself had an effect, because the physicians said that they became more critical about the prescribing of tranquillizers. The number of patients to whom a tranquillizer was prescribed in 1974 per 10 000 patients, by sex and age, is given in Fig. 1.

The sentinel stations will never provide an overall picture of drug utilization because, in order to avoid overburdening the general practitioners, the data collected remain very concise.

The dispenser

In principle, the pharmacies offer extensive possibilities for the collection of drug utilization data by means of the prescription forms and patient records.

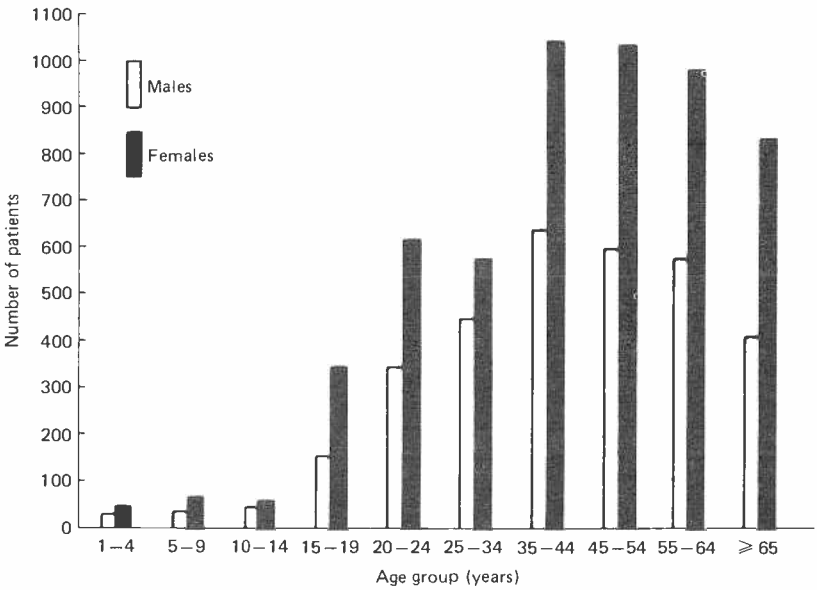
In the Netherlands, the pharmacist's fee for dispensing drugs is determined in two ways. The privately insured persons pay the wholesale price for their prescription medicines plus a certain percentage, whereas the sick funds reimburse the pharmacist in such a way that his personal income is independent of the amount of drugs dispensed. The bill made up by a pharmacist for a sick fund contains several components:

(*a*) a fixed sum per year for each registered sick fund patient;

(*b*) a fixed sum for each prescription unit covering the dispensing costs (a prescription unit, in Dutch "aflevering", is a certain amount of a drug prescribed in a given form, e.g., up to 30 tablets is 1 unit, from 31 to 60 tablets is 2 units, and so on);

(*c*) the wholesale costs of the medicines and dressings dispensed.

Fig. 1. Number of patients for whom a tranquillizer was prescribed in 1974, by sex and age per 10 000 inhabitants[a]



[a] Source: *Continuous morbidity registration sentinel stations,* annual report 1974 (*5*).

For the purpose of simplifying the administration, prescription calculating and controlling bureaus were set up – usually nonprofit agencies jointly operated by pharmacists and sick funds. The main task of these bureaus is to determine the number of units dispensed and the costs of drugs and dressings prescribed to sick fund patients. The prescription data are computerized and made available to the pharmacists and the sick fund.

A number of data are available per prescription item:

(*a*) the code number of the drug, which gives its name, strength, and pharmaceutical form;

(*b*) the month in which the prescription was filled;

(*c*) the quantity in prescription units;

(*d*) the quantity in number (tablets), weight (ointment), or volume (syrup);

(*e*) the costs.

In this way detailed data are collected on a large scale. A major disadvantage, however, is the lack of data on drugs dispensed to the privately insured patients. Some sick funds are using the data of the prescription calculating

and controlling bureaus in order to trace the high prescribers among physicians. This is done by the medical adviser of a sick fund, who also tries to correct this high prescribing. Honhoff (*6*), medical adviser of a sick fund, studied drug treatment in the Twente region and concluded that the prescribing behaviour of general practitioners was mainly influenced by the prescribing pattern of the specialists.

Some local investigations have been carried out with sick fund data. Canta et al. (*7*) studied the prescribing of drugs by 43 dispensing general practitioners. They compiled a list of the top 10 drugs, and made a comparison of the prescribing of these drugs by 8 groups of physicians. Lamberts & Wolgast (*8*) investigated the prescribing pattern of 4 general practitioners in a group practice in Rotterdam over a period of 2 years (1972 and 1973) on the basis of drugs supplied to sick fund patients.

They demonstrated 4 mechanisms in prescribing behaviour, for instance the fact that general practitioners can partly channel the stress they experience into their prescribing behaviour – the pressures of running an extremely large practice can give rise to an increase in drug prescribing.

In many pharmacies in the Netherlands a drug control system has been set up. The major object is to control combined use of drugs prescribed by one or more physicians and to prevent over-use. This is done in several ways. For instance, in many cases a "drug card" is kept for each patient or family. In this connexion, it is important to know that each sick fund member is registered with one pharmacy of his choice. This is not so for the privately insured persons, although most of them visit only one pharmacy. The drug card carries some general data (composition of the family, dates of birth, address, general practitioner, etc.) and data concerning drugs dispensed: the patient (in the case of a family); the name, form, amount, and dosage of the drug; the prescriber (general practitioner or specialist); and the date of dispensing. In the case of a relevant interaction between two or more drugs, the physician is notified. Furthermore, this has resulted in publications concerning combined prescribing of benzodiazepine derivatives (*9*), drug interactions with oral anticoagulants (*10*) and drug interactions with insulin and oral hypoglycaemic agents (*11*). A more advanced method of drug control makes use of a computer. The most important advantage is that control and possible action can take place before a patient receives any drugs. The major drawback is, of course, that it is more expensive, in spite of the fact that drawing up bills, stock-keeping, and other administrative procedures can be incorporated in the automation system.

Present investigation

At the moment a project using the data of a number of sick funds is being carried out by the authors at the University of Leyden. This study on the utilization of drugs was initiated by the Ministry of Public Health and the Environment, which continues to provide financial backing to the project. The objectives are to acquire a better insight into the prescribing habits of physicians and to determine and quantify the factors influencing drug prescribing. Data covering more than 1.2 million sick fund insured persons, distributed over 3 regions, are being analysed.

The 3 regions are:

(1) Nijmegen region with 150 464 sick fund insured persons;

(2) Rotterdam region with 433 204 sick fund insured persons;

(3) the province of Limburg with 640 000 sick fund insured persons.

Apart from the data on prescribed medicines some additional information concerning the general practitioner and his practice was made available by the sick funds, such as:

(*a*) the number of sick fund members per general practitioner and their sex/age distribution;

(*b*) the number of referrals to each specialty per general practitioner;

(*c*) the year in which a general practitioner graduated;

(*d*) the existence, if any, of a joint practice between two or more physicians.

A first inventory of prescribing habits in the Nijmegen region for 1975 was presented at the 1977 meeting of the Drug Utilization Research Group at Noordwijkerhout (Netherlands, April 1977). To show the difference in prescribing among general practitioners, two frequency distributions are given (Fig. 2). The criteria used are the number of drugs per 100 insured persons and the cost per drug. The first distribution shows a remarkable variation in the amount prescribed. On the left there is one low prescriber, while on the right there are 2 general practitioners prescribing almost 3 times as much per 100 insured persons. The second figure shows a smaller variation and the distribution tends to the left.

Table 3 shows a difference in prescribing between general practitioners and specialists for some therapeutic classes. For every given therapeutic class the specialist's costs per prescription item are higher, owing to the prescribing of more drugs and/or a larger quantity.

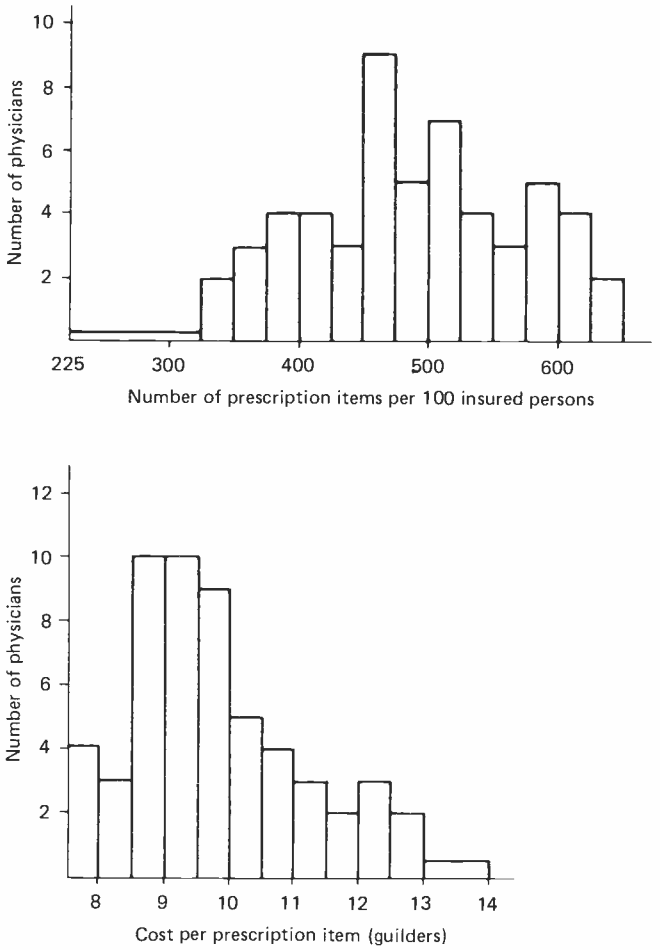
Using these data it is also possible to study the consumption of certain drugs on a monthly basis. For instance, a study on the effect of warnings concerning the use of practolol is in progress. So far no Dutch figures are available concerning drug utilization using the defined daily doses as a unit of measurement, but, with the detailed data on prescribed drugs being generated by the present study, it will be possible to fill in this gap and open the way to international comparisons.

The patient

A somewhat different approach in drug utilization research is to use the patient as a source of information. Both drug compliance and over-the-counter drug use are important; after all, the ultimate effect of drug administration depends to a large extent on the patient's cooperation.

One way of studying drug use among the population is by means of a questionnaire. In 1969/1970 such an inquiry was undertaken by the Sociological Institute of the University of Groningen. This resulted in a final report

Fig. 2. Prescribing habits of 56 general practitioners in Nijmegen in 1975: all drugs



in 1974 (*12*), with special sections on: (*a*) consulting a physician and self-medication; (*b*) use of drugs during the last month before the inquiry; (*c*) "left-over" drugs; (*d*) drugs in the home. This investigation showed, among other things, what people actually do with their drugs. For example, more than 50% of the people with a prescription had some drugs left over and only 10% discarded these. It was noticed that 9% of prescription drugs used during the last month before the inquiry were prescribed for someone else; 14% of prescription drugs were taken by patients who, on their own initiative, had resumed taking previously obtained drugs; 29% of all drugs used during the last month were obtained without prescription.

Table 3. Differences in prescribing habits between general practitioners and specialists, Nijmegen, 1975

Therapeutic class	General practitioners		Specialists	
	Prescription items (%)	Costs per prescription item (guilders)	Prescription items (%)	Costs per prescription item (guilders)
Analgesics	2.34	9.92	2.22	13.62
Antibiotics	9.10	15.24	5.02	31.14
Tranquillizers	8.39	5.65	5.93	10.87
Hypnotics and sedatives	5.92	4.85	6.80	7.62
All classes	100.00	9.73	100.00	16.17

Another method of studying drug utilization among the population is by determining plasma levels or drug concentrations in urine. In two districts, one with a predominantly urban population and one with a predominantly rural population, an epidemiological preventive study has been set up (*13*). A wide variety of data are collected, such as occupation, sickness insurance, religion, smoking habits, and medical history. In the next period of investigation questions will be asked concerning the use of analgesics. At the same time the urine, which is already collected routinely, is tested qualitatively and quantitatively for certain analgesics.

CONCLUDING REMARKS AND FUTURE DEVELOPMENTS

The collection of data for drug utilization studies in the Netherlands is not yet as detailed and comprehensive as researchers in this field would like it to be. Fortunately, there are some developments that will enable further investigations to be carried out in the near future.

Hospital data concerning sick fund patients are collected by an information centre of the sick funds. Plans are in progress to collect detailed figures on drug use during hospitalization of sick fund members, but the implementation of such a scheme will take some time.

One of the most interesting developments is a plan of the Health Insurance Fund Council to divide the Netherlands into 17 districts, with one prescription calculating and controlling bureau in each district. In this way, all outpatient prescriptions for sick fund patients will be registered.

Finally, it should be mentioned that a Health Interview Survey is being set up by the Central Bureau of Statistics. The object of this continuous survey is to acquire data on the total Dutch population concerning health status, consequences of sickness, drug consumption, etc. Questions concerning prescription drug use as well as self-medication drug use will form part of this inquiry.

ACKNOWLEDGEMENT

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CHAPTER 12

DATA COLLECTION IN CZECHOSLOVAKIA

L. Štika,[a] Z. Modr,[a] M. Salava,[a] & J. Hal'ko[a]

Czechoslovakia was the first European socialist country to supply drugs free of charge, both in hospital and in ambulatory health care. The drug utilization has been systematically investigated since 1952. From that date relatively precise data have been obtained on the utilization of individual drugs and whole groups of drugs, in terms of both quantity and costs.

Collection of these data was made possible after a uniform system of health care institutions had been gradually developed and after nationalization of the pharmaceutical industry and the wholesale drug trade, and later the pharmacies (*1*).

A system of committees for rational drug therapy, providing a complex tool for the control of therapeutic drug utilization, has been gradually created in Czechoslovakia (*2*). Its principal task is to help improve health care.

Generally speaking, there are 3 main sources of information on drug utilization in Czechoslovakia, namely:

(1) wholesale data provided by the state enterprise Zdravotnické zásobovaní (the Central Medicinal Stores) for the whole republic and for individual regions at 1-year intervals;

(2) prescription figures based on the data from medical prescriptions – in this respect the application of data processing systems is going on in several districts of chosen regions and in some hospitals.

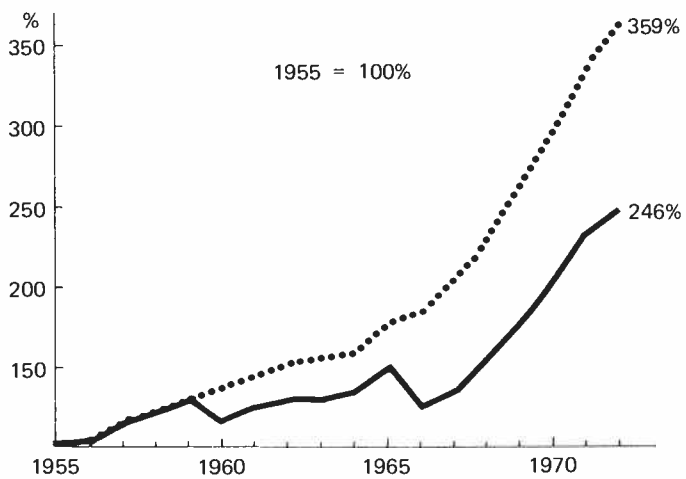
(3) analyses of the so-called "prescription sheets" in hospitals, all administrations of a drug being registered and finally processed by computer.

In the present communication we intend to describe the organization of data collecting systems. Some examples of the development and use of such systems in drug utilization analyses and in the regulation of drug prescribing are presented.

[a] District Institute of National Health in Prague 6, Research Centre of Clinical Pharmacology of the Institute for Clinical and Experimental Medicine, Prague, Czechoslovakia.

The simplest way seems to be to estimate total drug consumption from expenditure figures in retail prices. Provided that prices are sufficiently stable, the above data can be compared in relative terms (i.e., between drugs) as well as longitudinally in time. If, however, retail drug prices do change, then comparable (fictitious) prices have to be obtained by multiplying by an appropriate coefficient. Thus, after two price changes in Czechoslovakia the prices were converted to their original values in order to make possible comparisons of the general time trend. On this basis, Fig. 1 shows the development of expenditure on drugs in the course of 17 years since 1955. Drug expenditure rose by about 146% on the actual price basis but by about 25% on the converted price basis (*3*).

Fig. 1. Expenditure on drugs in Czechoslovakia[a, b]



[a] Full line — on basis of actual retail prices; dotted line — on basis of retail prices of 1955.

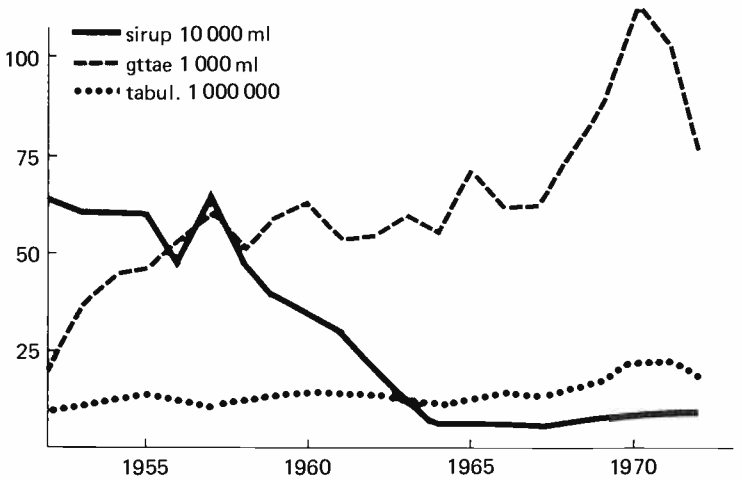
[b] Reproduced from Modr & Štika (*3*).

Logically, analyses of drug utilization based on expenditure figures always accentuate the economic aspect of this problem. Therefore, in basic analyses of the longitudinal development of drug prescribing from the professional point of view, it is more expedient to express drug utilization in terms of material units, i.e., quantity (*4*). An example is the change in the prescribing of

expectorants that occurred following a recommendation to prescribe syrups only for children: the prescribing of syrups sank to one quarter of its original level (Fig. 2).

Longitudinal surveys of drug utilization proved to be expedient from the national and regional points of view. The follow-up and analyses of chronological sequences are not, however, sufficient at the level of individual physicians.

Fig. 2. Consumption of expectorants in Czechoslovakia according to administration form[a]



[a] Reproduced from Modr & Pechek (*4*).

MANUALLY PERFORMED PRESCRIPTION ANALYSIS

New methods had to be sought. These methods are based on the exploitation of data marked on prescription forms, namely:

(*a*) the prescribing physician's name;

(*b*) the physician's department;

(*c*) the name, amount and price of the prescribed drug;

(*d*) the age and sex of the patient;

(*e*) the code of the dispensing pharmacy and day of delivery.

Thus, both the checking and appraisal of drug consumption came closer to both the physician and the patient, and the data thus obtained express more adequately the actual drug consumption by patients.

The prescription analyses are carried out either by members of the drug committees or by physicians delegated by them. The information thus gained can then be compared with the patient's other health documents on the occasion of so-called methodical visits paid by appropriate specialists to the physicians concerned. In practice, excellent results were also obtained when the physicians themselves analysed their own prescriptions; their results were then checked by experienced specialists.

Although the methods described proved to be very good in practice and contributed considerably to an improvement in the level of drug therapy in our Republic (obsolete drugs have been abandoned, the use of symptomatic remedies has markedly decreased, therapeutic incompatibilities have become rare, polypharmacy has declined, the prescriptions issued have been better documented in medical records, etc.), nevertheless, the procedure still suffered from many drawbacks. The most serious of these was the enormous tediousness of manual prescription processing so that the prescriptions of relatively few physicians could be analysed, and it was not possible to compare more than three criteria.

PRESCRIPTION ANALYSIS USING AUTOMATIC DATA PROCESSING

To expand the number of items that could be checked and to involve more, or all, physicians, a project in which electronic data processing was applied to prescription forms for the purpose of follow-up and analysis of drug utilization was elaborated as early as 1967 (*5*).

The basic data source was still the prescription form, but use of the computer made it possible to include additional data, namely, the patient's identification number (giving his date of birth and sex) and the code number of the diagnosis for which the drug had been prescribed (the WHO ICD[a] code number is entered on the prescription form by the physician).

The prescription form was adapted for this purpose. Four different modifications were made:

(1) addition of a stamp with the code number of the physician and a square where the diagnosis has to be filled in;

(2) use of a separate part of the prescription form for all codes to be entered; the first part is sent to the computer centre and the second, uncoded, part remains in the pharmacy;

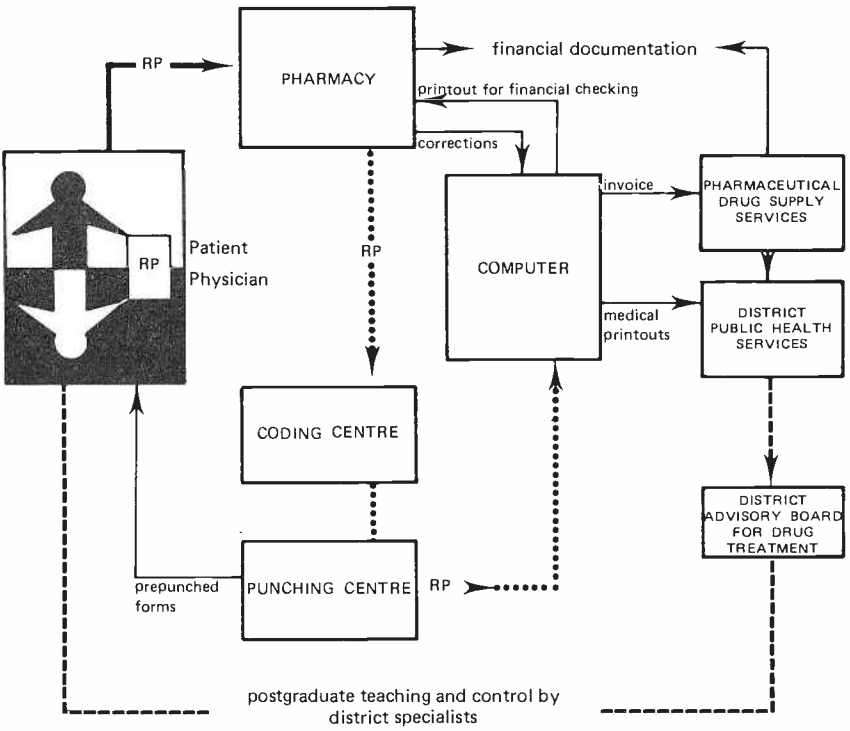
(3) concentration of all coded figures in one column of the prescription form in order to simplify the work of computer centre staff;

[a] *Manual of the International Statistical Classification of Diseases, Injuries and Causes of Death, ninth revision.* Geneva, World Health Organization, 1977.

(4) use of a punchcard prescription form. The code number of every physician, together with the code number of his specialization and his attachment to an individual polyclinic and its department, is prepunched on the card.

A diagram showing the route of the prescription form and of the information gained by this last system using a prepunched prescription form is presented in Fig. 3.

Fig. 3. Scheme of automated processing of medical prescriptions[a]



[a] Reproduced from Štika et al. (6).

In the future, an extension of a similar system should make it possible to cover all activities connected with the organization of the wholesale and even of the pharmaceutical industry.

In the Czech Socialist Republic, electronic processing of prescription forms has been performed in only a few health institutions so far, for instance, in Prague, in the regions of central Bohemia, eastern Bohemia and southern

Moravia, and in the health care system of the state railways. Similar methods are used in the Slovak Socialist Republic in several country districts and in the municipal health services of the Slovak capital, Bratislava.

All these systems also collect and store data on diagnoses for which drugs have been prescribed. The storage of the patient's identification number makes it possible, in case of need, to link it with other sources of information, e.g., the "working incapacity records", patients' histories recorded by hospitals, data in registers of births and deaths, etc.

The system may facilitate specialized selective investigations capable of processing several criteria in mutual combinations. Thus, for example, it is possible to find out what drugs have been prescribed for certain diseases, for what diseases a certain drug is prescribed, how the therapeutic stereotypes of individual physicians change, what drugs are prescribed for certain groups of the population (e.g., with regard to age, sex, occupation). It is known that stereotyped behaviour of physicians, even the repetitive prescribing of proven drugs, may hamper the introduction of new, more effective, therapy.

EXAMPLES OF THE USE OF DATA

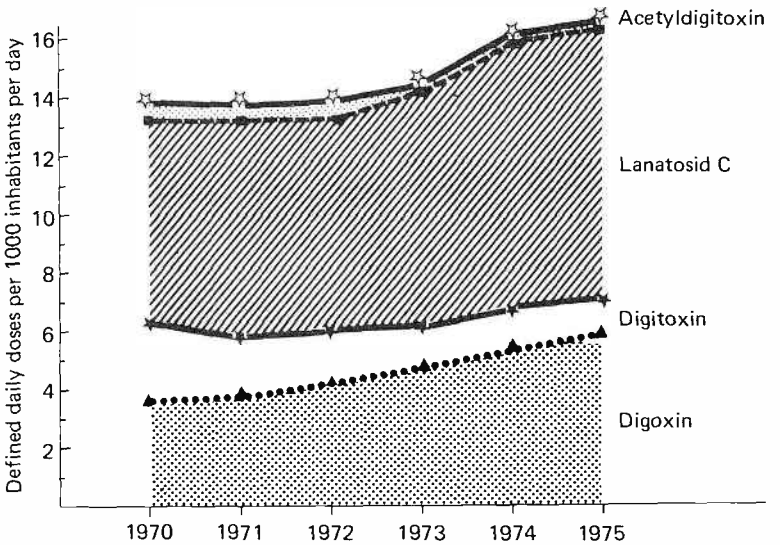
To illustrate the use of different data collection methods, some figures on the utilization of cardiovascular drugs are used. Moreover, the cardiovascular drug utilization analyses provided some opportunities for evaluating the influence achieved in practice by the Cardiovascular Diseases Control Programme. This Programme represents one of the main contemporary tasks of Czechoslovak health care policy.

The total consumption of cardiotonics in Czechoslovakia based on the data of the Central Medicinal Stores and expressed as defined daily doses (DDD) (*7*) is characterized by a steeper increase from 1973, when the first phase of our Cardiovascular Diseases Control Programme started (Fig. 4).

The increase in the total consumption of cardiotonics is caused mainly by the increase in lanatoside C consumption. However, this increase would be clearer if the DDD used expressed better the relative therapeutic potency of lanatoside C and digoxin. It is at present accepted that this ratio stands at 4 : 1. In our opinion, however, the ratio 3 : 1 would be more correct. According to the principles of the Cardiovascular Diseases Control Programme, the prescribing of digoxin is widely recommended. It has to be admitted, however, that we have not yet succeeded in restricting the traditional prescribing of lanatoside C in favour of digoxin.

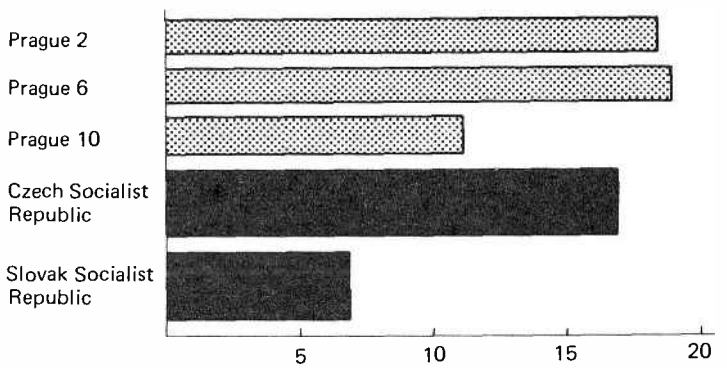
In 1972 the amount of cardiotonics prescribed in terms of DDDs per 1000 inhabitants per day, deduced from wholesale figures for the Czech and Slovak Socialist Republics separately, was compared with the figures gained by the automated processing of prescriptions in 3 districts of Prague (*9*). The great differences in consumption could not be fully explained by the different age structures of the areas studied (Fig. 5).

Fig. 4. Consumption of cardiotonics in Czechoslovakia, 1970–75[a]



[a] Reproduced from Modr & Štika (*8*).

Fig. 5. Consumption of cardiotonics[a] in 1972 in the Czech and Slovak Socialist Republics (black), deduced from wholesale figures and for 3 Prague districts (dotted), deduced from prescription figures[b]

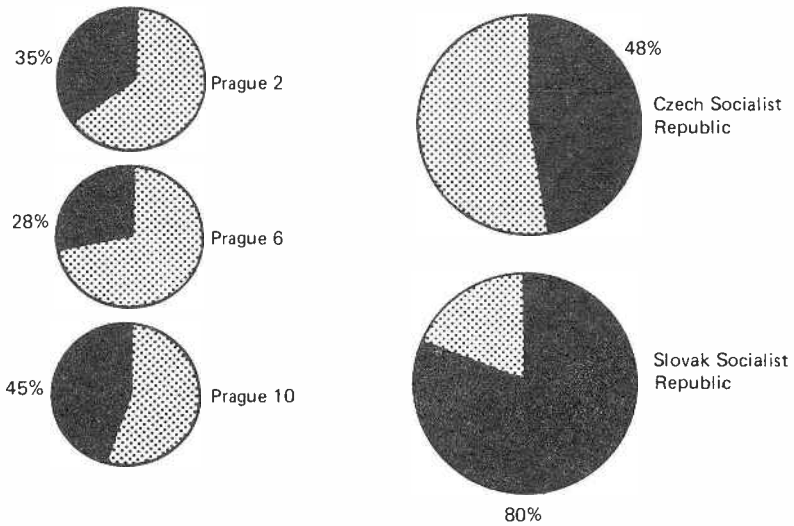


[a] Expressed as the number of DDDs per 1000 inhabitants per day.

[b] Reproduced from Uhlíř & Štika (*9*).

As to the age and sex distribution, lanatoside C is a typical drug for the elderly (*10*). In all the areas studied, striking differences have also been observed in the proportion of lanatoside C to the whole group of cardiotonics (Fig. 6).

Fig. 6. Consumption of lanatoside C[a] as a percentage of the total consumption of cardiotonics in 1972[b]



[a] Shown in black.

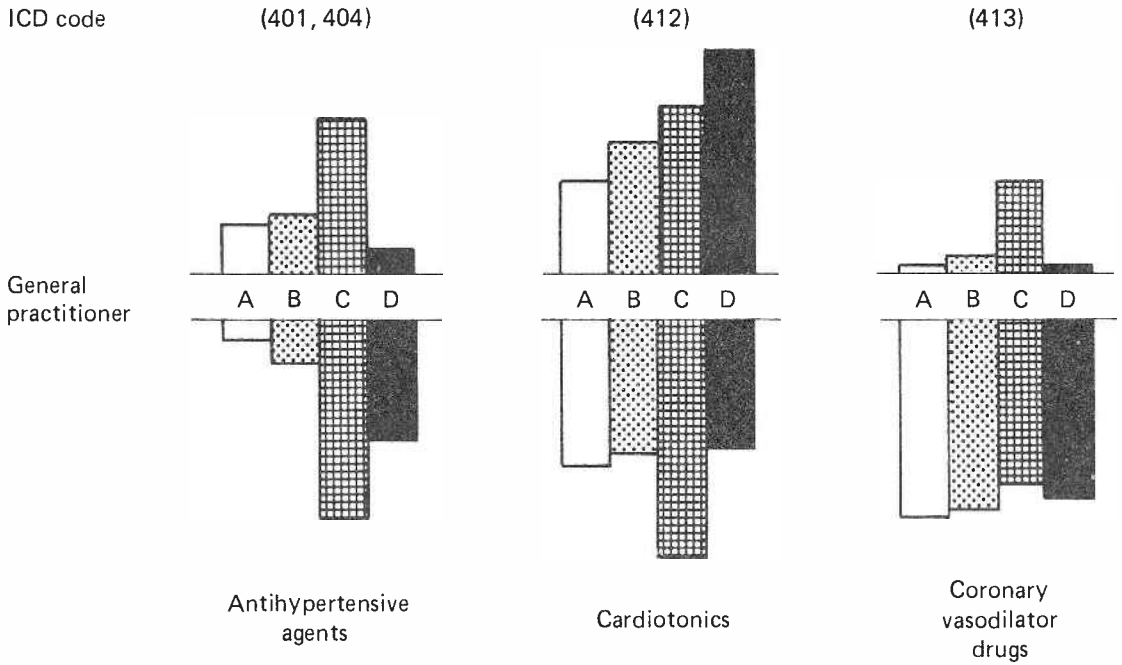
[b] Reproduced from Uhlíř & Štika (*9*).

In a study comprising the analyses of about 1000 prescriptions for a 1-month's sample of patients hospitalized in 12 medical wards of different hospitals, correspondingly great differences in the proportions of lanatoside C could be observed (*11*).

INDIVIDUAL PRESCRIBING HABITS

The individual prescribing habits of physicians offer another valuable source of information. A 1-month's sample of the prescriptions of 4 health community physicians (general practitioners) working in similar areas has been analysed. The frequency of 3 main cardiovascular diagnoses marked on their prescriptions and the frequency of prescribed drugs of 3 corresponding groups were the criteria (Fig. 7).

Fig. 7. Comparative prescribing habits of 4 general practitioners (A, B, C, and D)[a, b]



[a] The upper halves of the diagrams represent the frequency of diagnoses of different cardiovascular diseases: hypertension (ICD codes 401 and 404), ischaemic heart disease (ICD code 412), and angina pectoris (ICD code 413); the lower halves of the diagrams represent the relative frequency with which the 3 groups of drugs indicated were prescribed by the 4 general practitioners.

[b] Reproduced from Modr et al. (*12*).

Different attitudes towards drug therapy of cardiovascular diseases are reflected not only in the different amount of prescribed drugs (e.g., antihypertensive agents), but also in the very different frequency of diagnosis of angina pectoris. On the other hand, the number of coronary vasodilators prescribed is at a very similar level for all physicians.

Similar studies on the consumption of diuretics and antihypertensive agents (*8*), vasodilators (*13*), antiepileptics (*14*), antidiabetics (*15*), psychotropic drugs (*16*) and vitamins have been performed.

The processing of order forms revealed very interesting differences in the use of some important antibiotics in different clinics of a large paediatric hospital (*17*).

Although this system of gaining information on drug consumption is already fairly adequate with respect to its organization and function, further development is necessary. For this purpose use must be made of experience gained in Czechoslovakia and in other countries that organize their data collection along similar lines.

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CHAPTER 13

DEVELOPMENT OF PRESCRIBING DATA ACQUISITION, ANALYSIS, AND FEEDBACK AS AN OPERATIONAL RESEARCH TOOL FOR GENERAL MEDICAL PRACTICE

A.W. Patterson[a]

In the United Kingdom general medical practitioners are individually contracted to the National Health Service and maintain considerable clinical independence. In addition, the British public tends to resist centralization of computer-held records and is particularly concerned about the maintenance of the confidentiality of medical records to which it has been accustomed.

For the above reasons it has not been easy for the departments of health to influence or assist prescribing in general medical practice to any great extent, although there exists a sophisticated system of analysis of prescriptions issued under the National Health Service. The benefits and limitations of this system are discussed by Darby & Greenberg in chapter 8 of this book. A major limitation is lack of detail regarding the patient and the absence of any indication of the therapeutic intent of the prescriber and whether or not new therapy is being initiated or longer term therapy is being continued by means of repeat prescriptions.

THE PILOT STUDY

A coincidence of interest in such matters led 3 university departments in Scotland[b] to collaborate in a pilot study based on data collection by means of copy prescriptions generated during normal prescribing in general medical practice.

[a] Director, Unit for Research into Drug Usage, Department of Pharmacy, Heriot-Watt University, Edinburgh, Scotland.

[b] Department of General Practice and GP Research Support Unit, Dundee University; Medicines Evaluation and Monitoring Group, Department of Pharmacology and Therapeutics, Dundee University; Unit for Research into Drug Usage, Department of Pharmacy, Heriot-Watt University, Edinburgh.

Objectives

The objectives of the pilot study were:

(1) to assess the feasibility of applying the proposed data acquisition methods in general medical practice without too much interference with a prescriber's normal routine;

(2) to test the applicability of available coding techniques to the problems of the primary care situation in which the general medical practitioner works;

(3) to maintain confidentiality of patient information.

It was considered that if the above objectives could be satisfied it would then be possible to assess the usefulness of an information system based on such data acquisition in the pursuit of further objectives as follows:

(4) the development of methods of information retrieval to provide detail on:

(*a*) prescribing patterns with regard to the range and choice of drugs and dosage regimens used,

(*b*) morbidity patterns, the related drug therapy prescribed, and the length of treatment,

(*c*) age and sex of the patient, presenting problem(s), and treatment;

(5) the development of operational research methods appropriate to general medical practice; these would be based on the availability of the information resources listed in (4), an important aspect being informative feedback of a timely and useful nature to the originators of the data, i.e., the general practitioners in their practices;

(6) the development of both research and education potential. This could be done, for example, by organizing peer groups with access to expert advice. The facilities could also be used by the study organizers to assess the influence of various types of feedback to the prescribers who generate the data.

Data collected

The mechanics of the pilot study and its follow-up are described below, but a few details of the type of information derived from the pilot study may be appropriate at this point.

The data for the pilot study were collected for the month of February 1976 and comprised 4437 items prescribed by 16 volunteer physicians. It was found that 10 therapeutic classes of drugs accounted for 51% of all the drugs prescribed (Table 1).

Table 1. Top ten drug groups prescribed

	No. and title of therapeutic class	Class total	Percentages of total prescriptions (n = 4 437)
39	Penicillins	388	8.7
17	Expectorants and cough suppressants	365	8.2
23	Antipyretic analgesics	333	7.5
26	Tranquillizers	232	5.2
25	Hypnotics (nonbarbiturate)	187	4.2
10	Diuretics	186	4.2
40	Tetracyclines	174	3.9
78	Corticosteroid preparations acting on the skin	146	3.2
48	Other anti-infectives[a]	131	3.0
9	Preparations acting on the heart	128	2.9
	Totals	2 270	51.0

[a] This class comprises other anti-infectives, including antileprotic, antisyphylitic and antiprotozoal preparations.

The physicians used standard antibiotic regimes in respiratory tract infections but they used from 1 to 11 different kinds of cough medicine, although 1 or 2 types were particularly favoured. The antibiotics used for respiratory tract problems are shown in Table 2, as are also the problems for which they were prescribed.

The second largest category of prescribed drugs was the psychotropics, some details of which are shown in Table 3.

During the pilot study, similar types of data were extracted in detail for diuretics, beta-blockers, oral contraceptives, remedies for peptic ulcer, indigestion and other digestive problems, iron and vitamin preparations, topical preparations, and others. Relative costs of treatments were also investigated. On the basis of these preliminary analyses the potential of the system was considered to be useful and capable of substantial development.

The outcome of the pilot study was sufficiently encouraging for the team to proceed to a more elaborate study and this is being mounted at the time of writing.

Table 2. Prescribing for respiratory tract problems

Total number of prescriptions	1 085 (25% of 4 437)
Prescriptions for antibiotics:	
Total	418 (38.5% of 1 085; 9% of 4 437)
Penicillin	119 (29% of 418)
Tetracycline	97 (23%)
Amoxycillin	61 (15%)
Ampicillin	52 (12%)
Co-trimoxazole	44 (11%)
Others[a]	45 (11%)
Number of prescriptions for:	
Upper respiratory tract problems	673 (antibiotics: 223 = 33%)
Airways obstruction problems	161 (antibiotics: 18 = 11%)
Major respiratory infections	251 (antibiotics: 177 = 71%)

[a] None of these was prescribed more than 15 times.

MECHANICS OF THE STUDIES

The necessary data for these studies are generated as described below, then coded, prepared for computer input and analysed in various ways.

Self-copying pads of 50 National Health Service (NHS) prescription forms, printed on NCR (no carbon required) paper are interleaved with a specially designed copy leaf on yellow paper. The front of the form is shown in Fig. 1, the reverse in Fig. 2 and the yellow copy leaf in Fig. 3. A stiff card insert flap carrying instructions for use (Fig. 4) is flexibly hinged to the pad. Thus each prescription "set" consists of one white NHS prescription form (an EC10) with one yellow copy form below it. In addition to carrying the instructions, the stiff card insert flap serves to prevent the copy carrying through several layers of paper. After the prescription has been written as instructed, the top copy is given to the patient as usual. The yellow copy then has the "indication" for drug therapy written on it opposite the drug to which it refers. Either at the same time, or later, a patient identification code number, including a sex indicator, is constructed as the examples in Fig. 4 illustrate and then the copy of the patient's name and address is guillotined off from the top of the yellow copy. Medical record confidentiality is thus maintained.

Table 3. Prescribing of psychotropic drugs

This was the second largest category after prescriptions for respiratory tract problems. There were 665 prescriptions (15% of the total of 4 437) and the outstanding subgroups were:

benzodiazepine	228 (43% of 665)
tricyclics	119 (18%)
barbiturates	79 (12%)
phenothiazines	48 (7%)
others	131 (20%)

Prescriptions for psychotropic drugs as a whole formed from 12% to 21% of any one doctor's prescriptions. The benzodiazepines constituted from 36% to 57% (average 43%) of doctors' prescriptions for psychotropic drugs. For the other subgroups the figures were:

tricyclics	12–28% (average 18%)
barbiturates	5–25% (average 12%)
phenothiazines	2–14% (average 7%)

Mogadon (138) and Valium (93) were the most heavily prescribed of any psychotropic drugs, followed by amitriptyline (67), imipramine (30) and the barbiturates (35, including 2 Bellergal and 2 phenobarbitone + theobromine).

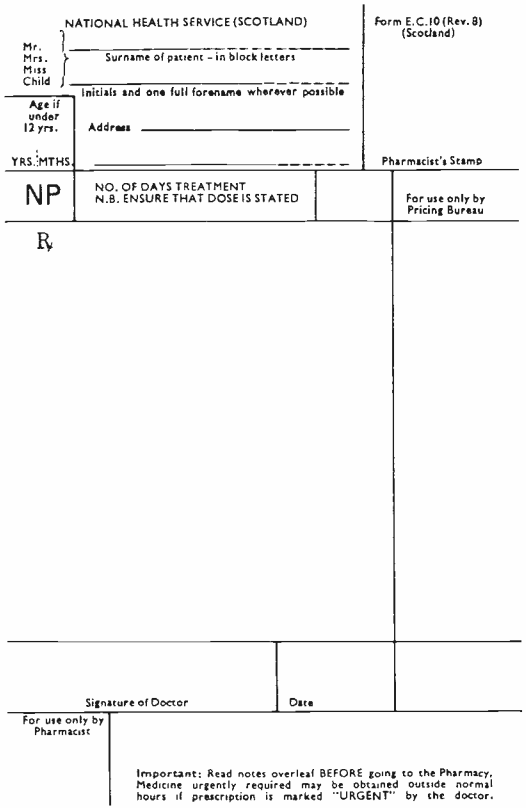
Approximate breakdown of problems treated (total, 665):

Insomnia, sleep disturbance	54%
Depression	24%
Anxiety neurosis and nonspecific "tension" states	16%
Psychoses	6%

THE FOLLOW-ON PROJECT

During the pilot study the "indication" was coded in the prescriber's own practice using the OXMIS problem code book (Oxford Community Health Project, 1975). Certain difficulties were sometimes encountered by the prescribers during the pilot study in allocating an appropriate code to the "indication". For this reason the follow-on project will use for comparison

Fig. 1. Front of prescription form (EC10)



NATIONAL HEALTH SERVICE (SCOTLAND)

Form E.C.10 (Rev. 8) (Scotland)

Mr. / Mrs. / Miss / Child — Surname of patient – in block letters

Initials and one full forename wherever possible

Age if under 12 yrs. YRS. MTHS.

Address

Pharmacist's Stamp

NP

NO. OF DAYS TREATMENT
N.B. ENSURE THAT DOSE IS STATED

For use only by Pricing Bureau

℞

Signature of Doctor

Date

For use only by Pharmacist

Important: Read notes overleaf BEFORE going to the Pharmacy. Medicine urgently required may be obtained outside normal hours if prescription is marked "URGENT" by the doctor.

Fig. 2. Reverse of prescription form

IMPORTANT NOTES FOR PATIENTS

1. Unless you are entitled to complete the declaration below you must pay a charge for *each item.*

2. If you need information about exemptions from the charge or refunds obtain leaflets EC91 (for general information) and PC11 (for exemption/refund on income grounds) from the Post Office. If you pay prescription charges frequently ask for form EC95 about prepayment certificates.

3. You cannot claim a refund unless you ask for a receipt *when the charge is paid.*

ONLY IF THE PATIENT IS EXEMPT FROM PRESCRIPTION CHARGES COMPLETE THIS DECLARATION (**BEFORE** going to the chemist)

I DECLARE that the patient named overleaf

- ☐ is **under 16** years of age
- ☐ is a woman **aged 60** or over / is a man **aged 65** or over

Please tick one box only

- ☐ holds a current **Executive Council** or **Health Board** exemption certificate
- ☐ holds a current **prepayment certificate** (EC96)
- ☐ is covered by a **Department of Health and Social Security** exemption certificate
- ☐ is a **War Service pensioner** with an exemption certificate Ref. No. (if available).....

AND THAT I AM

Please tick one circle

- ◯ the patient
- ◯ the patient's parent or guardian
- ◯ the patient's representative

I understand that enquiries may be made to check this Declaration and that a deliberately false statement may lead to prosecution.

Signed..... .. Date.....

NAME AND ADDRESS (if different from overleaf) (Block letters) .....

This form is the property of the Health Board

Fig. 3. Yellow copy leaf of prescription "set"

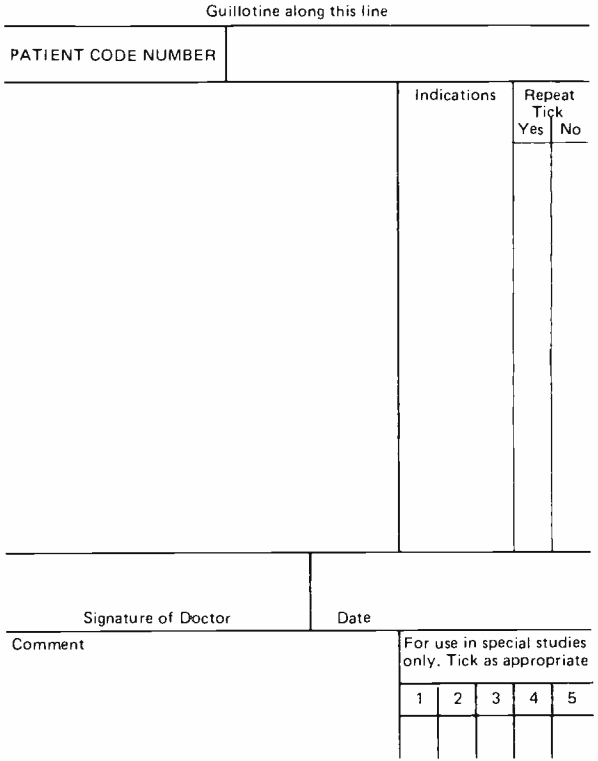


Fig. 4. Stiff card insert placed below prescription "set"

1. Place this insert below the yellow duplicate paper of a prescription 'set' before writing the prescription. It is essential to use a BALL POINT pen firmly.

2. 'HOGBEN' numbers for patient identification are constructed as follows:--

Sex	M or F
Age	Date of birth in six digits eg. 121172 or 030615 ie. day, month, year
Name	1st forename initial plus 1st four letters of surname, Mc or Mac to be contracted to M
Examples:	Miss Bonnie Dundee F121172BDUND Mr J L McTayside M030615JMTAY

3. Record 'Indication(s) for Use' of drug for later coding. (Including underlying pathology where appropriate).

4. Repeat.Tick 'YES' or 'NO' for every drug; 'YES' applies to any repeat whether patient seen or not.

5. 'No drug prescribed' problems. Destroy the white EC10 form. Draw a diagonal line across the prescription box of the yellow copy then complete as before but stating 'presenting problem(s)' in place of 'indication(s)'. Construct a HOGBEN number then sign and date the form as usual.

6. Comment. Leave blank if no comment required.

the codes of the ICHPPC.[a] It is also being arranged to have the "indications" coded centrally to ensure greater uniformity of interpretation. This will be done by a female coder with the supervision and guidance of a physician. The guillotined and partially coded forms will then be sent to the data processing centre in Edinburgh. The drugs will be coded by young female coders using the Drug Master Index coding system used by the Department of Health and Social Security. Specially structured forms will be used to carry the encoded data.

The maximum daily dose will be calculated and recorded where possible or appropriate and the quantity of drug prescribed will also be recorded together with the date on which the prescription was issued. The encoded data will then be punched on to 80-column cards, verified, validated by computer, and finally processed using specially developed programs.

The yellow copy (Fig. 3) has been partially restructured since the pilot study and, as will be seen, it can be used, additionally, for special studies according to the interests or requirements of a particular prescriber or group of collaborators.

The basic output from the computer consists of a series of tabulations that provide information on the frequency of both drugs and indications in rank order or by therapeutic class of drug. Tabulations based on age and sex are provided and also a series of tabulations that include patient identification codes. Tabulations are also available for any selected age/sex group or for any therapeutic category as required.

The system readily allows extension to include details of patient-physician contacts that do not result in a drug being prescribed. Thus, the whole spectrum of problems presenting in primary care can be catered for and the system need not be confined to drug prescribing alone. In this way it is hoped to develop the full potential of the system as a supportive function of use to the general practitioner in the management of his patients.

The ultimate objective of these studies is to develop a series of "packages" that can be used in general medical practice for the more efficient management of drug therapy and thus help to provide optimal patient care.

In the Tricker report[b] it is stated (page 30) that "a consistent view given in evidence was the need for information that would enable doctors to assess and develop their prescribing practice". It is hoped that the scheme outlined above will go some way towards satisfying this need.

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[a] **The Royal College of General Practitioners.** *International classification of the health problems of primary care (ICHPPC).* London, December 1976 (occasional paper 1).

[b] **Tricker, R.I.** *Report of the inquiry into the Prescription Pricing Authority.* London, Department of Health and Social Security, 1977.

ACKNOWLEDGEMENTS

The author is grateful for the opportunity to collaborate in these studies, which would not be possible without the support of the departments of health in related projects. One of these is mentioned in chapter 8. The figures quoted in the tables were extracted from the computer printouts by Dr L.J. Christopher, formerly Director, Medicines Evaluation and Monitoring Group, Department of Pharmacology and Therapeutics, Ninewells Hospital, Dundee.

CHAPTER 14

INTERNATIONAL COMPARISONS OF DRUG UTILIZATION: USE OF ANTIDIABETIC DRUGS IN SEVEN EUROPEAN COUNTRIES[a]

U. Bergman[b]

In an initial attempt to obtain internationally comparable data on drug utilization per inhabitant, marked differences were found between Northern Ireland, Norway, and Sweden in the use of insulin and oral antidiabetic drugs (*1*). Wholesale statistics for a quarter of a year from Norway and Sweden and prescription figures from Northern Ireland were compared on the basis of "daily doses" per 1000 inhabitants per day (see below). Antidiabetic drugs were chosen since the diagnosis of diabetes mellitus is a reasonably clear one. Of these drugs, insulin has well defined indications compared with the oral antidiabetic drugs. The validity of the methodology with respect to antidiabetic drugs has been confirmed in a field study on the island of Gotland, Sweden (*2*), in which the patients' actual use of these drugs was studied. In this paper, an international working party has collected comparable data on the utilization of antidiabetic drugs in 7 European countries – Czechoslovakia, Denmark, Finland, Iceland, Norway, Sweden, and the United Kingdom (Northern Ireland) – for the period 1971–1974.

MATERIAL AND METHODS

An estimate of drug utilization was obtained by relating the drug amounts supplied to each country during each year (in Northern Ireland, each second quarter of the year) to the number of inhabitants. The population data for each country are listed in Table 1.

[a] This study was carried out in collaboration with J. Elis and L. Štika, Czechoslovakia; A. Køster and J. Mosbech, Denmark; A. Grímsson and Ó. Ólafsson, Iceland; J. Idänpään-Heikkilä, Finland; C. McMeekin, Northern Ireland; P.K.M. Lunde, Norway; and F. Sjöqvist and B. Westerholm, Sweden.

[b] Department of Clinical Pharmacology, Karolinska Institutet, Huddinge University Hospital, Sweden. The author's participation in this study was financed in part by the Karolinska Institutet.

Table 1. Population sizes, 1971 to 1974

Country or area	Number of inhabitants (millions)
Czechoslovakia	14.4–14.6
Denmark	5.0
Finland	4.6–4.7
Iceland	0.2
Northern Ireland	1.5
Norway	3.9–4.0
Sweden	8.1–8.2

Unit of comparison

Since the initial paper was presented (*1*) a list of defined daily doses (DDD) of drugs registered in Norway (see chapter 2) has been published (*3*). For some of the oral antidiabetic drugs the "daily doses" initially used were revised.[a] The DDDs used in this study are listed in Table 2. The utilization has been expressed as the number of DDDs per 1000 inhabitants per day. This gives a rough estimate of the number of subjects for whom the drug might have been prescribed per 1000 population.

Sources of information

The Norwegian and Swedish figures represent the gross sales level, while the figures for Northern Ireland represent the amount of drug actually supplied on prescription to patients outside hospitals with an addition of the amount distributed to hospitals (*1*).

The figures for Czechoslovakia, Denmark, Finland and Iceland also represent the gross sales level, although in the figures for Finland some hospital data are missing.

In Czechoslovakia all patients with diabetes are taken care of by special diabetic dispensary care units in every district (of about 100 000 inhabitants). Each year these report to a central authority the number of patients treated with insulin, oral antidiabetic drugs, and diet only. The number of patients reported to be on insulin and oral antidiabetic drugs in the Czech Socialist Republic from 1970 to 1974 (*4*) have been compared with the gross sales figures expressed as the number of DDDs per 1000 inhabitants per day (Fig. 1).

[a] To overcome differences in potency and dosage schedules between drugs within a certain group, such as oral antidiabetics, "daily dose" units were defined (cf. Table 2) for each drug (*1*).

Table 2. Defined daily doses (DDD) of antidiabetic drugs

		DDD	
1	Insulin[a]	40	IU
2	Oral antidiabetic drugs		
	(*a*) *Biguanides*		
	Phenformin[a]	0.1	g
	Metformin[a]	2	g
	Buformin	0.2	g
	(*b*) *Sulfonamides and others*		
	Glibenclamide[a]	10	mg
	Chlorpropamide[a]	0.375	g
	Tolbutamide[a]	1.5	g
	Glibornuride[a]	37.5	mg
	Glymidine[a]	1	g
	Acetohexamide	0.5	g
	Chlorbenzylsulfonylcyclohexenylurea	0.4	g
	Carbutamide	0.75	g
	Tolazamide	0.5	g

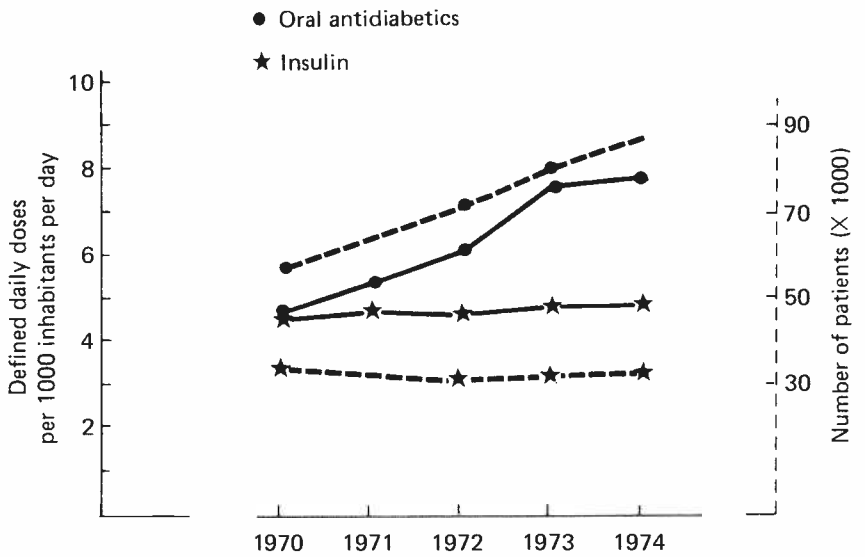
[a] From Baksaas Aasen et al. (*3*).

RESULTS

Insulin

The trends in using insulin were rather consistent in each of the 7 countries from 1971 through 1974 (Fig. 2). The level of use was similar in Czechoslovakia, Denmark, Finland, Northern Ireland, and Norway, while Sweden consistently used about twice as much and Iceland half as much as 4 of the other 5 countries. In all countries, the medium-acting type of insulin was the most frequently used form. The use of the rapidly acting type varied in 1974 from 4% in Norway to 37% in Northern Ireland.

Fig. 1. Treatment with insulin and with oral antidiabetics in the Czech Socialist Republic[a]



[a] Broken lines, number of patients reported per year; continuous lines, number of DDDs per 1000 inhabitants per day.

Oral antidiabetic drugs

As in the initial study (*1*) the variation in drug utilization between countries was more marked for oral antidiabetics (Fig. 3) than for insulin. Finland and Sweden are the biggest users of oral antidiabetics, their consumption being about 5 times that of Iceland, which is the lowest user.

The relative use of oral antidiabetics and insulin differs markedly from one country to another, suggesting differences in the indications for antidiabetic drugs. In Northern Ireland the ratio of oral antidiabetics to insulin is 0.7, whereas in Finland it is 2.0 (Fig. 4).

In Finland the biguanides constituted 35% of the oral antidiabetics compared with 14% in Norway (Fig. 5). Furthermore, the trends in the use of biguanides were quite different in the 7 countries, from an increase in Czechoslovakia to a decrease in Sweden. In all countries, 2–3 drugs were responsible for the major part of the utilization. Different drugs predominated, chlorpropamide being the major drug in 4 countries (Iceland, Northern Ireland, Norway, and Sweden), tolbutamide in Czechoslovakia, tolbutamide and glibenclamide in Denmark, and the biguanide phenformin in Finland (Tables 3 and 4).

Fig. 2. Utilization of insulin in 7 European countries

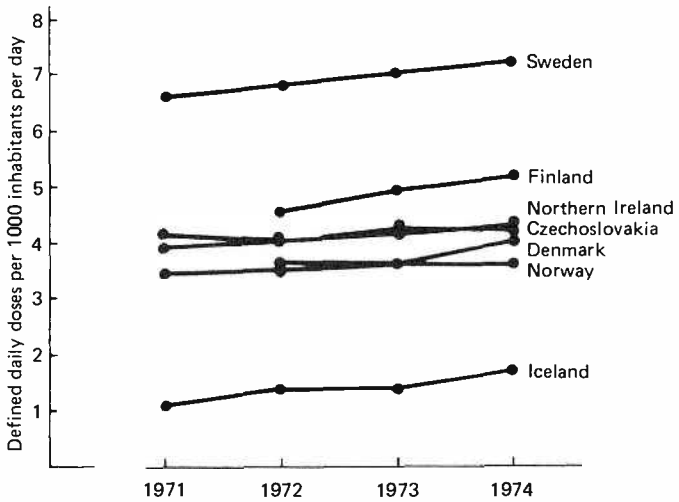


Fig. 3. Utilization of oral antidiabetic agents in 7 European countries

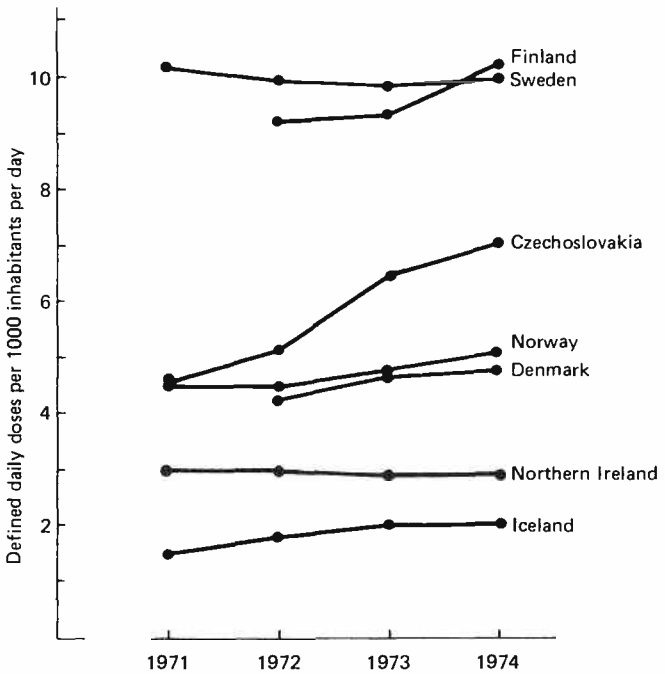
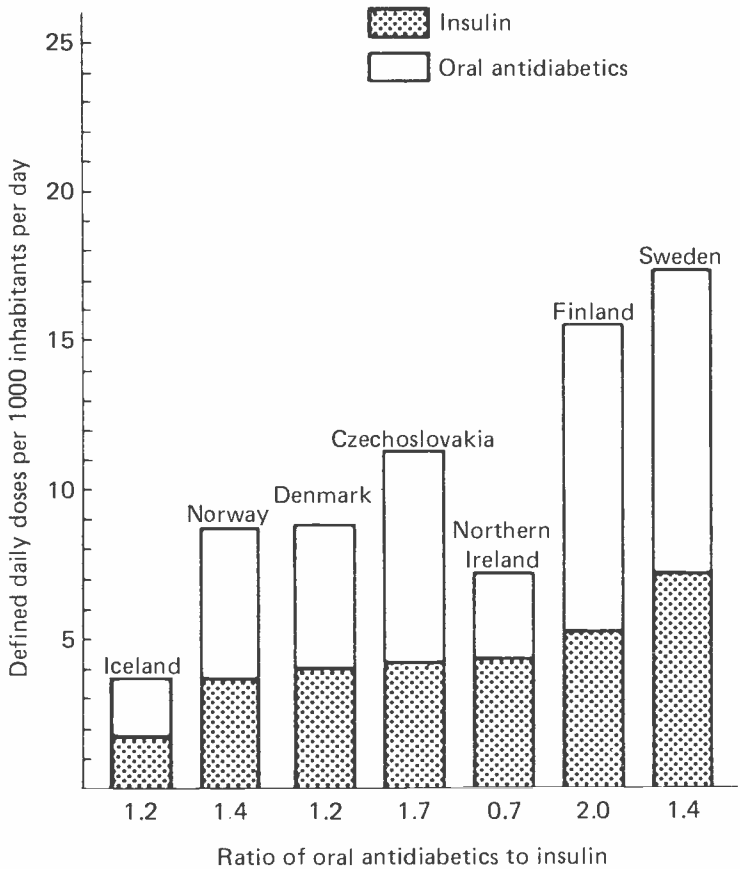


Fig. 4. Relative use of insulin and oral antidiabetic drugs in 7 European countries, 1974



DISCUSSION

For insulin a 4-fold, and for oral antidiabetic drugs a 5-fold, difference in utilization was demonstrated between 7 European countries. The fact that the drug utilization figures were based on gross sales data in 6 countries and on prescription data only in 1 probably does not invalidate the results. In the island of Gotland, Sweden, gross sales statistics and prescription figures for oral antidiabetic drugs agreed well (*2*). Provided the time period studied was sufficiently long the same was true for insulin (*2*). In Northern Ireland, the suitability of a quarter of a year for data collection was demonstrated in the previous study (*1*). Agreement between morbidity and drug utilization data in the Czech Socialist Republic (Fig. 1) supports the usefulness of the methodology.

Fig. 5. Utilization of biguanides as a percentage of oral antidiabetic drugs in 7 European countries

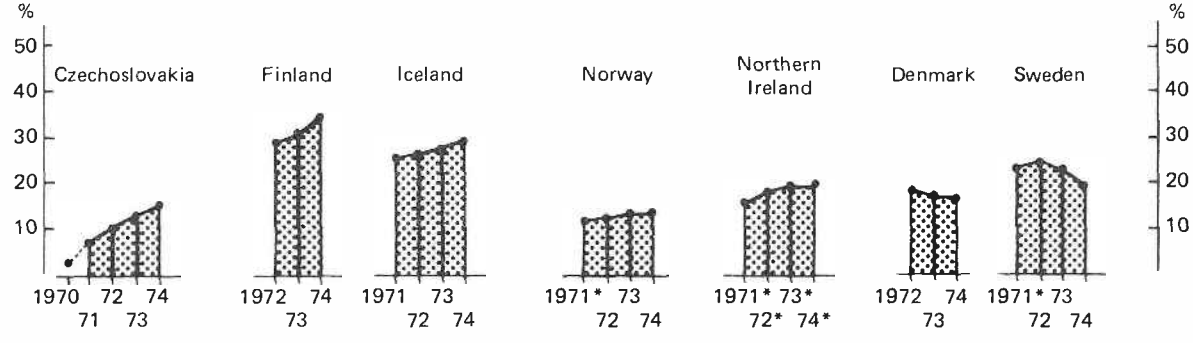


Table 3. The utilization of oral antidiabetic drugs (sulfonamides and related compounds) in 7 European countries, 1974

	Number[a] of defined daily doses per 1 000 population per day						
	Czechoslovakia	Denmark	Finland	Iceland	Northern Ireland	Norway	Sweden
Acetohexamide	–	–	–	–	0.0	–	0.1
Carbutamide	0.3	0.1	1.9	–	–	–	0.2
Chlorbenzylsulfonyl-cyclohexenylurea	0.5	–	–	–	–	–	–
Chlorpropamide	0.5	0.7	2.3	1.1	1.6	3.5	4.1
Glibenclamide	1.3	1.5	1.7	0.3	0.2	0.7	2.5
Glibornuride	–	0.0	–	–	–	0.0	0.0
Glymidine	–	–	0.1	–	0.0	0.1	0.0
Tolazamide	–	0.0	0.1	–	0.0	–	0.1
Tolbutamide	3.4	1.7	0.5	0.0	0.5	0.1	1.0
Total	6.0	4.0	6.6	1.4	2.3	4.4	8.1

[a] –, drug not available in the country at the time; 0.0, negligible prescribing.

Table 4. The utilization of oral antidiabetic drugs (biguanides) in 7 European countries, 1974

	Number[a] of defined daily doses per 1 000 population per day						
	Czechoslovakia	Denmark	Finland	Iceland	Northern Ireland	Norway	Sweden
Buformin	1.0	–	–	–	–	–	–
Metformin	–	0.2	0.0	0.0	0.4	0.0	0.3
Phenformin	0.1	0.6	3.6	0.6	0.2	0.7	1.6
Total	1.1	0.8	3.6	0.6	0.6	0.7	2.0

[a] –, drug not available in the country at the time; 0.0, negligible prescribing.

The variation in the utilization of antidiabetic drugs in the 7 countries might depend on differences in any of the following: morbidity; actually prescribed daily doses of antidiabetic drugs; therapeutic tradition (diet versus drug treatment); compliance with various therapeutic regimes; and sales promotion (e.g., number of clinically equivalent drugs on the market).

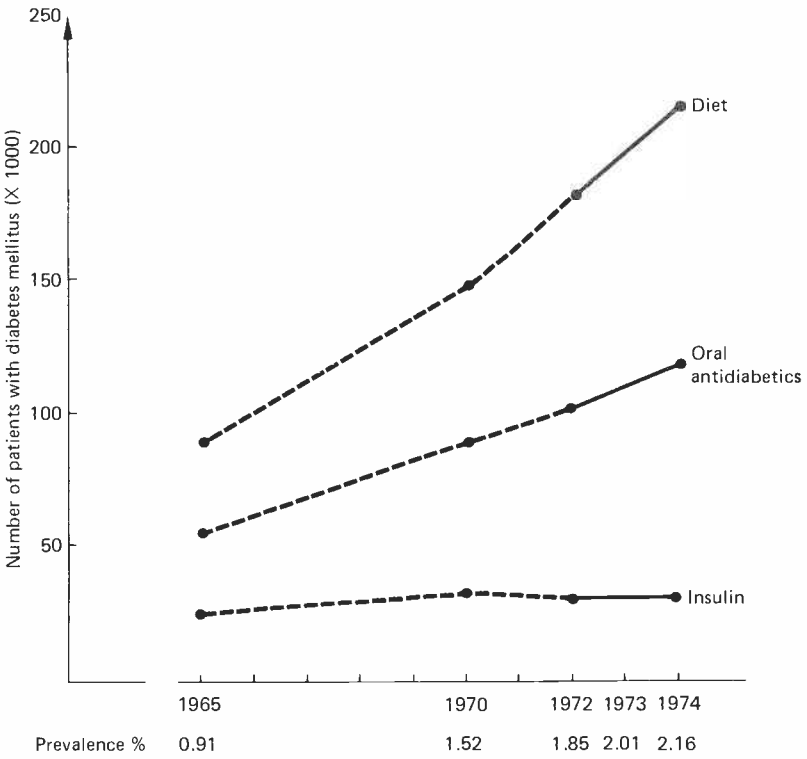
An ongoing nationwide prescription survey in Sweden (*5*) has shown that oral antidiabetic drugs are prescribed predominantly to elderly patients (*2*). As is apparent from Table 5, there are differences between the countries in the proportion of people aged over 60 and over 75 years. Finland and Sweden, which have the highest utilization of oral antidiabetic drugs, show very marked differences in this respect. Taking age differences in the population into account, for persons aged 60 years or more there is still an approximately 4-fold difference between Iceland and Finland in the utilization of oral antidiabetics. If only sulfonamide derivatives are compared (age-adjusted figures) the same difference is found.

In 1974, 2.16% of the population were reported to be suffering from diabetes in the Czech Socialist Republic, 1.19% on drug treatment and 0.97% on diet alone (Fig. 6) (*4*). Corresponding data do not exist for the other countries. In two nationwide interview surveys in Sweden, diabetes was found in 1.58 ± 0.35% (1968) and 1.69 ± 0.23% (1975) of the population aged 16–74 years (Rosenqvist, U. & Allander, E., unpublished observations). The type of treatment was not reported. In 1974 the utilization of antidiabetic drugs in the county of Jämtland (Boéthius, G., personal communication) was found to correspond well with the Swedish mean: 7.4 against 7.2 DDDs per 1000 inhabitants per day for insulin, and 10.8 against 10.0 for oral antidiabetic drugs. Purchases of drugs in Jämtland (*6*) gave 1.8% of the population on antidiabetic

Table 5. Proportion of the population in the categories 60 years or over and 75 years or over, 1973–1974

	Percentage of the population aged:	
	60 or over	75 or over
Czechoslovakia	17.5	3.7
Denmark	18.4	4.8
Finland	15.2	3.0
Iceland	12.6	3.6
Northern Ireland	15.8	3.8
Norway	18.8	5.0
Sweden	20.7	5.4

Fig. 6. Therapy of diabetes mellitus in the Czech Socialist Republic, 1965–1974[a]



[a] The prevalence in 1974 (2.163%) was based on 10.011 million inhabitants (*4*). In 1974, 0.32% of the population on insulin therapy corresponded to 4.8 DDDs per 1000 inhabitants per day (4.2 in Czechoslovakia) and 0.87% on oral antidiabetic therapy to 7.8 DDDs per 1000 inhabitants per day (7.1 in Czechoslovakia).

drugs in 1974, of which insulin accounted for 0.6%. In 1974, 2.0% of the population in the district of Tierp purchased antidiabetic drugs on prescription (Smedby, B., personal communication), and during one quarter of 1972 at least 1.7% of the population in the island of Gotland were on antidiabetic drugs (*2*). In 1974, to judge from data by Reunanen et al. (*7*), diabetics on drug treatment constituted 1% of the Finnish population aged 0–74 years.

In Czechoslovakia 0.30% were on insulin in 1974 (*4*) corresponding to 4.2 DDDs per 1000 inhabitants per day (Fig. 2). In Gotland, 0.5% and 7 DDDs per 1000 inhabitants per day were found during a 3-month period in 1972 (*2*). Similar figures for daily use of insulin per patient were found in Gotland

(57–59 IU/day) and in Czechoslovakia (56 IU/day); for comparison, the DDD is 40 IU (*2, 4*). The overall utilization of insulin was not influenced by the type of insulin used (short, medium, or long acting) in this study. Five countries have a similar utilization of insulin, of which Czechoslovakia is one (Fig. 2). The indications for using antidiabetic drugs may differ between the Nordic countries (*8*); this is supported by the higher utilization of insulin in Sweden. In Reykjavik, Iceland, clinical diabetes was found in 0.9% of men aged 34–61 years (*9*). In the nationwide interview survey in 1975 this corresponded to 1.5% in Swedish men of the same age (Lundin, E., personal communication). In conclusion, there are no data available to suggest that the incidence of diabetes differs as markedly as does drug utilization between the countries.

The DDD is a technical unit of measurement (*3*) and in the interpretation of drug utilization data its accuracy must be considered. Average prescribed daily doses for oral antidiabetic drugs obtained from various sources are given in Table 6. The data suggest that there may be as much as a 2-fold variation in average prescribed daily dose.

Nearly half (45.1%) of the diabetic population in the Czech Socialist Republic were on diet alone (Fig. 6). In 1972–1975, one third (32–34%) of diabetes patients were on diet alone at one diabetic clinic in Belfast (McMeekin, C., personal communication). In Northern Ireland an area with "high" prescribing of oral antidiabetics was compared with a "low" area (*10*). Patients in the former were prescribed oral drugs in much larger daily doses. The most important difference between the areas was the availability of a trained dietitian in the "low" area. The highest use of oral antidiabetic drugs was found in Finland and Sweden, both of which are short of dietitians. However, they have become increasingly available between 1970 and 1974 in the county of Jämtland (Boéthius, G., personal communication). In agreement with the Northern Ireland findings (*10*) there is a significant decrease ($P < 0.001$) in the mean chlorpropamide dose prescribed in this area from 1970 to 1974 (Table 6). The variability in chlorpropamide doses was higher in 1974 (0.125–1.0 g) than in 1970 (0.25–0.75 g).

Patient interviews in the island of Gotland, Sweden, revealed that elderly patients with adult onset diabetes were less concerned about a balanced diet (*2*). Their interest in their disease was rather small, especially when related to their concomitant illnesses. Differences in compliance with antidiabetic regimens may thus partly explain the variation in drug utilization between the 7 countries. The relative use of dietary, as against drug, treatment may be partly related to the proportion of elderly persons in the population (Table 5). The higher utilization of both insulin and oral antidiabetic drugs in Sweden suggests that drug treatment is used at the expense of dietary treatment alone.

Combination antidiabetic drug therapy was more common in Gotland than in Prague (*2*). Biguanides were used to quite a different extent in the 7 countries, with Finland as the biggest user. Finland also uses more oral antidiabetic drugs in relation to insulin than any of the other countries. Northern Ireland, which uses smaller amounts of oral drugs than insulin, is also

Table 6. Defined daily doses (DDD) and average prescribed daily doses[a] for oral antidiabetic drugs in 4 countries: data on most prescribed drugs in each area

	DDD	Czechoslovakia[b]	Finland[c]	Northern Ireland[b]		Sweden		
		1971	1976	1972	1975	1970[d]	1972[e]	1974[d]
Chlorpropamide	0.375 g		0.402 (183)	0.331 (212)	0.309 (132)	0.362 (384)	0.35 (329)	0.286 (377)
Glibenclamide	10 mg		9.2 (187)	5.2 (75)	5.8 (125)	– –	9.1 (210)	11.0 (301)
Tolbutamide	1.5 g	0.93 (609)						
Carbutamide	0.750 g	1.17 (292)						
Phenformin	0.100 g		0.083 (335)			0.070 (255)	0.082 (250)	0.065 (172)
Metformin	2.0 g			1.7 (260)	1.6 (214)			

[a] Data for Czechoslovakia from an annual report in one district of Prague (Štika, personal communication), for Finland from a nationwide sample of 824 prescriptions studied by the Social Insurance Institution in Finland (Olli, personal communication), and for Northern Ireland from records of outpatients attending the antidiabetic clinic at R.V.H. in Belfast (McMeekin, personal communication).

[b] Number of patients in parentheses.

[c] Number of prescriptions in parentheses.

[d] Data obtained from prescriptions purchased in the county of Jämtland, Sweden (Boéthius, personal communication).

[e] Data from prescriptions purchased in the island of Gotland (*2*).

a low user of biguanides. Where the therapeutic tradition is to use combination drug therapy this may tend to increase the use of oral drugs relative to insulin.

Sweden was the biggest user of sulfonamide derivatives in 1974 (Table 3) and it also had most generics on the market, with as many as 11–13 trade names. The utilization of biguanides was highest in Finland and exceeded that of Iceland and Northern Ireland 6 times (Table 4). Furthermore, more proprietary preparations of biguanides (6) were available in Finland than in any other of the participating countries. Thus, there appears to be an increased utilization of these drugs, with an increasing number of clinically equivalent drugs.

The higher cardiovascular mortality in diabetics receiving phenformin or tolbutamide as compared with those treated with insulin or diet alone reported by the University Group Diabetes Program (UGDP) (*11, 12*) has initiated a controversy on the use of oral antidiabetic drugs. In 1977, Shen & Bressler (*13*) concluded that: "At present oral hypoglycemic agents have no demonstrated useful role in the management of maturity onset diabetes mellitus, asymptomatic or symptomatic". In 1971–1975, in Sweden, oral antidiabetic drugs (mainly phenformin) headed the list of drugs that had been implicated as a cause of death (*14*). In the WHO report on the selection of essential drugs, no oral antidiabetics were included (*15*). In Norway, it has not been possible to reach any agreement on the indications for using oral antidiabetics (*16*). Norway withdrew phenformin on 1 January 1977, and this policy has been followed by several other countries, including Sweden.

The availability of detailed DDD statistics from various countries with different therapeutic traditions will facilitate epidemiological studies of the side-effects of drugs. As an example, Sweden had a relatively high utilization of biguanides. A significantly lower frequency of the serious side-effect lactic acidosis was reported for metformin than for phenformin (*17*).

CONCLUSIONS

There are marked differences in the utilization of antidiabetic drugs between 7 European countries. This is particularly true for the controversial oral antidiabetic drugs. Finland and Sweden are high users of oral drugs compared to the others. Iceland and Northern Ireland are low users of these drugs as well as of insulin. Field information from Czechoslovakia, Northern Ireland, and Sweden suggests that there may be a reciprocal relationship between dietary and oral drug treatment. Analysis of the utilization data relative to the spectrum of drugs available on the different markets suggests that the usage of oral antidiabetic drugs is increased with increasing number of clinically equivalent drugs. There are no data available to suggest that the incidence of diabetes differs as markedly as does drug utilization between the countries. On the contrary, marked differences exist in utilization patterns between countries with similar morbidity.

ACKNOWLEDGEMENTS

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THE UTILIZATION OF PSYCHOTROPIC DRUGS IN FINLAND, ICELAND, NORWAY, AND SWEDEN

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Since the use of psychotropic drugs has been the subject of intense debate during the last few years (*1–8*), it was considered that it would be useful to present some Nordic data on the utilization of these drugs and to discuss the possible conclusions that can be drawn from them. Bearing in mind that data on drug utilization are limited in Denmark, it was decided to restrict the comparisons to the 4 remaining Nordic countries. The present investigation comprises the period 1971–1976. The results of an earlier investigation covering the period 1971–1975 have been presented in the Nordic medical press (*9*).

MATERIAL AND METHODS

The data on the utilization of psychotropic drugs were based on sales data.

Classification system

In order to ascertain that the same drugs or the same therapeutic groups were investigated in the 4 countries the so-called "anatomical" classification, the EPhMRA system, was employed (see chapter 2).

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Unit of comparison

In order to obtain comparable data the sales were recalculated to defined daily doses (DDD) per 1000 inhabitants per day, as described in chapter 2. The doses presented in the Norwegian *Drug dose statistics* were used (*10*).

Drug groups

The analysis encompasses hypnotics, sedatives, tranquillizers, neuroleptics, and antidepressants (EPhMRA codes N05 A–C as well as N06 A). Psychostimulants are not included in this study because the rules for the availability of these drugs to the public vary between the countries in question.

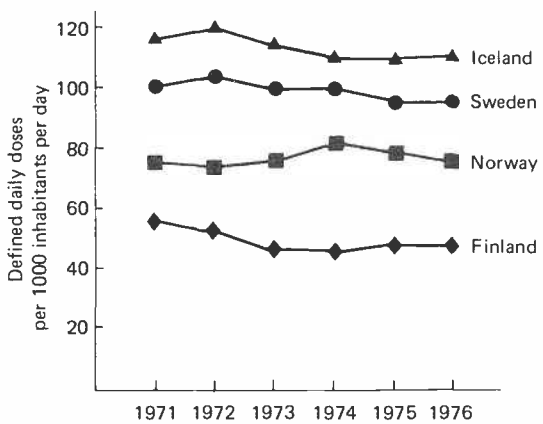
RESULTS

The total sales of psychotropics vary from one country to another, but taken as a whole the level has been quite stable during the 6-year period investigated (Fig. 1).

Hypnotics, sedatives and tranquillizers

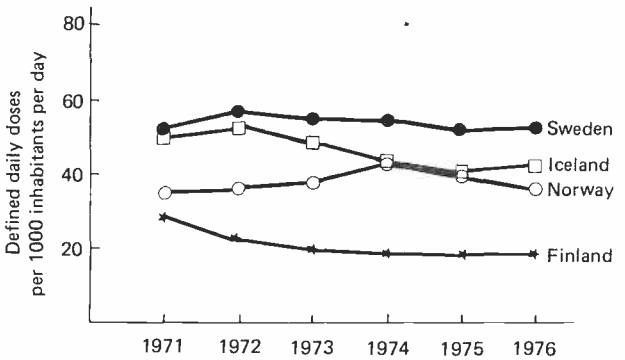
The sales of hypnotics and sedatives in Iceland, Norway, and Sweden were practically on the same level during the latter part of the investigation period

Fig. 1. Sales of psychotropic drugs in Finland, Iceland, Norway, and Sweden



(Fig. 2). By contrast, sales of these drugs were on a significantly lower level in Finland. During the period, the consumption shifted from barbiturates to non-barbiturates (Table 1), owing to an increased use of nitrazepam (Fig. 3).

Fig. 2. Sales of hypnotics and sedatives in Finland, Iceland, Norway, and Sweden



The tranquillizers displayed a different picture. Sales in Finland, Norway, and Sweden were approximately on the same level, whereas in Iceland they were double. The benzodiazepines represent the largest part of this group, and it is apparent from Fig. 3 how markedly Iceland differs from the other 3 countries in this respect.

Hypnotics, sedatives, and tranquillizers were used mainly by outpatients. In 1975, 83% of the daily doses of these drugs sold in Sweden were prescribed for outpatients and the corresponding figure for Finland was 82% in 1973. With regard to closed wards, considerable differences were found to exist between different clinics and/or hospitals (Table 2). Although the investigation periods are not identical, the available data suggest that the values also differ

Table 1. The sales of nonbarbiturates as a percentage of the total sales of hypnotics and sedatives in four Nordic countries

Country	1971	1972	1973	1974	1975	1976
Finland	58	60	66	69	73	72
Iceland	44	47	54	65	73	
Norway	70	73	77	78	76	86
Sweden	61	58	63	67	71	75

Fig. 3. Sales of benzodiazepines in Finland (SF), Iceland (Is), Norway (N), and Sweden (S)

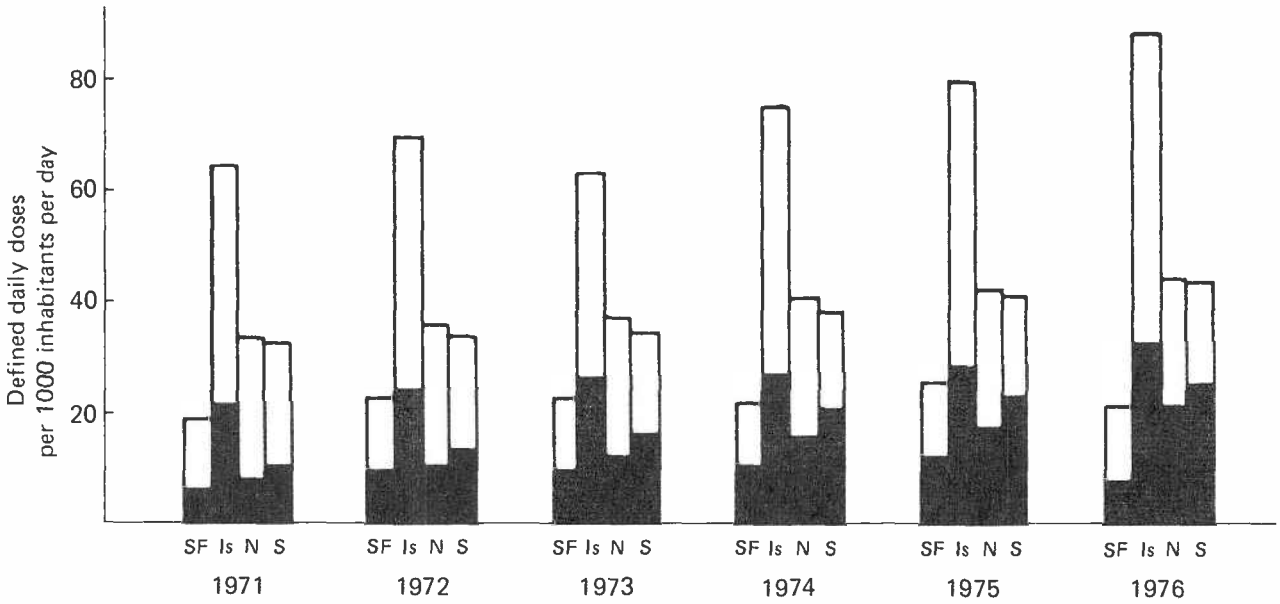


Table 2. Deliveries of hypnotics, sedatives and tranquillizers to some hospital departments in eight Swedish regional (university) hospitals during 1975 and of hypnotics and sedatives to one Norwegian university hospital during July–September 1974

Country	Department	Number of defined daily doses delivered per bed day	
		Mean	Range
Sweden	Medicine	0.57	0.20–0.92
	Gynaecology-obstetrics	0.43	0.24–0.71
	Psychiatry	0.52	1.37–5.15
Norway	Medicine	2.66	
	Gynaecology	0.66	
	Psychiatry	0.41	

between countries. According to a Swedish analysis of data obtained from prescriptions, female patients purchased more of these drugs than males and it can be seen that the consumption increased with the age of the patient (Table 3).

Neuroleptics

When Sweden is compared with the other Nordic countries regarding the sales of neuroleptics, it is evident that a considerable difference exists (Fig. 4). A plausible explanation is that in Sweden neuroleptics are prescribed for more indications than in the other countries. If this theory is correct, it should be reflected, for example, in the choices of tablet strengths for some neuroleptics. However, it is evident from Table 4 that there is no difference between Norway and Sweden in regard to the distribution of tablet strengths of some of the drugs that are most commonly used. The higher strengths are, however, relatively more common in Finland. It can be seen from the Swedish data that the lower strengths are prescribed to a relatively larger extent for outpatients, whereas the higher strengths predominate in closed wards. In Sweden (1975) and in Finland (1973) 65% of the total number of daily doses were sold to outpatients.

Antidepressants

On the whole, the sales of antidepressants were quite stable in 1971–1976 (Fig. 5) except for a certain increase in Norway, which may be attributed

Table 3. Number of prescriptions of psychotropic drugs related to age group and number of inhabitants in Sweden in 1976

Drug group	Number of prescriptions per 1 000 persons in age group:									
	0–14 years		15–44 years		45–65 years		65–74 years		75 and over	
	men	women	men	women	men	women	men	women	men	women
Hypnotics, sedatives and tranquillizers	0.19	0.23	2.0	2.7	5.2	8.6	6.4	10.7	11.6	13.1
Neuroleptics	0.13	0.15	0.86	1.1	1.8	2.5	1.6	2.5	3.5	3.4
Antidepressants	0.15	0.05	0.25	0.57	0.65	1.6	0.64	1.4	0.98	1.4

Fig. 4. Sales of neuroleptics
in Finland, Iceland, Norway, and Sweden

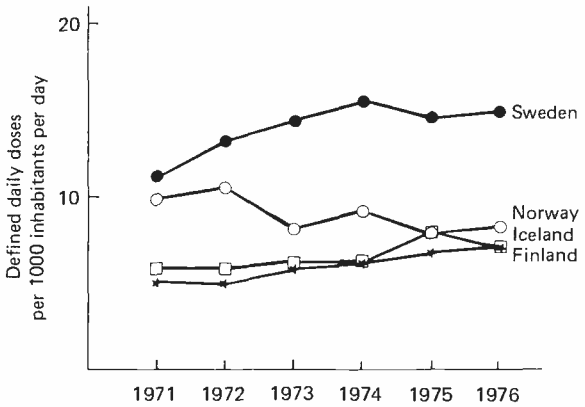
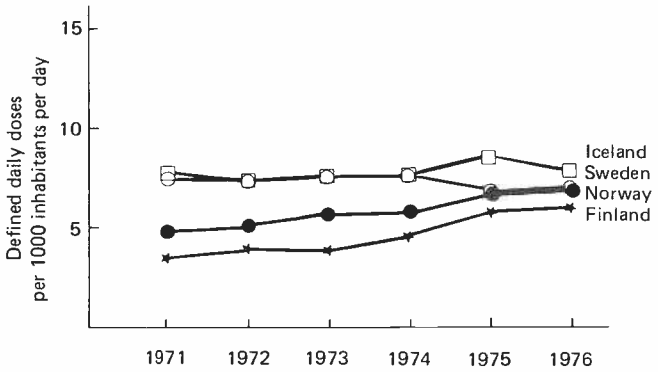


Table 4. Sales of different strengths of some neuroleptics
as a percentage of total sales (1975)

Drug	Strength (mg)	Finland	Norway	Sweden	Sweden distribution (%) to	
					inpatients	outpatients
Chlorpromazine	10	0.6	12	12	12	13
	25	14	49	47	38	52
	50	29	24	25	27	23
	100	57	15	16	22	12
		100	100	100	100	100
Clopenthixol	5	2	23	23	20	26
	10	16	24	30	27	34
	25	82	48	47	53	40
	100	–	5	–	–	–
		100	100	100	100	100
Chlorprothixene	5	0.4	11	10	8	10
	15	8	44	58	51	59
	25	17	23	22	21	22
	50	43	19	10	18	9
	100	31	3	0.4	2	0.1
		100	100	100	100	100

Fig. 5. Sales of antidepressants
in Finland, Iceland, Norway, and Sweden



to the use of doxepin (Sinequan). In Sweden, 84% of the total sales in 1975 were to outpatients. It follows from the prescription data that there were more females than males among the patients (Table 3). The utilization increased markedly in the age groups 45–64 years, but stabilized in higher age groups.

DISCUSSION

As explained above, it proved to be impossible to obtain entirely comparable statistics on drug utilization, even though defined daily doses (DDDs) were employed as the unit of comparison. The defined daily dose generally corresponds to the dose that is employed for a drug's main indication. In the case of drugs that are used for many indications and, consequently, in different doses and administration forms, or in combination with other drugs, it is evident that differences will exist between actual doses and DDDs. Among the psychotropics, the neuroleptics show the most extreme variations, since between the doses employed against neuroses and psychoses there is a difference of approximately one order of magnitude (i.e., 10-fold). With drugs that are administered intermittently, e.g., sustained-release neuroleptics, special problems arise. On the other hand, it is of great importance to define one unit of comparison within a given drug group, even though it may be of questionable value from a medical point of view.

Other approaches to the comparison of drug utilization have been discussed (*11, 12*), but until more is known about the background against which sales data are compiled it is desirable to refrain from the use of over-complicated techniques. For the time being, the aim must be to obtain primary data that can be used as a basis for a more comprehensive discussion of the techniques used as well as for analyses of the prescription of drugs.

Suggestions for further studies

Comparison of the total sales of psychotropics in Finland, Iceland, Norway, and Sweden immediately reveals that certain differences do exist, and these difference imply that a closer analysis should be made of what is prescribed, who receives the drugs, and for what indications they are taken.

For example, it is not possible to explain why the sales of psychotropics are less in Finland than in the other countries. A number of preparations that are combinations of analgesics and sedatives or of spasmolytics and sedatives are, by definition, not included in this survey. A comparison of the use of these preparations seems justified, bearing in mind the differences between Finland and the other 3 countries. It would also be of interest to perform a close analysis of the use of psychotropics in general, especially concerning the prescriptions for hypnotics and sedatives. In the 1970s, the risk of overconsumption has been widely discussed in professional journals as well as in newspapers and periodicals. These discusssions may conceivably have had certain effects on the prescribing habits of physicians.

Why are benzodiazepines so widely used in Iceland?

When the sales are illustrated by means of a drug-profile, Iceland is clearly distinguished from the other 3 countries by the greater use of tranquillizers, especially the benzodiazepines. It is also because the sales of benzodiazepines are so high that the total sales figures for all psychotropics are highest in Iceland. As yet, it is only possible to speculate about the reasons for the difference in sales of benzodiazepines. As long as the criteria upon which the prescriptions are based are unknown, it is not possible to form an opinion as to whether the sales are to be considered as being on an adequate level or not. These differences seem to deserve an in-depth study.

Are there differences concerning the indications for neuroleptics?

Judging from the data on sales, neuroleptics are employed to a greater extent in Sweden than in the other 3 countries. It would be of interest to learn whether there are differences of opinion concerning the indications for the use of these drugs in the countries in question. In Sweden, it has been recommended that neuroleptics should be employed as alternatives to hypnotics, sedatives, and tranquillizers (*13*). This recommendation may have resulted in a more frequent use of neuroleptics for the treatment of minor psychiatric disorders in Sweden than in the other Nordic countries. An analysis aimed at finding the reasons for the prescriptions of psychotropic drugs at the district health centre at Örnsköldsvik revealed in 1973 that sleep disturbances and psychoneuroses accounted for about 50% of the prescriptions for neuroleptics (*14*).

Is it appropriate to prescribe hypnotics and sedatives for elderly patients?

It is evident from analyses of the prescription material in Sweden that psychotropics are more frequently prescribed for females than for males and that the number of prescriptions increases with the age of the patients. The same pattern has also been found in a number of other investigations (*1, 5, 15–17*). It appears doubtful if the prescribing of hypnotics and sedatives for patients of advanced age is always to be considered appropriate, judging from observations indicating that these agents can induce states of confusion in these patients (*13*). However, whether the prescribing of these agents is appropriate or not can only be decided by carrying out an investigation into the reasons for the prescriptions and by following up how the patients comply with the instructions for taking the drugs and how they react to them.

The variations in the use of psychotropics in different hospitals and clinics may reflect differences in the type of patient, but it may also be due to different treatment patterns. Here, too, an investigation into consumption data at the sales (or dispensing) level could possibly reveal which parts of this problem need closer study.

CONCLUSIONS

Comparisons of sales data based on DDD statistics can reveal differences in therapeutic practices between countries as well as changes with time. Moreover, these data can provide pointers to the areas of the drug utilization complex that deserve a closer study from the point of view of therapeutic attitudes and results. Likewise, comparisons between hospitals and clinics can reveal where problem areas are to be found.

It emerges from this investigation that it may be justified to perform a closer study of the prescribing of hypnotics, sedatives, and tranquillizers, particularly in relation to prescriptions for elderly patients. By means of prescription data it should be possible to follow the results of drug information of different kinds. On the other hand, analysis of the present data demands considerable manual work in order to obtain the desired comparisons. The use of computer techniques as well as of a unified coding system greatly facilitates investigations of this kind.

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CHAPTER 16

DRUG UTILIZATION STUDIES IN PERSPECTIVE

M.N.G. Dukes[a]

AN INFORMATION GAP

One of the most puzzling features of the world of medicines at the present day is the astonishing, and in some respects disastrous, lack of information about the way in which – and the extent to which – drugs are used and misused. At the best of times, drugs are commodities on which "hard" data are appropriately hard to come by. It is often difficult enough to assess the therapeutic merits of a drug and much more difficult to identify its adverse effects with any degree of certainty but, because this information is so vital to the employment of drugs, complex and time-consuming methods have been developed to elicit it, particularly for new medicinal compounds about to be released on the market. Yet at the same time society has, on the whole, been remarkably indifferent to the subsequent career of these drugs and to the vast volume of quantifiable information that is needed to indicate what role these products are playing in health care, and what good or harm they are doing. In most major countries of the world it is still impossible to find out how many specialities are on sale, much less what the turnover of these products may be. Even where this basic information is to be found, one is still left wondering which physicians are using these products, for which patients, and why. The result is that public health authorities commonly have the greatest difficulty in determining their priorities with respect to drug control, and in identifying problems as they arise. Even when one is faced with spectacular drug accidents – such as the occurrence of sclerosing peritonitis associated with practolol in the 1970s – the lack of exact information on the pattern of use of the drug concerned, its analogues and congeners, make it well-nigh impossible to determine the most appropriate corrective measures, which may range from mere warnings relating to a particular type of patient to a general prohibition of a family of related compounds. And even where such measures have, wisely or unwisely, been taken it is not possible to measure their effects with any degree of certainty.

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The pressing need for concrete data on drug utilization is particularly evident when one consults a report such as that on *Abuse of medicines* which was issued by the Council of Europe at Strasbourg in 1975. The working party concerned pointed to the existence of much over-use of drugs, some ill-directed usage, and a little under-use, but clearly found difficulty in pinpointing the location and extent of these problems. It may be quite justifiable to identify such problems as these on the basis of experience alone, and as an exercise in unquantified analysis the Council's report is well worth reading, but before one can design effective solutions to the problems and allocate appropriate resources to deal with them, one must be able to define and measure them more exactly.

THE USE OF SALES DATA

The most basic information on the use of any drug relates simply to its current total usage (and hence to its sales volume) in a particular country. It is hard to see why elementary information of this type is still regarded as confidential to the manufacturer concerned. The pharmaceutical industry, which has traditionally taken the view that a manufacturer's sales figures are sacrosanct, long ago developed (with delightful inconsistency) panel techniques with the aid of which any drug manufacturer can, at some considerable expense, determine the turnover of any or all of the drugs on the market, including, of course, those supplied by his competitors. The figures obtained in this way, from large groups of pharmacists and physicians, are reliable, detailed, and up-to-date. The end result of this exercise is that any pharmaceutical house worthy of the name has access to all the information that it requires, and that the primary (i.e., competitive) reason for maintaining confidentiality has, to all intents and purposes, disappeared; the only party that stands to lose is society at large, which is deprived of ready access to a valuable fund of information. It is hard to see how anything could be lost were the pharmaceutical industry to be obliged to publish detailed figures on the sales of its products; certainly much would be gained and a lot of effort and expense would be saved.

UNITS OF COMPARISON

Total turnover figures represent, however, only a starting point, and even at this basic level the figures obtained may be grossly misleading unless techniques are developed to take into account variations in dosage forms, packaging, and prices. The concept of the defined daily dose, as developed in Norway (see chapter 2), provides an essential tool for translating any figures on the use of drugs into comparable units, with the aid of which data on different

drugs or drug groups and from various practices, regions, or countries can be set alongside one another. This concept of the defined daily dose (DDD) is so simple, logical, and essential that one must hope for its universal acceptance; there is need for a procedure that will ensure that an arbitrary DDD is established for each new drug as it enters the market anywhere in the world.

BROADER CORRELATIONS

The comparisons that become possible with the aid of this technique open the door to meaningful study of drug utilization, both long-term and in the acute situation. They are of particular value when one penetrates more deeply into the problem and makes use of data relating, not to entire populations or hospitals, but to the individual for whom the drug is ultimately intended, to the physician who prescribes it for him, and to the reasons for his doing so. That one needs individual data of this type, in order to dispel myths that may be created by meaningless averages and in order to analyse apparent discrepancies, is beyond doubt. The physician who at first sight appears to be overprescribing particular drugs may in fact have a preponderance of aged patients; the data from his practice, far from meriting a rebuke, may provide useful evidence of drug needs in later life. In order to determine this, however, one will need to know how old the patients are who have received these drugs. For similar reasons, data on the individual patient should at least include information on why the drug was prescribed (i.e., the diagnosis) and the previous drug history. Ideally, one will also want to know whether the patient was admitted to hospital, and if he dies one should also know the cause of death. All this and other information must be provided with sufficient identification, by name or number, to ensure that data on one individual remains separate and distinct from data on another.

The aim is thus to bring together information that is to be found in part on the physician's prescription, in part in the records of one or more pharmacies, and in part in the civil register. Brought together in a data bank these facts provide a splendid tool for studying the use and effects of drugs, but taken as a whole they also constitute an intrusion into the individual's privacy, which is only defensible if there are firm guarantees that the information will not be misused. The individual has the right to object firmly, even to any government authority gaining such an insight into this part of his private affairs, if such guarantees are lacking; if the data were to become available to other parties – who might include prospective employers, detective agencies, or blackmailers – much graver problems could arise. The physician for his part, could object to the use of this information in such a way that his freedom of prescribing is jeopardized and his treatment of the individual patient opened to scrutiny (either scientific or economic) by others. Each country will have to find its own solution to these practical problems.

As suggested above, the great merit of the newer techniques for studying drug utilization lies in the fact that one can make comparisons. Wherever a

discrepancy is detected between the pattern of drug use in one situation and in another, it is justified to look for an explanation. It may occasionally be that the one pattern is entirely right and the other entirely wrong; more commonly it is found that there is a golden mean (from which major deviations in any direction are reprehensible), or that one is dealing with a mere artifact (in which case one must look again at one's methodology), or that the discrepancy throws new light on some aspect of drugs, disease, physicians, or populations. Such a finding may justify some type of action – most commonly, educational – to ensure that drugs are better used in a given situation.

THE NEEDS OF REGULATORY AGENCIES

The need for this type of feedback from practical medicine is nowhere more evident than in the field of drug control. In recent years, some astonishing differences have arisen between drug markets in different countries, largely as a result of variations in the approach to the control of drugs. Norway now has a mere 1500 specialities on sale. In the Netherlands, there are 3500, including some 1400 older products that have yet to be evaluated. Across the border, in the Federal Republic of Germany, the total number of marketed drugs is not even known though estimates range from 20 000 to 60 000; certainly few of them have been submitted to strict registration procedures according to present-day standards. What do such discrepancies mean in terms of public health? In all honesty, we do not know. The establishment of adequate drug control procedures is an extraordinarily costly matter, yet the universal trend now is to establish such procedures and to apply them with increasing rigour in the belief that public health will benefit. One is inclined to believe that the trend is laudable, but have we proof that it is indeed so? If one takes Norway and the Federal Republic of Germany as representing extreme situations within western Europe, one would at least expect to find the marked differences in drug policies reflected in some way in the public health statistics. Either the population of Norway, to put it crudely, ought to be suffering incapacitating symptoms on a large scale, deprived as they are of 50 000 prohibited drugs, or else the cemetries in the Federal Republic of Germany ought to be filled with the mouldering remains of those who have taken so many ineffective and dangerous drugs. Yet, surprisingly enough, these differences are not found, even when more subtle parameters are used. The resilience of the human frame may be one explanation; the lack of adequate data on which we can base our comparisons is certainly a more important one. And if one fails to obtain information on such basic and essential questions as these, how can one hope, in the present situation, to measure the efficacy of an educational campaign to physicians or study the cost-versus-benefit relationships of various therapeutic agents? Drug utilization statistics provide only one of the entities needed for meaningful analysis of these matters, but it is a vitally essential one.

VALUE TO THE DRUG INDUSTRY

If this type of information provides a basis on which health care systems can operate more efficiently and effectively, it should also be of value to the pharmaceutical industry. In determining how research into new pharmaceutical products should be directed and how information to physicians can best be presented, the pharmaceutical industry is in fact dependent on the same type of feedback as the government services require, and if we are to condemn unnecessary secrecy in one quarter we should not condone it in another. The drug manufacturers can provide a most valuable input of information for the study of drug utilization and if they do so they should be allowed to reap its benefits. Its benefits should also accrue on a wider front, even to those whose interest in the field of drug use is primarily sociological or economic. And not least, the feedback provided by drug utilization studies should help the practitioner.

PIONEERING STUDIES

It is curious, though in retrospect entirely understandable, that the prime initiative with respect to drug utilization studies, as they came to be performed during the 1970s, was taken in a small group of northern European countries. They were all countries – the Scandinavian nations, Scotland and Northern Ireland – where drug control and drug information were already well regulated, and where one would not expect to encounter the world's most acute problems with respect to excessive or improper use of drugs. On the other hand, as areas where new techniques in this field could be developed and tested, they could hardly be bettered. The relatively small size of the populations concerned, and the existence of such centralized organizations as the National Pharmacy Corporation in Sweden, the Norsk Medisinaldepot in Norway, and the National Health Service in the United Kingdom, provided some basic advantages including ready availability of certain types of data, albeit unprocessed for the present purpose. Of the other countries involved, Czechoslovakia was particularly important in that it provided a testing ground for developing analogous approaches in a socialist state.

But in all these countries, without exception, the enthusiasm of small groups of investigators was primarily responsible for the initiation and continuation of this work; support from the Regional Office for Europe of the World Health Organization and from national drug control agencies, however valuable it may have been, was secondary to the persistent enthusiasm of the pioneers. We have now reached a point in time at which there is every reason to seek an extension of this work. The techniques available have been identified; as described in this book they may not be perfect and they will certainly require adaptation to differing national and regional situations, but they have been tested in practice and some of the principal pitfalls have been identified. There

is now a need to apply them to those areas of Europe – and other parts of the world – where the tradition of drug use differs; new and instructive comparisons are bound to emerge.

FIELDS FOR STUDY

At the same time, there is a need to employ these techniques to probe more deeply into specific topics of importance to public health. Do we know why such a large proportion of our populations chronically take benzodiazepines as hypnotics and sedatives, and can we characterize the users and their mode of treatment so as to identify less fortuitous modes of use? How do some insurance systems affect the quality of therapeutic care that a patient receives? How do the newer drug delivery systems affect patient compliance? Can we correlate specific side effects with age and diagnosis? How does a government drug information bulletin influence prescribing? Who takes the many hundreds of tons of acetylsalicylic acid that are manufactured yearly, and why? Why does Sweden have a relatively high usage of antihypertensive drugs, and what are the consequences – good or evil – in terms of public health? These are intriguing questions, but they – and many like them – are also important if we are to understand the role that drugs, prescribed or unprescribed, play in society, and if we are to adjust that role so that society's real needs are met. Drug utilization studies have until now been the experimental tool of a handful of pioneers. It is time that they be adopted by governments, and vigorously applied as yet another means of ensuring that, at a time of soaring costs, the public health resources that industrialized society is able to deploy are used both effectively and efficiently in the interests of every one of us.

CONCLUSIONS

1. There is a pressing need for a rapid expansion of drug utilization studies in view of their importance for the optimization of drug therapy and drug control.

2. The methodology of such studies should be standardized, insofar as possible, so that meaningful comparisons can be made between different physicians, regions, and populations, and discrepancies and problems thereby identified.

3. Essential to the standardization of such studies is the adoption of a uniform classification of drugs and of an international system by which the defined daily dose (DDD) of any drug can be established and made known with a minimum of delay.

4. Sales data on pharmaceutical products should, in view of their importance for drug utilization research, cease to be regarded as confidential to manufacturers and become generally available for scientific purposes.

5. Since there is a clear need for correlating drug utilization data with personal and prescribing information, means of mobilizing such data, e.g., from prescribing records and the civil register, should be developed, together with legal and ethical safeguards to prevent misuse of such data.

ANNEX

LIST OF INSTITUTIONS IN THE WHO EUROPEAN REGION WHERE INFORMATION ON DRUG UTILIZATION STUDIES CAN BE OBTAINED

CZECHOSLOVAKIA

Central Committee for Rational Pharmacotherapy, Ministry of Health of ČSR, Box No. 60, **120 37 Praha 2.**

DENMARK

Sundhedsstyrelsen Avd A, Store Kongensgade 1, **DK-1264 Køben havn K.**
Tel.: 01 – 14 10 11

FINLAND

Research Institute for Social Security, The Social Insurance Institution of Finland, Nordenskiöldinkatu 12, **002 50 Helsinki 25.**

The Finnish National Board of Health, Siltasaarenkatu 18, **005 30 Helsinki 53.**
Telex: 12 – 17 74

ICELAND

Heilbrigdis- og tryggingamálaráduneytid, Lyfjamáladeild, Skólavördustig 46, **Reykjavík.**
Tel.: 91 – 25 000

NETHERLANDS

Department of Pharmacology and Pharmacotherapeutics, Subfaculty of Pharmacy, State University of Leyden, Wassenaarseweg 72, **Leyden.**
Tel.: 071 – 14 83 33 ext. 6211

NETHERLANDS (contd)

Department of Clinical Pharmacy, St Radboud Hospital, State University of Nijmegen, Geert Grooteplein Zuid 10, **Nijmegen.**

Tel.: 080 – 51 91 11

NORWAY

Norsk Medisinaldepot, Postbox 100 Veitvet, **Oslo 5.**

Visits: Sven Oftedals vei 10, Oslo 9.

Statens legemiddelkontroll, (The National Centre of Medicinal Products), **Oslo.**

Visits: Sven Oftedals vei 4–6, Oslo 9.

Helsedirektoratet, (The Directorate of Health at the Ministry of Social Welfare), Postbox 8128, Dep., **Oslo 1.**

Visits: Akersgaten 42, Oslo 1.

SWEDEN

Department of Drugs, National Board of Health and Welfare, Box 607, **751 25 Uppsala.**

Visits: Husargatan 8, Uppsala.

Tel.: 018–10 03 60

National Corporation of Pharmacies, **S-105 14 Stockholm.**

Visits: Humlegårdagatan 20, Stockholm.

Tel.: 08 – 24 08 00

UNITED KINGDOM

Branch PIE, Department of Health & Social Security, Hannibal House, Elephant and Castle, **London SE1 6TE,** England.

Northern Ireland Central Services Agency for Health and Social Services, 27 Adelaide Street, **Belfast BT2 8FH,** Northern Ireland.

Department of Therapeutics and Pharmacology, The Queen's University of Belfast, The Whitla Medical Building, 97 Lisburn Road, **Belfast BT9 7BL,** Northern Ireland.

Scottish Home & Health Department, Trinity Park House, South Trinity Road, **Edinburgh EH5 3SF,** Scotland.

Aberdeen-Dundee Medicines Evaluation and Monitoring Group, Department of Pharmacology & Therapeutics, Ninewells Hospital, **Dundee**, Scotland.

Enquiries: Dr L.J. Christopher.

Aberdeen Section, Department of Community Medicine, Aberdeen University Medical Buildings, Forsterhill, **Aberdeen**, Scotland.

Department of Pharmacy, Heriot-Watt University, 70 Grassmarket, **Edinburgh EH1 2HJ**, Scotland.

Enquiries: Mr A.W. Patterson.

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