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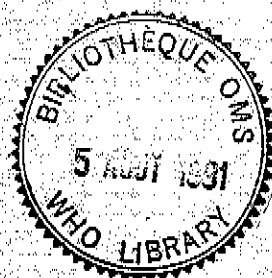
REGIONAL OFFICE FOR EUROPE

EUR/ICP/DSE 127(II)
0941s
ENGLISH ONLY
UNEDITED

36257

DRUG UTILIZATION STUDIES

Report of the
WHO Drug Utilization Research Group



Nordwijkerhout
5-7 June 1989

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1991

EUR/HFA TARGET 31

This activity was organized by the WHO Regional Office for Europe to promote work aimed at achieving the following target in the health for all strategy.^a

TARGET 31

ENSURING THE QUALITY OF SERVICES

Index terms

DRUG UTILIZATION
RESEARCH
CZECHOSLOVAKIA
NETHERLANDS
UNITED KINGDOM
UNITED STATES

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^a *Targets for health for all.* Copenhagen, WHO Regional Office Europe, 1985 (European Health for All Series, No. 1).

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1. Introduction

There is general agreement that the use of drugs should be rational; that is, that the right drug should be used for the right indication, by the right patient, in the right dose, in the right dosage form, for the right period of time and at a reasonable cost. The rational use of drugs is one of the aims of WHO and ways of achieving it are specified in various resolutions passed by the World Health Assembly. Drug utilization research is an important part of the activities necessary to improve the use of drugs. Without a clear knowledge of what is being consumed, by whom, at whose instigation, in which doses and at what cost, nobody can reliably identify problems and set priorities in the pharmaceuticals field, or measure the effect of regulatory or educational activities intended to change current practice.

The first meeting of a group of European scientists, later known as the WHO Drug Utilization Research Group (DURG), was convened in Norway in 1969. In those days, drug utilization data were not available to research workers in most places, and only a small number of countries were represented at the meeting. Since then drug utilization research has developed rapidly, and the number of countries and research workers interested in this field has steadily grown. Meetings of the Drug Utilization Research Group have been held at regular intervals in collaboration with the WHO Regional Office for Europe. These meetings aim at bringing together workers actively engaged in drug utilization research to discuss current projects, decide on common methodology and set priorities for future activities.

The 1989 meeting of the WHO Drug Utilization Research Group was held in Noordwijkerhout, the Netherlands. From 5 to 7 June 86 participants, 19 observers and 6 staff members from WHO Headquarters and the Regional Office for Europe were gathered to discuss various issues of drug utilization research. The International Narcotics Control Board was also represented. When the WHO Drug Utilization Research Group started, it was a mere European matter. In 1989 the attendants came from all over the world.

The main objective of this meeting was to discuss the methodology of drug utilization research in various age groups, ranging from the unborn child to the elderly. Furthermore, overviews were presented of the facilities available for drug utilization research in various countries and a proposal for national coordination of drug utilization research was drawn up.

2. Opening of the meeting

The meeting was opened by Ms Inga Lunde. On behalf of the WHO Regional Office for Europe and the Regional Director, Dr J.E. Asvall, she welcomed everyone present. She expressed gratitude to the supporters of the meeting, the Dutch Ministry of Welfare, Health and Cultural Affairs, the Royal Dutch Association for the Advancement of Pharmacy, the Royal Dutch Society of Physicians, the Royal Dutch Academy of Sciences, and the Dutch Health Insurance Fund Council. Without the financial support of these organizations, many participants and speakers would not have been able to attend the meeting, bringing in their specific knowledge and experience. She also thanked the local organizing committee (Professor Dr Albert Bakker, Dr Flora Haaijer-Ruskamp and Dr Chiel Hekster) for all the work they had done in preparing this meeting.

Finally she spoke some words in appreciation of the Drug Utilization Research Group and all the important work the Group has carried out so enthusiastically in order to achieve a healthy use of drugs. This work has always supported the Pharmaceuticals Programme of WHO in an essential way.

Then the Director-General for Health in the Netherlands, Professor Dr J. van Londen, welcomed the participants on behalf of the Dutch Minister of Welfare, Health and Cultural Affairs and the State Secretary of Health. In his opening speech he emphasized the significance of drug utilization research for the health of our society.

Nowadays drug consumption is an integral part of society. However, as consumption changes, the impression emerges that drugs are increasingly used to correct complaints generated by unhealthy habits or lifestyle and not merely to combat illness. At this point the political question evolves how well society can handle the availability of drugs. In a political debate, wise as well as unwise use of drugs must be defined. The knowledge that drug utilization researchers have gathered can help to answer these political questions, but only if policy makers obtain the appropriate information.

Professor van Londen argued that the information needs of policy makers are different from those of drug utilization researchers. The approach of policy makers and researchers differs because motivation for research and allowed time span are not the same. To bridge the difference in approach, one must understand one another's needs. Policy makers need a stable research methodology, an uninhibited flow of raw data, and results tailored to their information needs. A stable methodology can be developed by meetings such as the DURG meetings. An uninhibited flow of data can be ensured by creating a political and financial basis. Tailoring the results of research to the information needs of policy makers, e.g. to the economical aspects of drug use, will require the incorporation of appropriate parameters into research projects and the adaptation of a current methodology may be needed.

He recommended cooperation between researchers and policy makers in order to achieve mutual understanding of each other's needs, and to find consensus on the methodology of health-policy-related drug utilization research. In this way society may benefit from the results. Cooperation could be achieved by creating an appropriate independent body, responsible for developing drug utilization methodology. He mentioned that the Dutch government has already taken the initiative to this end towards the WHO Regional Committee for Europe.

Professor Albert Bakker then welcomed the participants on behalf of the local organizing committee.

After the opening speeches, Professor Albert Bakker was elected Chairman and Dr Gerd Glaeske Vice-chairman of the meeting.

Dr Owen Corrigan and Drs Tanja Geldorf acted as Rapporteurs.

3. Overview of drug utilization research in the Netherlands and other countries

3.1 Drug utilization research in the Netherlands

by F.M. Haaijer-Ruskamp

During the past decade drug utilization studies in the Netherlands have gained increasing attention, both by universities and bodies of public health. Furthermore, a special section of drug utilization research is expected to be established soon within the Dutch Society of Pharmaceutical Sciences. Several reasons can be mentioned for this growing attention:

- health authorities have recognized drug utilization research and its results as important tools for their cost-containment policy;
- pharmacists are becoming more active in rationalizing drug utilization; they supply information for monitoring drug use;
- society does not tolerate the occurrence of adverse drug reactions any longer; this asks for better drug-monitoring systems and post-marketing surveillance.

Dr Haaijer-Ruskamp described the types of studies that are carried out in the Netherlands and gave some examples. She also described the data and databases available as well as the problems that the Dutch drug utilization researchers encounter. The types of studies that are being or have been carried out can be divided into descriptive studies, studies of determinants of drug utilization, and studies of the impact of drug use.

Descriptive studies are being done in the areas of:

- drug use by specific population groups like children, the elderly, pregnant women (e.g. the use of diuretics by hypertensive pregnant women);
- use of specific drug groups, such as benzodiazepines in different neighbourhoods, antibiotics in hospitals and hormones with long duration of action in Europe and developing countries;
- drug costs (analysis of trends in drug use and drug expenditure to reach transparency of the market and evaluate prescribers' drug choices);
- interdoctor variation (studies within specific therapeutic areas);
- anthropological view on drug utilization (crosscultural study on drugs and children's perspectives in Europe; the treatment of diarrhoea, cough and fever in the Philippines);

Studies of determinants of drug utilization can be divided into drug-policy-related studies (e.g. the availability of drugs versus drug use) and studies of the influence of information/knowledge about drugs and drug use. The influence of knowledge and attitudes of physicians and the knowledge and attitudes of patients are being studied as well as the influence of pharmacy-supplied drug information, e.g. the impact of monitoring and feedback of the prescribing figures of general practitioners.

Studies of the impact of drug use concern:

- adverse effects (detection of adverse effects by prescription sequence analysis with flumarizine; detection of population at risk by medication history as a source for risk indicators; reference work);
- drug use and quality of life (anti-epileptics);
- effects of chronic drug use (feasibility study of how effects can be detected).

In the Netherlands the following five kinds of databases from different organizations exist for use in drug utilization studies:

- health fund data, containing information about the kinds, amount and costs of drugs that are used by the health fund patients; the data refer only to outpatient drug use and are available at regional level (per health fund) and, until 1984, also on national level (approximately 60% of the total population); on the regional level the data can be differentiated per individual doctor or pharmacist. A new database is being built up at the moment. It will contain differentiated health fund data on national level (a sample of approximately 30% of the total health fund population) from 1988 onwards. The data are collected in a central database at the Dutch Health Insurance Fund Council;
- pharmacy records; almost 90% of the pharmacies are computerized (individual), which offers possibilities for (local) drug utilization studies related to patient data, such as age and gender;
- hospital pharmacy records; in some hospitals data are available on the dispensing of drugs per ward;
- the Institute of Medical Statistics (IMS) has complete figures on the turnover for every drug, in counting units and in costs. Also diagnosis-related data are collected from panels of physicians by registration in their practice. IMS data are not easily accessible to research workers;
- in a national study of general practice, diagnosis-related drug-prescribing data are collected from 160 physicians (1986/1987).

The problems of research in the Netherlands are problems of methodology, conceptual problems and practical problems.

Methodology problems are met mainly in the field of data collection: lack of coordination between different databases, difficult access to databases and lack of instruments for record linkage. There is also a problem of validity and reliability of the different data and data sources.

Conceptual problems refer to the fact that not enough studies are carried out from the patient's perspective, that there is a lack of prospective studies and a lack of endpoints (how to integrate known scales and indices in drug utilization studies);

Finally, the practical problems, which can also be seen in many other countries, are caused by privacy-aspects of the data, vested interest and insufficient financial support.

3.2 Drug utilization research in other countries

by K. Griffiths

In order to assess the main areas of recent drug utilization research an online search was undertaken using MEDLINE. This search identified 732 major references published between January 1979 and May 1989, representing research from 41 different countries. The three leading countries in terms of published studies were the USA (43.6%), the UK (11.5%) and Czechoslovakia (5.2%). No growth in annual research paper numbers during the decade 1979 to 1988 was apparent. A survey was also carried out by the Drug Utilization Research (DUR) centres to ascertain activity and drug strategy at national level and to assess liaison with the WHO Collaborating Centres in Oslo and Uppsala. From the mailing list of the WHO Regional Office for Europe (WHO/EURO) 18 national centres were identified - potentially there are 11 more that could be set up.

Wide variability in the activities between centres was identified. Some centres were mainly acting as contact points for drug utilization researchers, while others were more active; keeping lists of past and current DUR projects, making national drug lists available on computer tape or disc or reviewing the national hospital formulary. In other countries DUR groups of interested professionals existed, rather than a formal centre. Collaboration with the WHO Collaborating Centres was generally perceived as an essential objective but several centres admitted that the collaboration was not yet as close as it might be. No centre produced an annual report and in several cases developments appeared to be hindered by insufficient financial resources.

A particularly positive finding of the survey was the widespread adaptation of the ATC and DDD methodology.

Arising from the paper the author proposed draft terms of reference for national DUR centres as follows.

The WHO DURG should actively encourage the setting up of national DUR centres to:

- (a) coordinate work with governmental and other agencies involved in aspects of drug utilization, set priorities and acquire and make best use of data in this field to the benefit of patient care in terms of community needs;
- (b) encourage collaborative drug utilization research through informal or formal DUR groups or associations;
- (c) act as a link with the WHO Collaborating Centres for Drug Statistics Methodology in Oslo and for International Drug Monitoring in Uppsala;
- (d) act as a contact point for drug utilization researchers in that country;

- (e) if possible, ensure that a list is kept of all drug products on that country's market, giving:
 - (i) defined daily doses (DDD)
 - (ii) anatomical-therapeutic-chemical (ATC) classification which, preferably, will transfer on computer tape or disks;
- (f) keep a list of that country's sources of drug utilization, information and morbidity/mortality data;
- (g) keep a list of that country's published DUR references and, when possible, unpublished references - preferably with key work indexing, especially for data sources and methods;
- (h) when possible, keep an indexed directory of past and current DUR projects;
- (i) send annual reports on the activity of national DUR centres to WHO/EURO.

3.3 Discussion

In the discussion that followed many participants found it disappointing that so few drug utilization studies were concerned with quality of care issues, despite the fact that improving quality of care still is one of the main objectives of drug utilization research (DUR).

Today the development of a DUR methodology, the testing of hypothesis (e.g. testing strategies to reach rational drug use) and pharmaco-epidemiology are generally considered as important research fields. With regard to pharmacoepidemiology, the importance of linking ADR data collected by the WHO Collaborating Centre in Uppsala, to drug utilization data was stressed as was the need to secure the availability of these data to drug utilization research workers.

As drug utilization research workers and others frequently encounter problems when looking for appropriate DUR publications, it was proposed to agree upon and develop an international list of keywords and their sequence for DUR publications. The list should also be used for literature databases.

Finally it was stated that it would be for the benefit of all drug utilization research workers if the national DUR centres would prepare a bibliography with references to all DUR in their country. In this way the existing discrepancy between the different literature databases could be eliminated.

4. Reports from WHO Collaborating Centres

4.1 Collaborating Centre for Drug Statistics Methodology

by K. Öydvín

The WHO Collaborating Centre for Drug Statistics Methodology started its activities in 1982, as result of an agreement between WHO/EURO and the Norwegian Medicinal Depot. The terms of reference for the WHO Collaborating Centre in Norway are:

- to classify drugs according to the ATC system;
- to allot DDDs to drugs which have received an ATC classification;
- to review and revise, as necessary, the classification of individual drugs under these two systems;
- to survey the literature on drug utilization and publish a bibliography at regular intervals.

The Collaborating Centre handles requests from scientists, research centres and institutions to classify drugs according to the ATC system and it establishes preliminary DDDs for these drugs. Drugs with single substances take priority over combination preparations.

The Centre is advised by an Advisory Board which consists of international experts. The members are appointed by the DURG each three years (latest in Oslo, 1987). In 1988 and 1989 the Board discussed its future work, the principles for making alterations in the ATC system and for the establishment of DDDs and DDD alterations, as well as the cooperation between the Nordic Council on Medicines and WHO.

The main work of the Centre during the report period has been to take care of the distribution of the ATC register to governments, the pharmaceutical industry, organizations and research workers in many countries. Furthermore, much ATC/DDD work has been done in connection with specific requests and research projects. In cooperation with the Nordic Council on Medicines a revision of the guidelines for ATC classification is being prepared. The new guidelines will be published in 1989 and will make the coding of combination preparations easier. The revision of the DDD guidelines will start in 1990.

Much work has been done for the MONICA project; this project intends to relate cardiovascular drug-consumption figures to mortality data and population structure. Because of lack of such data a questionnaire was sent to the participating centres to try to map the existing figures on drug consumption. The results are not yet available.

Finally it may be of interest to mention that the development of an ATC-like classification for veterinary drugs is under discussion and that proposals are made for codes for herbal medicines.

4.2 Collaborating Centre for Clinical Pharmacology and Drug Policy Sciences

by F.M. Haaijer-Ruskamp

The WHO Collaborating Centre for Clinical Pharmacology and Drug Policy Science was established in February 1988, at the University of Groningen, the Netherlands. The centre's work is partly a continuation of projects undertaken at the university from 1984 onwards. The programme is designed to support and ensure an optimal use of medicines. Research activities and educational activities are integrated issues in the programme.

The research activities at the centre are:

- (a) collection and analysis of basic data on the existing situation. At present the focus is on drug use in high-risk groups, notably pregnant and lactating women and the institutionalized elderly and on the use of psychotropic drugs, selfmedication and drug use in hospitals;

- (b) supportive research on official policies and determinants of drug use and development of means to influence the way in which pharmaceuticals are sold, dispensed, prescribed and taken. Economic drug policy measures in Europe and their repercussions are analysed and the feasibility of integrated drug policies is investigated. Furthermore, the attitude and knowledge among health professionals as well as the public are analysed, with special attention paid to the relevance for drug information (research subjects in this field are: drug choice process in general practice and hospitals, impact of written versus verbal information on prescribing, impact of the area clinical pharmacologist, impact of written information for patients). Special focus is on iatrogenic drug-induced injury, and the development of legal and ethical norms with regard to drug-induced injury.

The educational activities are:

- (a) the development of new undergraduate and postgraduate teaching programmes and materials in drug therapy and (b) the development of prescribing with a problem-solving approach.

Future activities will be the editing of a newsletter on drug policy matters, the issuing of documents relevant to drug policy and the development of a protocol for a study of how to stop unnecessary chronic medication.

4.3 Collaborating Centre for International Drug Monitoring. Use of Drug Utilization Methods

by M. Lindquist

In 1971 a drug monitoring centre was established in Geneva at WHO Headquarters. A pilot programme had then been running for three years. In 1987 Sweden took over the operational responsibility for the programme and a Collaborating Centre operating from Uppsala, Sweden was formed. The number of participating countries is currently 28. At the latest meeting of the national centres, held in Uppsala in 1988, observers participated from countries that had announced their interest in the programme, including the USSR and China. National centres forward adverse reaction reports, either on magnetic tape, diskettes or as papers, and these are stored in a database. About 90% of the reports are sent by computerized media. Following processing, quarterly and yearly compilations are sent to national centres. A quarterly newsletter, which contains adverse reaction information, is also prepared and circulated.

The database currently contains 660 000 individual reports. A major aim of the centre is to generate signals of new adverse drug reactions as early as possible. To achieve this, the database is screened both automatically and manually. Standard programs are used to produce a yearly document of all adverse drug reaction combinations in the database. Four times per year, lists of foetal disorders, deaths, neoplasms and drug dependence are produced together with a document of all adverse drug reaction combinations which are new to the system. These documents are sent to all national centres.

To be able to follow up adverse drug reaction signals generated within the program it is therefore necessary to establish collaborative links with expertise on drug utilization and epidemiology and with databases containing

information on drug use. In September 1988 a symposium was organized jointly by Uppsala University, the WHO Collaborating Centre and the Swedish Department of Drugs of the National Board of Health and Welfare. Representatives of National Drug Monitoring Centres were invited together with representatives of the industry, epidemiologists and other interested parties to discuss the possibilities of linking signal generation and signal follow-up.

Another important issue is the question of wider access to data. Because of confidentiality restrictions, data held at the Collaborating Centre are at present only available to the drug authorities in the 28 participating countries. It will indeed take time and effort, but we hope to reach the point where data generated within the collaborative programme can be better used and serve to improve drug safety worldwide.

4.4 Discussion

The report of the Centre for International Drug Monitoring gave rise to the question if adverse drug reaction (ADR) signals generated by the centre had led to withdrawal from drugs in any country. It seems that the signals serve as background information for measures taken by drug registration authorities in the various countries, but it remains unclear if the signals directly have led to withdrawal.

Furthermore, it was mentioned that initiatives have been taken to ensure that ADR data from the Uppsala centre are made available to countries that need them (e.g. developing countries).

On a national level cooperation between Drug Monitoring Centres and DUR centres should be encouraged to improve the interpretation of spontaneously reported ADR.

5. WHO/EURO Copenhagen and WHO/Headquarters Geneva

5.1 Appropriate technology for health and drug utilization research

by V. Thambypillai

As a consequence of the policy document "Health for all by the year 2000", the WHO Regional Office for Europe has concentrated on 38 target objectives and has responsibility for ensuring quality of care and assessment of health technologies. In this context three specific projects were discussed as they represented examples in drug utilization research. The first related to antibiotic policies. The aim of this project was to investigate if a relationship exists between the occurrence of multiple resistant strains of bacteria and aminoglycoside consumption. A strong correlation between resistance patterns and aminoglycoside consumption was observed and the banning of aminoglycoside use in primary health care was advocated.

The second project discussed related to acute tonsillitis, the aim of which was to determine the relationship between diagnosis, prescribed therapy and clinical outcome. Among the questions to which the project expects to provide answers are the following:

- (a) How common is acute tonsillitis among clients seen in general practice?

- (b) How severe is the episode at the time of contact with the general practitioner?
- (c) What antibiotics are prescribed?
- (d) What are the dosage, cost and duration of treatment?
- (e) Is the antibiotic prescribed the drug of choice?
- (f) How often is treatment failure encountered?
- (g) Is the prescription based on a bacteriological sample?

The outcome will result in recommendations from national guidelines.

The third project reviewed was on the effect of iron in milk formulas on child growth and health. The objective of this comparative randomized study is to determine whether a high or low content of iron in milk formulas is better for a child's growth and health. A comparison will also be undertaken of routine iron prophylaxis versus selected iron treatment during pregnancy.

5.2 Utilization studies of psychoactive drugs

by I. Kahn

Dr I. Kahn stressed that, in the light of the continued escalation in drug abuse, the need for having data on drug utilization of psychoactive drugs was now more urgent than ever.

The evolutionary programme of WHO to promote the rational use of drugs means very little unless one is aware of the details of the drugs that people are consuming in a particular society. The WHO Expert Committee on Drug Dependence, which tries to establish a benefit/risk ratio of a psychoactive substance, remains at a loss because on various occasions data on the utilization of the particular drug are not available.

WHO has restructured all drug-related programmes at Headquarters and grouped them within a new Division of Drug Management and Policies. This was done with the objective of increasing coordination and collaboration. Thus, the functions assigned to WHO by the International Drug Control Treaties, previously part of the Division of Mental Health, are now within the new division. The new Unit of Psychotropic and Narcotic Drugs (PND) will continue to evaluate psychotropic and narcotic drugs with dependence liability for their benefit/risk ratio.

The second important task of the PND is to promote the rational use of licit psychoactive drugs. A WHO publication, Psychoactive drugs - how to improve prescribing (1988), lays down the basic principles that WHO considers to be important. The obvious approach is to review the educational efforts by schools of medicine, pharmacy and nursing.

In June 1987, an international conference was convened in Vienna by the Secretary-General of the UN to consider drug abuse and illicit trafficking (ICDAIT). The document "Cumulative multidisciplinary outline (CMO)" was finalized by the conference. The Drug Action programme of WHO had prepared guidelines for more accurate forecasting of the therapeutic requirements of all types of drugs. The improvement of prescription, delivery and utilization practices regarding psychoactive drugs requires an intensification of the cooperation between national pharmaceutical services, medical and pharmaceutical bodies, research institutions, the pharmaceutical industry and others.

It was therefore concluded that the WHO programmes in PND which try to promote the rational use of narcotic and psychotropic drugs remain handicapped because of lack of drug utilization data. It is the singular class of drugs which, when not properly used, causes dependence, abuse and public health and social problems. New developments during the past two years, such as the International Conference on Drug Abuse and Illicit Trafficking, have further emphasized the need for drug utilization data.

6. Drug use in different age groups

6.1 Drug use in different age groups

by G. Tognoni

In connection with the main subject of this meeting, drug utilization research (DUR) in specific age groups, professor Gianni Tognoni put forward some general principles and topics for drug utilization research. He proposed a new, more epidemiological, more culture-oriented approach to DUR.

In order to explain why DUR needs a different approach, he showed some results of the Italian drug utilization studies to illustrate the achievements of DUR. Until now, the methodology of DUR has been determined by quantitative macrovariables, such as number of prescriptions, amounts of defined daily doses (DDDs), etc. These macrovariables are used to reveal problem areas in drug prescription. One of these areas is the broad variation in national and international drug prescription profiles. The explanation of this variation is sought in epidemiological and demographical differences, and in soft indicators, such as drug information, knowledge, education, attitude, cultural background, etc. However, there is no uniform methodology in the search for explanations since these are often based on assumptions only. Until now this approach has proven to be insufficient in solving the problems of drug prescription. The reason for this is that DUR is always "running behind"; drug utilization researchers only observe the quantitative outcome of a combination of all kinds of influencing factors and variables. DUR needs a more anticipating approach in which not only quantitative drug utilization (DU) data are sampled but also the factors and variables that influence drug prescription are monitored systematically.

Professor Tognoni proposed to develop this new approach to DUR in a European setting. DUR should try to become integrated with clinical pharmacology, clinical epidemiology and public health.

Automated recording of drug prescriptions in general practice with linkage to basic demographic data on exposed populations is becoming available in most European countries. By using flexible designs, a regular monitoring of ongoing activities would be allowed. For example, it may be decided to focus on samples which represent areas expected to vary in their drug exposure because of different composition and cultural environment, and which may be analysed with a problem-oriented approach, e.g. psychotropic drugs in the elderly, the menopausal female population and hypertensive treatment in different age groups.

Professor Tognoni discussed the interest in establishing a European network of units of epidemiological surveillance which could adopt a combined age- and problem-oriented approach to compare frequency of prescription and to provide baseline data to be used in the assessment of the cultural setting

where prescriptions are generated. Dr G. Boëthius, as invited discussant, added some remarks to professor Tognoni's proposals for future methodology and future research issues. He stated that future DUR had to be clinically relevant. DU researchers should cooperate with clinicians to define relevant research areas and also with the practical carrying out of the studies.

Dr Boëthius also suggested that DUR ought to be part of the pharmacotherapeutic training of clinicians; improvement of patient care has to be the ultimate goal of DUR and integration of DUR in medical education is therefore, important.

Dr Boëthius agreed with Professor Tognoni's proposals for a future DUR methodology in an international setting. But he also advised first to test the new research methodology in a homologous situation in one country, before setting up international, comparative studies.

He illustrated how a comparative study had recently been started in a more homogeneous field in Sweden, using an integrated methodology. The study is carried out in the field of bronchial asthma and related obstructive diseases. Antiasthmatic therapy can be considered as a clinically relevant issue. The prevalence of asthma is increasing and approximately 5% of the total population in Sweden are now infected. Utilization and cost of antiasthmatics have also increased strongly but treatment is still far from optimal. The mortality rate in patients with obstructive lung diseases is not decreasing. There are also large variations in the use of antiasthmatic drugs in different parts of Sweden. In the study the counties with the highest and lowest use of antiasthmatic drugs are compared. A comprehensive set of data sampled in each county is being examined (e.g. demographic factors, environmental factors, morbidity figures, diagnostic criteria and degree of treatment). In cohorts of different age groups the extent to which each of these factors influences drug utilization is being investigated. The study is not yet finished, but Dr Boëthius expected that the percentage of over- and undertreatment could be assessed when all data had been collected and combined. It will then be possible to start intervention studies to improve drug treatment.

If this methodological concept gives satisfactory results in one country, it will probably also be possible to carry out international cohort studies using the same methodology.

6.2 Discussion

In the discussion that followed, some of the DURG members strongly supported Professor Tognoni's proposals for a more culture-oriented approach to the drug utilization research methodology and international, comparative drug utilization studies. Professor Tognoni was asked how the international, interdisciplinary DUR work should be organized in practice. In his view it would be preferable if the different disciplines could study the same object from their own point of view, following parallel protocols.

Furthermore it was remarked that in culture-oriented DUR not only the attitude and medical knowledge of the population should be investigated but also those of the medical profession itself as these are important issues when cultural differences are being investigated.

It was also put forward that a country should first solve its own problems by creating a nation-wide DU-information system, before joining an international study. Governmental support (financial, availability of data) is necessary to build up the technical framework for the international DUR.

The chairman closed this session by concluding that international, culture-oriented, comparative DU studies can be an important tool in finding the reasons why the DU patterns differ so broadly between nations. He invited the DURG members to join both the ongoing international studies and those proposed by professor Tognoni.

7. Drug use in pregnancy and lactation

7.1 Drug use in pregnancy

by M. Bonati

The vast number of studies of pharmacokinetic and metabolic aspects of the developing foetus and newborn child and the few major epidemiological studies on malformation risks have created a cautious attitude towards drug use in pregnancy. The results of controlled trials on selected pharmacological interventions (e.g. for hypertension, preterm labour) have helped to clarify some controversies on drug prescribing during pregnancy. However, it seems that the question of the quality of prescribing and using drugs in pregnancy has not been adequately covered in general. In view of the lack of clear guidelines, overmedication is an ever present risk.

A detailed evaluation of international literature data on population surveys on drug use during pregnancy showed that a median of 4.7 drugs are taken by every woman ranging from 2.9 to 5.5 drugs in comparative studies. The most commonly used classes of drugs are: iron and vitamins (taken by all women), followed by analgesics/antipyretics/anti-inflammatory agents (mostly aspirin); anti-emetics and antacids (1/4 of the women); and anti-infectives (including tetracyclines, sulphonamides and chloramphenicol). Although the review is based on data obtained from widely differing contexts, times and study methods, it may be concluded that the quality of drug use in pregnancy is still questionable. There is a need for a broad, international, epidemiological study of drug use in pregnancy. Such a study should be carried out with a good research protocol, including comparative variables and covering the different contexts of drug utilization in the various countries.

With this objective a collaborative international research network has been set up to provide a collection of comparable data on a population large enough to represent the current situation in this field across the various cultural backgrounds and health care settings. A network of hospitals/centres which provides obstetric and perinatal care has been established to assure a readily available resource to test and validate therapeutic or prophylactic measures and to study drug safety issues. The hospitals provide records with obstetrical history, data on delivery, hospital data, and vital data on the newborn. The pattern of drug use in pregnancy is assessed through standardized interviews with women admitted for child delivery to the sample hospitals. Data on the mother's education and habits (alcohol, smoking, etc.) are also recorded.

The women were interviewed during the first week after delivery. So far, 13 participating countries from Europe, United States, Asia and Africa (106 hospitals) have returned 9714 forms (a response rate of 52%). An analysis of the responses shows that 15% of the enrolled women took no drugs at any stage during pregnancy, while those who did, received an average of 2.6 (range 1-13) prescriptions. Intra- and intercountry differences in prescribing habits were found. Besides, the observed drug-use profiles differed from the results of the literature review. This indicates that drug use is influenced by a combination of different variables, such as time, country, etc.

To evaluate how representative the sampled data are, the findings in each country of a few general variables (i.e. methods of contraception, mode of delivery, malformation at birth, breastfeeding) were compared with data already available. A good agreement was found.

The usefulness of the data sampled can be illustrated by the following example: the use of oral iron supplements in pregnancy. In general, a normal, monitored and adjusted unsupplemented diet in pregnancy can be considered sufficient to maintain a required amount of iron in the body stores and to prevent pregnancy-related anaemia. However, the high iron-utilization figures show that this consideration is not generally accepted: the use of oral iron supplements in pregnancy in the 13 countries ranges from approx. 15 to 90% of the interviewed women. From a medical as well as an economic point of view, this high routine use of oral iron supplements is questionable.

The large amount of sampled data will have to be analysed more profoundly. When all the findings of this study are available, the information on this topic may become more complete. Repeating this exercise in the future by comprehensive surveillance programmes may give a constantly updated picture of drug utilization during pregnancy.

The approach to this study, which involves the use of data generated by a collaborative network for monitoring and measuring the influence of scientific information, changes in cultural attitudes towards medicines in pregnancy and initiatives likely to be taken by health authorities, was found to provide reliable results by the research workers participating in the study.

Having complimented the researchers from the coordinating centre for this important work, ms L. de Jong discussed this collaborative study on drug use in pregnancy. She mentioned that a similar study will start in the Netherlands, with a somewhat different protocol. About 75% of the deliveries in the Netherlands take place at home or in an outpatient clinic. Therefore the Dutch study will be more complex than the collaborative one.

She discussed three items with respect to the collaborative study: reliability of data, comparison between different countries and future objectives.

Considering the reliability of the drug exposure data from the collaborative study, it should be realized that different methods of data sampling can lead to incomparability of data. It is of interest to know to what extent the data obtained from the two different sources in the collaborative study (by interviewing mothers 1 to 9 months after the drug was consumed and by hospital records) are comparable. Earlier investigations of drug use in pregnancy had shown that the extent of agreement between questionnaire data on drug exposure on the one hand and hospital records on

the other depends on the mother's recall period. A study focusing on events associated with childbirth, conducted three weeks after delivery, showed an almost perfect agreement between the mother's self reporting on drug exposure and medical records, while two others with a recall period of between 9 months and 30 years showed poor agreement. A relatively short recall period seems to result in more accurate self-report data.

Another problem in the interpretation of questionnaire data is the specificity of the questions. Mitchell et al. (1986) evaluated the effect of questionnaire design on the ascertainment of drug use in pregnancy. It was concluded that the reported antenatal drug-exposure rate varies greatly in accordance with way the mother is questioned. Open-ended questions (Were any medications or treatment prescribed to you?) can lead to a high rate of underreporting, while specific questions about indication (Did you take any drug for the following reason?) and drug names (Have you taken any of the following medications?) are far more successful.

With regard to the reliability of the data collected in the collaborative study it is important to know if the above-mentioned findings are taken into account in the study design.

Ms de Jong explained that the study on drug use in pregnancy in the Netherlands will contain specific questions with respect to drug use and also to patient compliance. Moreover, data from pharmacy records will be used to ascertain the reliability of the questionnaire data.

The second point of discussion in the collaborative study is the difficulty to compare data from different countries. For example, the percentage of women who deliver at home or in the hospital varies between countries. This can influence the characteristics of the study populations and should be taken into account when comparing the data from different countries. Furthermore, women's attitude towards non-prescription drugs can influence drug-use reporting. It is possible that in some countries non-prescription drugs are not considered as real drugs.

The last item for discussion regards future objectives for DUR in pregnancy. The first priority is to be given to a good description of drug use in pregnancy. Then, from the drug use figures, rationality (quality) of drug therapy in pregnancy has to be analysed. For this purpose Ms de Jong recommended the use of a drug-classification system that divides drugs into five pregnancy categories, according to the degree of risk to the foetus. Such classification systems are used by the FDA (Food and Drug Administration) in the USA and in Sweden and Australia. The combination of data on drug use on the one hand with such a quality-category-system on the other hand offers an opportunity to detect the real problem areas; a necessary feedback for health-care workers, patients and public health authorities.

7.2 Discussion

The methodology of DUR in pregnancy was the main subject of the discussion.

Professor Tognoni commented on Ms de Jong's remarks about the reliability of the data from the collaborative study. He made it clear that the questionnaire was designed according to the results of the studies she has quoted; the questionnaire contained a combination of open-ended and specific

problem-oriented questions, in order to relate the date of the drug use report to the perception of women. He also made a general remark about the methodology of data gathering by interviews versus data collecting from medical records. In his opinion interviews with populations are much more reliable, especially when comparing different populations. The use of data from medical records can give a far higher bias because the quality of medical records can vary enormously, depending on the institutions and organizations.

Professor Laporte said that Spanish studies, comparing data collected by a questionnaire with two questions (open-ended as well as specific indication-oriented questions), versus data from a questionnaire with 3 questions (also specific drug names asked), showed no important differences in drug use

Ms de Jong argued that it is important that the various research groups exchange experiences with the different study designs, in order to find out which is the best design.

Dr Hogerzijk pointed to the fact that the method of data collection in the collaborative study could lead to problems when comparing data from different countries. Medication (incl. selfmedication) will only be detected in those women who are admitted to hospital for delivery. In some countries (e.g. developing countries like Zimbabwe, that also collaborated in the study) the percentage of hospitalization for child birth is very low (approximately 10-15%), while in the developed countries it is much higher. How will this difference be dealt with? Besides, he noted that the shown figures on selfmedication in Zimbabwe are unlikely low (10% of the interviewed women), while the general impression is that almost everyone selfmedicates.

Dr Bonati replied that in the study protocol enough room was left for data collection on deliveries outside the hospital; the place of delivery had to be specified in the form. The data received also included home deliveries.

Some final remarks:

The young generation is not aware of the teratogenic risks of drugs. Disasters such as those seen with thalidomide are almost forgotten.

When the 18 new studies of DU during pregnancy will start again, it is proposed not to stop at child birth, but to follow-up at least during the first year of life (lactation period and infancy).

7.3 Drug use in lactation studies. Issues and pitfalls

by I. Matheson

Comprehensive data on the extent of drug use by mother and infant during the entire lactational period (sometimes lasting for 2 years) is missing. Data from recent studies in maternity wards based on prescriptions, medical charts and hospital records showed that the proportion of mothers receiving medication during the first days' post partum varies between 70 and 100%, depending on whether iron and vitamins are included. Analgesics, laxatives and hypnotics are the therapeutic classes most often prescribed. Unpublished data from drug interviews with 482 women in two Norwegian hospitals in 1988 showed that 80% of the mothers received analgesics, 60% hypnotics and 30% laxatives. Only a few studies have differentiated between drug use in

breastfeeding and non-breastfeeding women. Besides hospital surveys, drug utilization in post partum women in a home setting has been investigated for defined periods. Several drugs are still insufficiently documented in human milk. Epidemiological studies in breastfeeding women may serve as a basis for selecting drugs that are candidates for investigations of breast milk and the breastfed baby. In one study it was found that 6 of the 10 most commonly used drugs in the maternity wards lacked data on breast milk. Surprisingly enough, this list included drugs like phenoxymethylpenicillin and nitrazepam.

Besides drugs, breast milk may be contaminated by cigarettes, alcohol and coffee consumed by the mother. These intakes should therefore be included in the surveys, as they may be important predictors of infant disorders. One such example is the higher prevalence of colic in infants of smoking breastfeeders compared with that of those of non-smoking breastfeeders. Cases of infant diarrhoea and irritability, probably because of maternal coffee consumption, have also been seen.

In a few studies the relationship between breastfeeding and number of drugs and dose used has been investigated. During a 2-week period it was found that the drug use in mothers who weaned their babies during the first months is significantly higher (307 versus 1266 DDD/1000 mothers/day) than it is in those who continued breastfeeding for 4 months. No difference in the number of drugs/person during the 4-month period was found according to the breastfeeding group and duration of breastfeeding. When multiple regression models were used variables which seemed to predict drug use during a 4-month period were maternal attitude to drugs, maternal education and infant disorders.

In our studies one of the aims was to calculate the dose received through breast milk. The possibility of comparing the infants' direct (active) as well as indirect (passive through breast milk) exposure to drugs should also be emphasized. The active exposure was calculated in appropriate doses for a three-month-old infant, infant Defined Daily Doses (iDDD), which averaged 10% of the adult DDD for the most common infant medications. The dose through breast milk was 1% of the mothers DDD, multiplied by 10 to obtain iDDD.

Comparing mothers who breastfeed with those who do not, usually presents problems because of covariables, of confounding factors. Breastfeeding mothers are normally older, better educated and non-smokers. One of the more interesting findings in our mother and infant study was a significant correlation between the drug use of the mother and that of the infant. In fact, this finding confirms the Swedish results that indicates a correlation between the number of prescriptions written for the mother and those written for the infant. In addition the number of drugs taken by mother and infant in the study increased with increasing education.

A positive correlation between the number of infant disorders and the educational level in working women and a negative correlation between the number of infant disorders and housewives raised the questions: Do professional women complain more or do they create more symptoms in their infants?

Against this background Dr Moore undertook a simple questionnaire type survey of pediatricians, general practitioners and specialists and concluded from the results that while there seemed to be few side effects occurring, physicians did tend to try to prevent them and to ask mothers at risk not to lactate.

In conclusion Dr Moore agreed with Ms Matheson that considerable work remained to be done to answer such questions as the following:

- What is the drug utilization level in lactating mothers and what is it in comparison with non-lactating mothers?
- What role do drugs play in the decision to breastfeed children?
- What are the risks for the breastfed children of women taking medications?
- What drugs should be looked at most carefully in terms of pharmacokinetics and effects?

7.4 Discussion

With regard to Dr Matheson's presentation it was put forward that this type of individually oriented DUR in mothers and children is important and it can bring us closer to the determinants of drug use. It would be interesting to expand the study to include other social and demographic factors. For example, fathers and other members of the family could also be included in the studies.

Referring to the positive relationship between education and breastfeeding as demonstrated by Dr Matheson, it was remarked that in the developing countries this relationship is negative.

The discussion was closed with the remark that it is in fact a very limited number of drugs that are harmful to the infant when taken by the breastfeeding mother. The state of the art of drugs and lactation is given in a recent publication prepared by a WHO working group (Drugs and Human Lactation, Elsevier, 1988).

8. Drug use in children

8.1 Drug use in non-hospitalized children

by E.J. Sanz

Drug utilization (DU) studies aim at a better and more rational drug therapy. Not only technical-pharmacological aspects have to be taken into account in DU studies, but also many other factors which affect drug prescription, intake and effect. This is also the matter for DU research in children. There are several problems of drug use in non-hospitalized children, which may be identified and solved by using DU statistics. After outlining the problems of drug use in outpatient children and the possibilities of DU research to solve these problems, Dr Sanz described the direction of DU research in outpatient children.

The problems of drug use in non-hospitalized children are related to the children's age and development, and to the fact that children are not responsible for their medical treatment. Three main aspects can be recognized: patient's and parent's problems, pharmacological problems and physician's problems.

With regard to the patient's and parent's problems the general impression is that children require less medicines than adults. Several investigations have shown that most of the pediatric consultations in open-care are devoted to symptomatic relief or simple, self-limiting diseases. Children visit doctors more frequently than adults, but they do not visit the doctor alone. Children's symptoms are often described by their parents, who normally also are responsible for the therapy compliance.

The drug effects in children do not only depend on the pharmacological action of the drug and the physio-pathological state of the child, but also on patient's (and parents') beliefs and conceptions about drugs, drug effects, illnesses, and disease improvement after drug therapy. Placebo and anti-placebo effects will play a part. It is important to observe that the cultural background of the family and the society in which children and parents live determine many of the aspects of drug use in children, and, sometimes, even the clinical outcome.

The pharmacological problems of drug use in children are mainly related to the fact that clinical trials are not carried out in children. In general, efficacy and safety of drugs are investigated in clinical trials in a limited number of healthy adult volunteers and adult patients, but not in children. Children's response to drugs is not always similar to that of the adults, and it may also vary with age, growth and development. Drug trials are difficult to carry out in children either for ethical reasons or because the parents refuse to give their consent. There is therefore a lack of information on drug effects and side effects in children, including information on dosage, kinetics or proper use. This makes it difficult to formulate therapeutic recommendations and standards for drug treatment of children.

Children are exposed to drugs not only by being treated with them, but also if the mother takes drugs during pregnancy and lactation. The pharmacological effects of drug use during pregnancy and lactation on embryo, fetus or the newborn child are not extensively investigated, but our knowledge is growing.

Physicians may have problems with drug use in non-hospitalized children because when they treat children, they are influenced by many different factors. Not only by their medical education, their colleagues and pharmaceutical representatives, but also by the parents with their fears and pressures. All these factors influence prescribing and decide the prescription patterns in children. The results are not always positive. For example, the prescribing habits in the antibiotic and psychotropic field seem quite irrational.

Antibiotics are extensively used in outpatient children and cover almost one third of all prescriptions, while the most common infections in outpatient children are viral infections (which do not need antibiotic treatment). Less than one third of the children has a bacterial infection requiring antibiotic treatment.

Psychotropic drugs are also very much used in non-hospitalized children. It seems that at least 5% of the children receive on ore more prescriptions for psychotropics each year. The use of these drugs increases with age and goes sharply up in girls over 11 years of age. This field is not yet fully investigated.

However, the available drug-utilization and disease-incidence data are not sufficient to fully judge the prescription patterns or to formulate recommendations about specific therapies.

Another problem is the use of symptomatic medications for the alleviation of several symptoms (cough, fever, nasal congestion, pain, etc.). The therapeutic effect of most of these drugs is dubious; indiscriminate use of these drugs may, however, replace proper therapy of the underlying disease or make the diagnosis more difficult. More than 50% of children visiting the physician have already been treated by their parents; the physician should be aware of this fact.

In conclusion the following topics deserve further study:

- parents' and patients' compliance;
- parents' and children's conceptions on illnesses and drug use;
- embryonic and fetal pharmacology;
- exposure to drugs via the mother; i.e. during pregnancy and lactation;
- the use of antibiotics in children;
- the use of psychotropic drugs in children;
- parent-selected medication with over-the-counter remedies;
- the appropriateness of drugs and doses at various ages;
- evaluation of existing prescribing practice in order to identify the groups of drugs not used to their full therapeutic potential or otherwise not used optimally.

Drug utilization statistics as a tool to identify and solve the problems

Information on drug utilization statistics in non-hospitalized children is available together with other types of utilization data, but sometimes these data should be analysed in a different manner. As over-the-counter drugs account for about half of the drugs used by children, non-conventional sources of information, such as parent-directed questionnaires or over-the-counter drug statistics, are essential.

Three information sources may be used.

- General sales statistics. These are less useful because it usually is quite difficult to separate the drugs used for children from those used for adults (pediatric formulations excepted).
- Prescription surveys from chemists or doctors. The surveys from chemists do not usually link prescription data to diagnoses or symptoms or the patients' age. One can, however, be sure that the drug really is bought by the patient. The surveys from doctors give more reliable data, because they will include patient characteristics, indications and drug schedule. In most cases, doctors' data can only be obtained from a limited sample of prescriptions. Prescription data can only tell what has been prescribed; they do not tell whether the patient actually purchased the drug. Drug utilization studies based on a continuous data

recording can provide the basis for Drug Utilization Review Programmes. These may be used to produce profiles of various treatments over time and for performing cohort and case control studies. Until now only a few such studies have concentrated specifically on drug use in children. Most of the available data on drug use in children are provided by time-limited studies, commonly performed in hospitals and outpatient children.

- Data from patients and their parents can give an accurate picture of what and to what extent drugs have actually been prescribed and used; the data can, however, be unreliable owing to poor understanding of the illness and the therapy.

Direction of drug utilization research in non-hospitalized children

The main problems of drug use in non-hospitalized children have been identified. There is nevertheless still a lot to do in the practical field. The knacks and pitfalls of prescription habits of general practitioners and pediatricians have to be discovered in order to help them in their practical work.

At least four steps of DU research can be carried out in non-hospitalized children.

1. Descriptive analysis at various levels (national, regional and local). Drug sale statistics, drug utilization reviews or prescription surveys are the most commonly used tools for identifying the problems and for investigating the extent of these problems in different communities.
2. Hypothesis testing studies. Which are the factors affecting prescription, compliance and drug effects? Diagnosis and treatment should be compared with outcome. Prescription patterns and theoretical drug appropriateness should be compared with actual clinical data and patient records.
3. Intervention studies. How can we change unwanted prescribing habits and which are the best methods to do so? This type of studies includes evaluating the effect of promotional activities, educational campaigns, drug formularies and academic recommendations.
4. Social science-oriented studies. Most of the factors affecting drug use and prescription may be included in a more general, sociological framework. A more penetrating understanding of the non-pharmacological basis of therapeutics is essential; collaboration with professions of the social sciences is therefore desirable (anthropologists, sociologists, psychologists, etc.).

Dr Sanz concluded his lecture with the remark that we have a huge amount of work in front of us. We have to help general practitioners and pediatricians with our expertise and direct our efforts to a more rational drug therapy in the practice of today. Practitioners should be involved in drug utilization research to ensure that the results will be of interest for their practice.

The invited discussant to the subject of drug use in non-hospitalized children, Professor Stanulovic, first recapitulated the circle of activities linked to DU studies. The starting point is data collection, followed by evaluation of the collected data and planning of action (interventions), aiming at behavioural modification. To evaluate behavioural modification again data collection is needed, by which the circle is closed.

After some remarks about the methods for data collection and evaluation, Professor Stanulovic gave a few examples to explain that behavioural modification has to be the most important part of the circle of activities in DUR in non-hospitalized children.

For the collection of data an appropriate unit of measurement for the utilization data for children is needed. In the recent literature several units of measurement are described; number of prescriptions, number of prescribed items, and pediatric Defined Daily Dose (pDDD). The pDDD is the fraction of the adult DDD which corresponds to the fraction of the body surface area of an adult person. Like all units of measurement the pDDD has its advantages and disadvantages. The usefulness depends on how it is brought up in the arguments, but, in general, the pDDD can be considered as an acceptable unit of measurement for drug use by children.

Evaluation of DU data means that the observed situation is compared with the expected situation (derived from data from controlled clinical trials). This can be illustrated with a few examples.

In a study in the working region of Professor Stanulovic (Novi Sad) the pattern of prescribing for outpatient children was compared with that for hospitalized children. One of the findings was that the use of (combined) vitamins in outpatient children turned out to be higher than that in hospitalized children and medically spoken far beyond expectation.

The same problem exists for drugs for the respiratory tract. Outpatient children use much more of these drugs compared with hospitalized children; there is no clear medical reason for this fact. If respiratory drugs are used in hospital, an effective opiate derivative, such as codeine, is usually preferred. In the outpatient situation synthetical antitussives are most frequently used. These are less effective and act mostly as placebos.

The use of antimicrobial drugs is also a problem in Professor Stanulovic's working area. Antimicrobial medication in three age groups of children in two cities was investigated. The use of antibiotic agents varied in the two cities in all three age groups.

From these examples the conclusion emerges that differences in drug utilization patterns in non-hospitalized children cannot be regarded as a purely medical problem. Other types of factors play a role: state of mental development, attitudes, parent/child interaction, expectations and so on. The real problem in optimal drug use is not the lack of medical knowledge. The discussion about the reasons for differences in drug utilization has to address itself to expectations, attitudes and behavioural aspects of drug use. Not only do we need controlled clinical trials to reach optimal therapeutical regimens, we need just as much the technology of modern behavioural sciences to achieve that accepted therapeutical regimens will be followed in practice.

8.2 Discussion

In the discussion Professor Tognoni touched the methodological problems in the kind of studies presented by Professor Stanulovic. These problems have to do with comparability of e.g. social factors and other macrovariables. Without a good methodological concept it will be impossible to find and judge correlations between drug utilization and social factors and other variables and the surveys will turn into chaos. With respect to Professor Stanulovic's recommendation that behavioural aspects of drug use should be investigated with priority, he had some reservations. In his opinion looking for behavioural determinants is just a refinement of the sociocultural macrovariable. To his mind it would be more important to investigate drug market characteristics. The drug market can be considered as the most influencing factor in drug utilization. From his point of view the drug market can be broadly defined; including not only the amount and sort of drugs that are available to a society, but also the role of doctors in a society, the diagnostic "market", the pharmaceutical industry with its representatives, etc.

Some further remarks made in this discussion

When measuring children's utilization of drugs in specific therapeutic areas, it should be kept in mind that a lot of drugs are being prescribed for children but not necessarily for the proper indication. This varies between different age groups. Due to this it is difficult to break down drug utilization figures from specific drug categories to various age groups (except for specific pediatric formulations).

8.3 Drug utilization in hospitalized newborn patients

by J.V. Aranda

Under the auspices of the Canadian National Health and Welfare the epidemiology of drug utilization and adverse drug reactions were investigated during the period 1977 to 1981 in an intensive prospective study.

Dr Aranda's paper focused on a report of the final descriptive data analysis on drug utilization, the limitations of the data and the advantages and disadvantages of the model used. The results indicated that out of the 1200 babies 76% were exposed to 151 different medications excluding those routinely prescribed for perinatal care such as vitamin D, umbilical cord dye and ophthalmic antimicrobials. An average of 5.7 drugs per baby was given and 15% of neonates received more than 10 medicaments.

Data gathered included:

- (a) biographic data (e.g. birth weight, gestational age, perinatal age, ethnic group, blood group, etc; antenatal history);
- (b) diagnoses and problem list;
- (c) all clinical symptoms;
- (d) all physical findings and physiological monitoring (e.g. temperature, heart rate, etc.);

- (e) all diagnostic procedures;
- (f) all treatments other than drugs (e.g. surgical);
- (g) all medications dose, route, frequency, etc.)
- (h) clinical outcome;
- (i) adverse drug reactions and their management;
- (j) outcome.

The design of the study and the flexibility of the raw data input and management allowed for multiple use of the data obtained in these studies.

The data could therefore be used in the following ways:

1. In the identification of research priorities. Thus the widespread use of diuretics was identified and this led to an investigative programme on the pharmacodynamics, pharmacokinetics and metabolism of furosemide.
2. To design and conduct continuing education programmes.
3. On-line computer-based prescriptions with relevant data on (a) age, (b) weight, (c) problems and diagnosis should be introduced. Hospital prescription pads should be designed to include this information.
4. Computerized prescription records should be linked with computerized clinical and laboratory records, if possible. Appropriate computer programmes can be designed to improve accessibility of databases.
5. The use of DDD in newborn babies and children is seriously questioned and should be evaluated carefully.

Discussion of Dr Aranda's paper

Dr Aranda's paper was discussed by Dr Y. Hekster.

With the increasing complexity of pharmacologic interventions in pediatrics, the risk to children of medication errors is likely to increase Dr Hekster said. In addition to drug use review, a close assessment of every drug order by a pharmacist, specialized in pediatric pharmacotherapy, can prevent medication-related disasters. However, this is not common practice in all hospitals throughout the world, not even in Europe.

To overcome this financial hindrance, several researchers have assessed the feasibility of studying drug utilization patterns in children admitted to hospitals in a retrospective way. To study drug use in children it is required that they are admitted to pediatric wards only. However, this is certainly not always the case. Drug utilization research is nowadays routinely carried out using the ATC and DDD methodology. The definition of DDD takes into consideration that the dose is related to the use in adults. To study drug utilization in children it has been suggested to use an adapted

value of the DDD, i.e. the pediatric DDD (pDDD). But the age and weight factor between adults and children vary widely. Professor Milan Stanulovic, among others, has used this methodology. He used the fraction of the body surface area as the fraction of the adult dose. In most calculations 1/6 of the DDD was taken for infants up to three months, 1/5 for infants aged 3 to 12 months, 1/3 for children aged 1 to 3 years and 1/2 for children aged 3 to 14 years. Such calculations require that the age of the child can be found even in the retrospective survey. Thus the process depends on medication carts. The use of ampicillin, amoxicillin, co-trimoxazole and gentamicin in a total of 766 children aged several days to 16 years was followed. For the above drugs the prescribed daily dose was compared with age to see whether a relation could be found. Large differences existed between the DDD and the PDD. It was clear that the PDD/100 parameter is much better than the DDD parameter. However, large differences still remain. In conclusion, the use of pDDD based upon age makes the assumption that a relation exists between age and dose. This, however, is not always the case. The use of one fixed pDDD is easy for studying drug use but lacks validity. Thus large differences can be found between pDDD/100 and the actual/100.

Therefore it seems difficult to study drug use in children retrospectively and Dr Hekster supported Dr Aranda's advocacy of prospective studies. However, the major drawback of such studies was their high cost and this raised the question of the cost effectiveness. An additional topic requiring consideration was the monitoring of medication errors, he said.

8.4 Children's perception of medicines

by D. Trakas and L. Sachs

This topic was introduced by Lisbeth Sachs who started by describing the theoretical and methodological perspectives when studying children's perceptions of medicines.

The drug utilization research group consists of people who use the same "language" and who have agreed on common methodologies to seek knowledge. Anthropologists have another type of "language" and use other approaches in their research. Such an understanding is essential if the different methodologies used are to be integrated in the field of drug utilization research.

9. Drug use in the elderly

9.1 Drug use in the elderly

by K. Laake, H. Knudsen Stromme, K. Engedol and F.B. Roervik

Dr Laake, who presented the paper stated that drug use in the elderly was an important research field, because elderly people (over 65 years of age) consume nearly 50% of all the medicines in the western world, but represent only 15% of the population. The most striking age effects, particularly in those over 75 years, are loss of reserve capacity and loss of adaptability, both processes implying reduced stress tolerance and an increased risk of diseases as well as adverse drug reactions. Furthermore, we witness, in old age, a general bleaching of clinical symptoms, making diagnosing more difficult. A typical complication of aging is thus a marked increase in undiagnosed diseases. Functional decline in old age, due to diseases or side

effects of drugs is, unfortunately, often misinterpreted as the effect of normal ageing. The main problem relating to drug use in the elderly is irrelevant medication. By this is meant the use of drugs that are of little or no benefit, but nevertheless puts the patient at risk of side effect, and of course has its economic cost as well. First priority should be given to sustaining the quality of life. To the elderly this means good functional capacity and freedom from pain. Achieving a statistically normal life expectancy comes second on our list of priorities.

Clinical experience and scientific studies indicate that it is more difficult to obtain an overall positive effect from pharmacological treatment in older patients. While drug utilization studies are necessary and efficient tools to improve medication in the elderly, an important problem is the failure to get the results implemented into a prescribing policy that really improves drug therapy.

Differences in drug utilization were observed when patients living at home were compared with those living in institutions, especially with regard to the prescribing of benzodiazepines, laxatives, neuroleptics and iron, the use of which was very high in the institutional setting. Analysis also showed that the most significant explanatory variable was the doctor in charge of prescribing. This represents perhaps the main reason why we have not witnessed any dramatic change in prescribing to the elderly during the last 5 to 10 years.

Future research should include drug utilization studies which have as one of their primary goals to demonstrate to doctors that improvement in medication can easily be encompassed, and that the doctor can achieve a more relevant medication for their elderly clients by quite simple means. Such studies will have to include clinical data, they must be prospective and, of course, longitudinal. For simplicity, one can focus on patients prescribed special drugs, for instance diuretics, digitalis, glycosides or benzodiazepines. Algorithms can be developed to aid in this task. Dr Laake concluded that perhaps the most efficient way of implementing what we already believe to be true, about medication for the elderly, would be to mobilize as much energy as possible in the field and come together in multidisciplinary teams consisting of pharmacists, nurses, home helpers, general practitioners, geriatricians and pharmacologists. Perhaps we can, in the future, undertake drug utilization studies to evaluate the results of implementing a multidisciplinary consensus.

Discussion of Professor Laake et al.'s paper

Dr Laake's paper was discussed by Dr A. Spagnoli.

In response to Professor Laake's paper Dr Spagnoli presented the results of a study, involving general practitioners of the Unita Sanitaria Local in Torino, entitled "Drug compliance and unreported drugs in the elderly". The study addressed the following issues: (1) Which are the most frequently prescribed drugs? (2) What is the level of compliance? (3) Do the elderly ask for drugs? (4) Do general practitioners miss many drugs (i.e. is there extensive unreporting of drug use)? A random sample of 46 general practitioners recruited 802 elderly outpatients and collected information about complaints and current drug treatment. Within a week each patient received a home interview and details were collected on drug compliance and use of drugs other than those reported by the general practitioner. On

average each patient was taking 3.6 drugs, of which 2.9 were correctly reported by the general practitioner and 0.7 were unreported. Among the most prescribed therapeutic groups were drugs with a narrow therapeutic index and substances the efficacy of which has never been fully documented. Age and number of complaints were positively and significantly correlated with number of prescribed drugs. Nearly half of the patients were taking one or more drugs not detected by the general practitioner, often benzodiazepines chronically. Full compliance occurred for 81.5% of the prescriptions and 59.6% of the patients were correctly taking all the drugs prescribed. Compliance was lower for the general practitioner's prescriptions compared with those of other doctors (e.g. hospital doctors) and the probability of correctly taking all the prescribed drugs decreased with the number of medicines concurrently taken. The most common reason for non-compliance was fear of side effects.

9.2 Discussion

In the discussion that followed the algorithm approach outlined by Dr Laake was considered to be very useful and its wider adoption was advocated.

The difficulties in getting patients to stop taking medication was another issue that was raised. The perception was that drugs started in the hospital were more difficult to discontinue.

Dr Laake suggested that a stepping down approach, rather than an abrupt withdrawal, had a better likelihood of success.

The issue of what rational prescribing constituted was also raised. As few guidelines, with the exception of hypertension, were available for drug use in the elderly, doctors, rather than patients, felt insecure; the doctor felt he was expected to know all the answers.

9.3 Elderly people

by Ann Cartwright

The paper was based on a community survey, conducted in 1984, the full results of which have recently been published in a book entitled "Elderly people, their medicines and their doctors" (Cartwright, A. and Smith C. (1998), Routledge, London & New York). The work arose from the anxieties expressed by a range of health care professionals regarding (a) the number, (b) the nature and distribution of medicines prescribed for elderly people, (c) the dual prescribing system in hospitals and in general practice, (d) inadequate review of medication, (e) the lack of awareness of general practitioners about the medicines their elderly patients were taking, (f) the susceptibility of older people to adverse drug reactions and (g) what the Royal College of Physicians in the United Kingdom described as impaired compliance. The study took the form of a national survey of a stratified sample; interviews being completed in 805 elderly people i.e. 78% of the elderly people identified. Information was also sought from the patients general practitioners and an assessment of drug use, drawn up by a clinical pharmacologist and applied by two pharmacists, was also undertaken. A selection of the survey results were presented and these revealed that while the average number of prescribed medicines being taken was two, roughly one third took no medicines, a third took one or two medicines, while 10% of the

sample were taking five or more medical prescriptions. Three quarters of the medicines had first been prescribed a year or more prior to the interview while a third had been prescribed at least five years earlier. One fifth of medicines was initially prescribed by a hospital doctor and these medicines were more likely to have been prescribed 10 years before or earlier.

Just over a third of the hypnotics, sedatives and anxiolytics were regarded to be prescribed in too high a dosage, while 31% of the prescribed medicines were assessed as pharmacologically open to question. Thirty-six per cent of the elderly were taking prescribed medicines their doctors were unaware of; 19% of the hypnotics reported were not apparent in the doctor's notes or consciousness. The survey also provided a number of possible indicators of the quality of care and indications that the younger doctors seemed more caring while women were more understanding and better at giving explanations to patients.

In summary this study has shown that it is possible to get a range of useful information from patients on the numbers and types of medicines taken and on the processes of prescribing - the source of prescription, the length of time over which medicines are prescribed and the frequency of possible review.

The data obtained from patients were enhanced by the professional expertise of the pharmacologist and pharmacist. Together they provide an indication of the quality of prescribing.

The processes and problems can be illuminated further if they are put alongside the experiences, knowledge and views of prescribers.

Such a survey results in a reasonably good response rate from patients, a less good one from doctors. There is likely to be a bias in the response from doctors and it is important to take the nature of this bias into account when interpreting results.

Discussion of Professor Cartwright's paper

Professor Cartwright's paper was discussed by Dr Pat Bush.

Having complimented Professor Cartwright's work for its lucidity, almost deceptive simplicity and freedom from academic "gobblygook" and esoteric statistical methods, Dr Bush addressed the problems associated with studies on the elderly. Posing the question of who were the elderly, she suggested that the elderly were defined by social expectations, by chronological age, by capabilities, by work status, by morbidity and by combinations of these. In most drug research the elderly are simply defined as those of 65 years and older. Dr Bush also addressed the issue of the perspective from which one views research on the elderly and specifically from the perspective of the utility of the results. Thus the definition of the elderly as 65 years and older is a useful demarcation for financial planners such as health insurance agencies, pension funds and reimbursement schemes, etc. The 65+ definition has the further utility of making one's findings comparable to those of others. It also permits use of a sampling frame based on age and thus proportional sampling which increases representativeness and thus generalizability.

However, defining the elderly by an arbitrary age may in fact be unhelpful when making the problem lists and their solutions.

In addition to surveys, there are two other types of studies of drugs and the elderly; those that involve the quality of prescribing and those that involve the quality of drug use. Generally there is no interface between these types of study, however, the Cartwright and Smith contribution is very much an exception. This work clearly shows that there are so-called elderly as defined by age, who have not presented themselves to a physician within the period under review nor have they taken any medicines. This clearly means that the problems, while they may occur more frequently in persons in certain age groups, do not derive from age but are defined by other factors such as morbidity, institutionalization, physical impairment, economic status, health beliefs, etc., i.e. the same characteristics that define other population groups.

There seems to be more studies investigating or evaluating solutions to the problems of elderly person's drug use than of prescribing quality, and those on the patient side are almost all related to compliance. From the prescribers' side, it is difficult for most of us to get data that will permit assessment of prescribing quality for the elderly or for anyone else. Some data reflecting prescribing quality are obtained from the patients' side, e.g. multiple or interacting prescriptions obtained from the same or multiple prescribers. For such an assessment, one must usually have access to the patient record with at least the diagnosis and preferably laboratory values and prescribing history. Then, unless the decision is clear cut and grossly in error, one must have a panel of experts to make a judgement and rationalize their differences. This type of work is, however, very labour intensive but does lead to the kind of results that may lead to specific changes being implemented.

Another general problem is the difficulty of collecting information on what people really do when they have a common health problem. To get access to this type of information the use of labour-intensive anthropological techniques may be required.

The Cartwright and Smith research goes an extraordinarily long way towards bridging the gap with its national sample of both patients and their doctors and yet provides many enlightening humanizing anecdotes and extended explanations that make the research findings real and tangible.

In conclusion Dr Bush made a plea for more intensive research, more cross-fertilization and collaboration among different disciplines. Professor L. Sachs from Sweden is interviewing four elderly women about their medicines and they are not likely to be representative of the population. Nevertheless, she may learn things that will hold prescribers and educators and lead to the generation of hypotheses that can be tested in larger representative surveys to be performed in the Cartwright and Smith mould.

10. Recommendations

The following recommendations were made.

Organization of research activities carried out by the WHO Drug Utilization Research Group

The WHO Drug Utilization Research Group (DURG) should continue to be a research group.

The DURG should be structured so as to contain permanent working groups in specific fields, such as

- methodology (basic);
- indicators and determinants of drug use for health and society (intervention studies, multidisciplinary studies, etc.);
- use of drugs in patient subgroups such as pregnant and lactating women, the newborn, the elderly, specific disease states, etc;
- use of special groups of drugs, such as psychotropic drugs, cardiovascular drugs, antibiotics, etc.

The DURG should actively encourage the setting up of national drug utilization research centres to:

- keep a list of that country's sources of drug utilization information and of morbidity-mortality data;
- keep a list of that country's published references and, when possible, unpublished references - preferably with keyword indexing, especially for data sources and methods;
- keep, when possible, an indexed directory of past and current drug utilization research projects;
- ensure, if possible, that an updated list is kept of all drug products on that country's market giving (a) anatomical-therapeutic-chemical (ATC) class and (b) defined daily doses (DDDs), which preferably transfer on computer tape or disks;
- encourage collaborative drug utilization research through informal or formal drug utilization research groups or associations;
- act as a link between WHO and its relevant collaborating centres;
- act as a contact point for drug utilization researchers in that country;
- coordinate work with governmental and other agencies involved in aspects of drug utilization and monitoring to set priorities, and to acquire and make best use of data in this field, to the benefit of patient care in terms of community needs;
- send annual reports on the activities of the national drug utilization research centre to WHO/EURO.

Ways of increasing the impact of the activities and recommendations of the WHO Drug Utilization Research Group

Recommendations and selected reports from the DURG should be published in widely read, specialized and general journals.

Scientific publications by DURG members should be indexed with standardized eywords in order to ensure correct quotation in major databases.

WHO should approach database officials to agree on drug utilization keywords.

DURG should consider organizing satellite meetings linked to other international meetings within related fields.

Drug policy makers and drug utilization research

There should be cooperation and information exchange between drug policy makers and drug utilization research workers.

Therapeutic audit projects should be initiated by the prescribers and run by them, not by drug policy makers.

Education/training of health workers

The education of physicians and pharmacists should include training in the use of drug utilization data.

10.1 Recommendations to WHO

WHO should ensure that there is cooperation and information exchange between the different activities within the Organization involving drug utilization research.

WHO should establish global and regional multidisciplinary drug utilization research groups.

Annex 1

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