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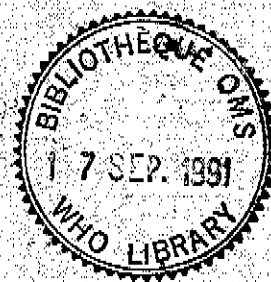
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CLINICAL PHARMACOLOGICAL EVALUATION IN DRUG CONTROL

The constraints on
treatment and trials

Report on the sixteenth European Symposium



Schlangenbad
13-16 October 1987

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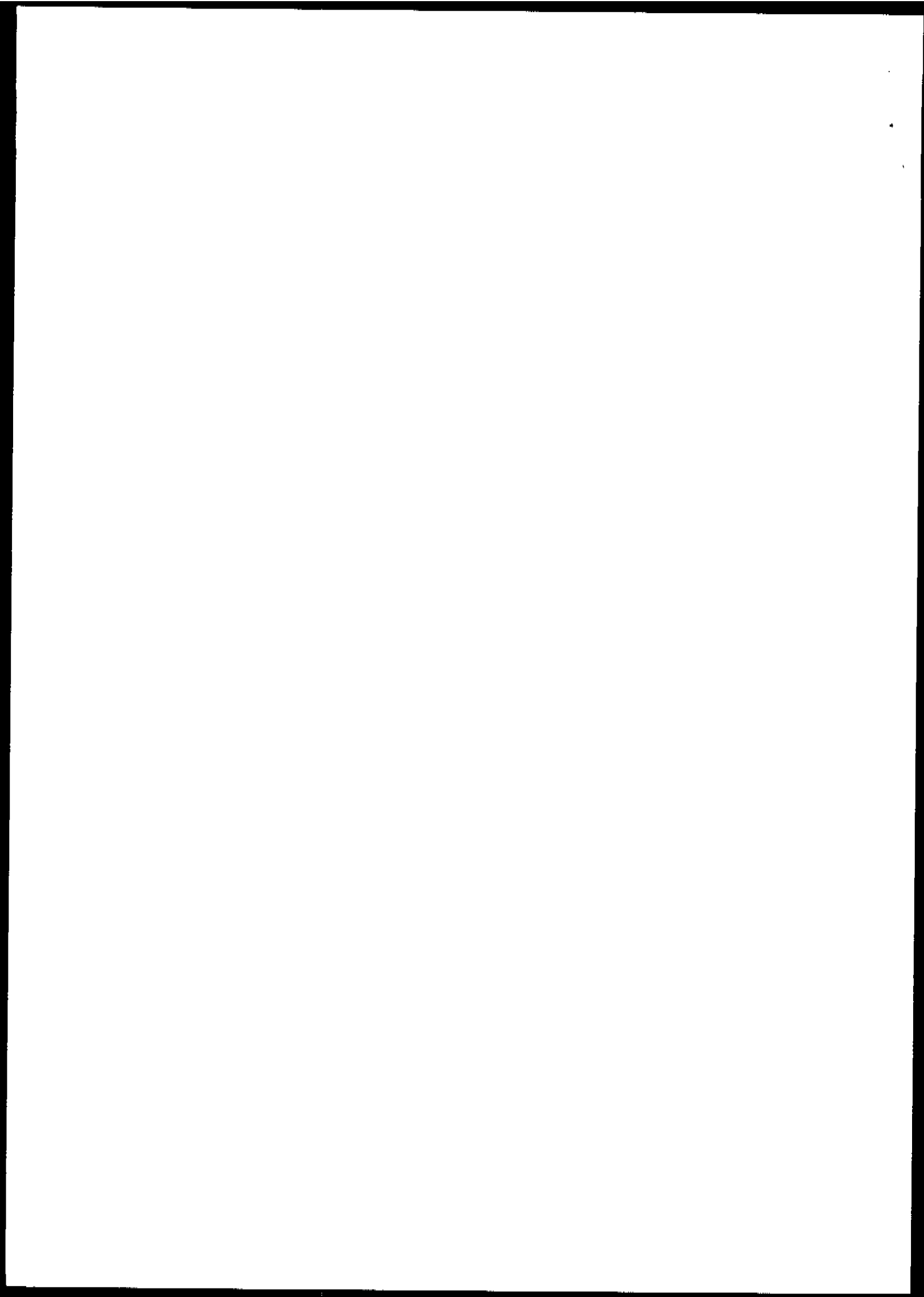
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^a *Targets for health for all*. Copenhagen, WHO Regional Office Europe, 1985 (European Health for All Series, No. 1).

CONTENTS

	<u>Page</u>
Introduction	1
The effects of restrictions on prescribing	1
Restraints on clinical trials	2
What kind of clinical trials should be carried out in general practice?	4
Training in clinical pharmacology in medical schools in Europe	8
Clinical pharmacology in primary health care	9
Adverse drug reactions in general practice	9
Patient package inserts (PPI's)	10
Restrictions on prescribing	
Conclusions	11
Recommendations	11
Restraints on clinical trials	
Conclusions	11
Clinical trials in general practice	
Recommendations	13
Training in clinical pharmacology in medical schools in Europe	
Conclusions	14
Recommendations	14
Clinical pharmacology in primary health care	
Conclusions	14
Recommendations	14
Adverse drug reactions in general practice	
Conclusions	15
Recommendations	15
Annex 1. List of participants	17



Introduction

The Sixteenth European Symposium on Clinical Pharmacological Evaluation in Drug Control was held in Schlangenbad from 13 to 16 October 1987. The topic for the Symposium was "the constraints on treatment and trials". It was attended by 40 participants from 21 countries.

Dr M.N.G. Dukes welcomed the participants to the Symposium on behalf of Dr J.E. Asvall, Regional Director for Europe of the World Health Organization. He expressed the gratitude of all participants to the Ministry for Youth, Family Affairs, Women and Health of the Federal Republic of Germany for their continued generous support of the Symposium. Dr Dukes expressed the view that the continued success of these meetings must indicate that they fulfilled a widespread need in the subject. The initial symposia were held against a background of expansion in health care budgets. However, since the early 1980s the world economy has been in recession and this behoves us to cut our cloth differently. There clearly are financial constraints on drug therapy and this Symposium should help to find ways of delivering drug therapy more economically and without a reduction in standards.

On behalf of the Ministry for Youth, Family Affairs, Women and Health, Dr Schorn welcomed participants to the Symposium. He expressed the view that communication and the ability to exchange information was particularly important in the modern era. He felt that international exchange of information about such things as side effects of drugs could best be achieved on a basis of sound education in pharmacology and clinical pharmacology.

The meeting then elected Professor W. Dölle as its Chairperson with Dr V.K. Lepakhin and Ms N. Inan as the two Vice-Chairpeople. Professor Dölle introduced the first session of the Symposium.

The effects of restrictions on prescribing

The first theme concerned the impact on the health services taking as the theme "less money - does it mean less care?". It was pointed out that it now costs some US \$250 million to develop a new marketable medicine and it is debatable whether all this expenditure is really necessary. It was suggested that less money did not necessarily mean less care and a number of questions needed to be asked. Physicians should think whether the medicine they use is really necessary, and if it was necessary, was it the most effective one available, and perhaps the most important question was would the patient comply with the therapy? It was felt that a lot of prescribing was unnecessary and that the physician could be helped in this self-audit process by being given a list of his or her prescriptions in the previous month or so. Other questions were aimed at the pharmaceutical industry. "Do they really need to spend so much money promoting a drug" and "Is this drug really needed?". The regulatory agency should also ask if the requirements for licensing could be eased. In discussion a number of points were raised although no concrete answers emerged. How do we judge whether a new drug really is needed? Should a licence authority consider financial aspects in the licensing of a new drug? On the economic front it was generally agreed that scientific aspects should take prime place in the assessment of a new drug. Only when these were satisfied should a comparison of costs be considered, preferably by a different group.

The participants then discussed the effect of restricting prescribing on the prescriber and on his or her patient. At least in the early stages after introduction of a negative restricted prescribing list the effect may be largely beneficial. It was pointed out that in a recent survey in Europe of the top 30-50 prescribed preparations in each country, there were major disparities between countries. Some countries would have say 8 or 9 analgesics in the list while only 1 or 2 would be seen in the list from other countries. In some countries the most commonly used preparations might have 5 or 6 different active ingredients compared to the single entities in other countries. It was felt that about 20% of these drugs could be classified as having doubtful or no therapeutic efficacy. Some 7% of medicines in this study were judged to be unacceptable preparations from the risk-benefit ratio point of view. The group accepted that some preparations were present as placebos (decorative drugs) and in discussion agreed that it was acceptable to prescribe placebos on occasion, although they have the undesirable effect of teaching patients that medicines are a solution to their problems when they are not. The study came in for minor criticisms from one or two Member States, largely because the initial questionnaire had been wrongly completed but these points did not alter the main thrust of the argument. The discussion of the limited list concept was itself limited. No real arguments about the usefulness of the list emerged, and it was felt that there was a need to monitor the system to see if money really is saved, and a need to educate prescribers in the assessment of the quality of therapy.

The group then heard the view of the pharmaceutical industry concerning limited lists. The negative list in the Federal Republic of Germany was described whereby certain items (e.g. cold medicaments, gargles, motion sickness remedies, laxatives, cough suppressants) could only be prescribed if the patient paid for the drugs directly. It was felt this might lead to research in these areas becoming less attractive. However, no convincing data about this was presented. The positive type of list (whereby doctors are prescribing only from a certain list) was not discussed at length.

The participants were concerned about another way of limiting prescribing, that of generic substitution. When the patent for diclofenac came out in the Federal Republic of Germany, some 30 generic equivalents emerged. It was suggested, from limited data with glibenclamide and ergot alkaloids, that bioinequivalence was likely in this situation but this view was heavily criticized in discussion. There was concern that doctors could not know from a long list of generic "equivalents" which ones were poor quality. Clearly, any generic that is made must have proved bioequivalence before it is licensed. There are in practice very few situations where known bioinequivalence has caused clinical problems.

It was felt that studies in the past had revealed problems of bioinequivalence but that recent data suggested that the bioavailability of generic substitutes was not a major problem. However, the area needed careful observation.

Restraints on clinical trials

The Symposium then addressed the question "How good are clinical trials in Europe?". This issue has been given added impetus in recent years by the new approach of meta-analysis, which is concerned with the analysis of all available published studies in regard to a particular problem. The minimum

requirements for a good clinical trial that would have a reasonable chance of obtaining an answer are that it address a validly phrased question, and that the trial should be controlled, for example to reduce the risk of placebo effect. Other aspects include the issue of randomization and blinding. Studies should be analysed on the basis of "intention to treat" to obtain fullest information. Statistical analysis should avoid the obsession with P-values and concentrate more on "confidence intervals" and the "power" of the study. Prior estimation of the number of patients likely to be needed is also important.

The discussion considered certain aspects of bias in clinical trials. The following forms of bias can each undermine the value of a clinical trial. "Dose-response" bias can be introduced in a comparative clinical trial if the reference drug is not used in an appropriate dose. "Citation-bias" is a problem revealed on examination of clinical trial literature and refers to the incorrect quoting of published reports. "Publication-bias" refers to the selective quotation in clinical trial literature of papers that have reached a positive conclusion and the ignoring of trials that have not done so.

The Symposium then considered the issue "Need clinical trials be controlled by law?". The public needs to be satisfied that a proper balance has been struck between the sometimes conflicting values of advancing knowledge to benefit human beings in general and of ensuring the safety of every volunteer who takes part in research. The fundamental ethical principles that apply to clinical research have not been translated into a coherent set of rules that will ensure that those principles are upheld in every case. There is, however, a dilemma in the adoption of a universally accepted set of rules for statutory requirements in that they tend to be rigid and may be thus unsuited in some areas of human activity. Clinical research is difficult to regulate satisfactorily by statute because there are no absolute standards and overregulation can cause delay in implementing a new treatment. Additionally, courts in many Member States have been unwilling to interfere in the relationship between doctor and patient more than is absolutely necessary lest a defensive type of medicine be provoked. The time may now, however, be right for legislation that states in broad terms the legal rights and duties of the investigator and the investigated, leaving properly constituted ethics committees to ensure adherence to more detailed ethical rules. The public will accept that what is legally acceptable must necessarily be ill defined but it will not accept that it must remain undefined.

The participants then turned to the issue "How useful are research ethics review committees?". Like the research that they review, these committees have the potential for beneficial and for undesirable results. The benefits of such committees are listed below.

1. Protection of research subjects from harm by ensuring that the risks of a study are properly considered.
2. The preservation of research subjects' personal rights, for example in respect of informed consent and privacy of personal medical records.
3. Assurance to the public that research is as safe as possible and conducted with full regard of potential fights.

4. Elevation of the standards of ethics and of scientific investigation. It is important that ethics committees take as their remit not solely ethical considerations but also in broad terms the scientific quality of research; it is unethical to undertake studies of poor scientific quality, which put subjects at risk or inconvenience without the possibility of useful information being gained.
5. Protection of investigators from undeserved criticism, for example in the case of an accident.
6. Facilitation of studies that are highly controversial but desirable, to allay public concern in difficult areas of research, for example studies in mentally retarded patients and in the elderly.

Ethics committees can have undesirable effects by:

- causing unreasonable delay in research;
- interfering with multicentre studies by inconsistent local decisions (nevertheless, multicentre studies should not override local review);
- being poorly constituted, leading to uninformed behaviour.

The membership of ethics committees is of prime importance. Membership tends to vary from centre to centre. Most committees contain individuals with medical, and nursing backgrounds but it is also essential that such committees should contain strong and capable lay members. Individuals with extremist views are unlikely to be helpful in this setting. Careful selection of members will remedy some of these aberrations, and individuals tend to gain from frequent meeting and exchange of ideas within the committee. There seems to be a need for guidance from national or international levels on the constitution and role of ethics or equivalent committees.

The Symposium then turned to the issue "How can drug control authorities insure the quality of clinical trials?". Regulatory authorities should ensure that the general principles of conduct of good clinical trials, as outlined earlier in this document, are adhered to. It is important to assess whether the results that have been obtained are likely to be reproducible in normal clinical practice. Some Member States provided general guidelines to clinical trialists. Contact between the regulatory authorities and investigators was to be welcomed. Attention was drawn to the report of the European Economic Community Working Party on efficacy of drugs, entitled "Recommended Basis for the Conduct of Clinical Trials of Medicinal Products of the European Community". An annex to the document summarizes national requirements for the regulation of clinical trials of medicinal products in the member countries of the EEC. There is now a considerable body of data on clinical trials held by Member States, and this poses issues as to the storage and retrieval of such data. The series of guidelines on the conduct of clinical trials in specific areas published by WHO was noted with approval, and the view was expressed that there may be a need for general guidelines on the conduct of clinical trials.

What kind of clinical trials should be carried out in general practice?

It was felt that this was a neglected area of research. About 80% of drugs were used in general practice but very few trials of acceptable quality

were done in primary care. This was not a satisfactory situation since many of the disorders commonly seen in general practice are rarely seen in hospital, where most clinical trials are performed. General practitioners need to consider the condition rather than the drug and they often have little training in the use of drugs. There are, too, particular practical problems in general practice such as very small units participating in a multicentre study with a high drop-out rate using inclusion criteria that may be difficult to define. The group felt that there were three types of trial in general practice:

- those that should be done in mild hypertension, mild diabetes, urinary tract infection, etc.;
- those that can be done, including utilization and epidemiology studies, monitoring of new drug usage and quality of life studies; and
- studies that should not be done, e.g. marketing or promotional studies; it is important that studies should be simple but they must be scientifically valid; double blind or randomized control studies could and should be done in general practice provided the design is kept simple.

The prime aim is to motivate general practitioners to do research studies and then to give them adequate training. It was felt that journal editors should be educated into rejecting manuscripts about trials that were poorly performed. In further discussion, it was agreed that general practitioners do not usually have the same outlook as clinical pharmacologists and therefore different approaches may be needed.

The next paper considered "How can the pharmaceutical industry help to improve clinical trials?". It was felt that trials should be economical to perform and that industry could do a lot to simplify the documentation and to ask only for the detail needed by the licensing authority. Protocols in general practice should be kept simple and protocol deviations noted quickly by regular monitoring of the trials by the coordinator from the company. Good communication here was clearly of prime importance. Discussion centred around how to motivate general practitioners to do clinical trials well. Some speakers felt that all too often the main motivating force was money since most trials were boring to perform and the outcome often had little real therapeutic benefit. It was accepted that pharmaceutical companies should pay for these studies but several questions arose. Should money be withheld if trials were poorly performed? This was discussed, but no real conclusions were made.

Should general practitioners benefit personally from money paid for a clinical trial? The situation clearly varies in different countries, but it was agreed that inappropriate payments should be avoided and the amounts of money paid should be reviewed by an independent body.

Would it not be better for any money paid for a clinical trial in general practice to go into a properly audited research and development account? This fund would then be available to benefit many aspects of primary health care (e.g. research, equipment or education). General practitioners can also be motivated by being closely involved in postgraduate activities.

Professor Hvidberg considered the role of the clinical pharmacologist. It was pointed out that clinical pharmacologists came from a number of scientific backgrounds (e.g. medicine, pharmacology, pharmacy) but by their training are ideally placed to take a major part in clinical trials. They usually have a good knowledge of statistics, extensive experience with medicines, and have worked in one or more medical disciplines. Thus the clinical pharmacologist is ideally placed to coordinate clinical trials at the local, national or international levels. They should be involved in teaching clinical trial methodology to doctors and, although this should be begun in the undergraduate years, it becomes of real practical importance after two to three years of clinical experience. They will inevitably be involved in protocol review committees as well as in ethics review committees. Clinical pharmacologists need to be well trained in clinical trials and to act primarily as leaders in the area. In this role they will recognize the skills among other groups such as clinicians and medical statisticians and will pass on their skills by teaching, especially in new courses concerned with clinical trial methodology.

At the national level, they will need to stimulate research councils and government bodies to become more supportive of large clinical trials. In this regard, the group foresaw a time when clinical pharmacologists might need to be involved in assessing priorities for clinical trials, because of a shortage of patients for all the projected trials. Thus a trial with one drug might be given national priority over a trial with a second drug. In discussion this latter point was widened considerably to consider the "need" element. Thus if a country had 25 non-steroidal anti-inflammatory drugs (NSAIDs) on the market, their licensing authority might not recognize the need to license or do clinical trials with the 26th NSAID. Norway established such a clause in 1928 in the registration process. Some countries would allow a clinical trial to be done but would not allow a licence to be given (e.g. Norway) if the trials did not demonstrate clinical advantages, while some countries (e.g. USSR) would not necessarily permit a clinical trial to be done. Scientific criteria were the prime reasons being these decisions but economic factors were also considered.

There was, however, considerable concern expressed over the widespread adoption of the "need" criteria because of the difficulty in making a valid assessment at the relatively early licensing stage. There was a risk of impairing drug development. There are many examples of drugs being developed for one clinical area but being found of more use in quite another area. There was a considerable difference between assessing priorities for performance of clinical trials, and allowing licensing of a drug only if it was felt to fill a perceived "need".

Studies should be kept relatively simple but scientifically valid. It was fully agreed that double blind or randomized control studies could be done in general practice, provided the design was fairly simple.

The prime aim is to motivate general practitioners to do research studies and then to give them adequate training from clinical pharmacologists. Journal editors should be admonished to reject manuscripts about trials that were poorly performed. In further discussion it was agreed that general practitioners do not usually have the same outlook as clinical pharmacologists and therefore different rules may be needed.

Dr R. Timmler then presented his paper on "How the pharmaceutical industry can help to improve clinical trials". He felt that trials should be economical to perform and that industry could do a lot to simplify the documentation and to ask only for the detail needed by the licensing authority. Protocols in general practice should be kept simple and protocol deviations noted quickly by regular monitoring from the clinical trials coordinator from the company. Good communication here was clearly of prime importance. Discussion centred around how to motivate the general practitioners to do clinical trials well. Some speakers felt they could be motivated by close involvement in the aims of the study but others felt that all too often the main motivating force was money since most trials were so boring to perform. It was accepted that pharmaceutical companies should pay for these studies but several questions arose.

Should money be deducted if trials were poorly performed?

Should general practitioners benefit personally from money paid for a clinical trial?

Would it not be better for any money paid for a clinical trial in general practice to go into a properly audited research and development account? This fund would then be available to benefit many aspects of primary health care. General practitioners can also be motivated by being closely involved in postgraduate activities.

Training in Clinical Pharmacology in Medical Schools in Europe:
questionnaire (presented by Professor Orme)

The WHO Regional Office for Europe set up a multinational group to consider the status of clinical pharmacology in Europe. The first meeting was held under the chairmanship of Professor F. Sjöqvist in late 1983 and a number of initiatives were begun. It was clear that the subject of clinical pharmacology was well developed in some countries but poorly developed in others and the overall aim was to improve the development of the subject in all countries of the Region.

A political document was produced stressing the role and importance of the subject and this is due for publication shortly. A brochure was written concerning the role of clinical pharmacologists in service, teaching and research. A guide to European units of clinical pharmacology is being developed, and there have been useful moves in the areas of primary medical care and the elderly. Two questionnaires were written. The first was sent to all known trainees in clinical pharmacology from 1965 onwards to find their views on the training. The second questionnaire was sent to all medical schools in the Region in February 1987 and the preliminary findings are presented below.

Over 400 questionnaires were sent out and 137 replies have been received so far. The relatively poor response rate of about 30% is disappointing. Some medical school deans refused to complete the questionnaire but many questionnaires may still be sitting in the pending tray. Maybe that questionnaire will stimulate some medical schools to fill clinical pharmacology posts. Many countries sent in so few completed questionnaires that their analysis is almost impossible at present. Any comment should be judged against the background of only a 30% return and therefore the data will be biased. A substantial number of returns came from France, the Federal Republic of Germany, the German Democratic Republic and the United Kingdom, with a smaller number coming from Spain.

The first question asked was do the medical schools have a pharmacology department? As 137 replies were received, it is clear that a few schools of medicine do not have a pharmacology department, merely a department of physiology. The questionnaire then asked whether the school had a department, division or section of clinical pharmacology. This definition is rather arbitrary but guidelines were issued to the deans on what constituted a section and what was a department of clinical pharmacology. The replies showed a very patchy development of the subject.

The next questions were devoted to finding the number of staff involved in clinical pharmacology. We asked how many staff had received training in clinical pharmacology and how many positions the medical school had for clinical pharmacologists. In some countries the basic qualification for a pharmacologist is the M.D. degree rather than the Ph.D. degree.

Finally we asked a number of questions to find out how much teaching time is devoted to pharmacology and to clinical pharmacology in each medical school at various stages in the medical course. In general, a large number of hours are devoted to teaching pharmacology in the second or third year of the

course. However, the teaching of clinical pharmacology or therapeutics was very patchy. In many schools no teaching is given to medical students in therapeutics in the final years of their training

Clinical pharmacology in primary health care

The Symposium noted that the information obtained by the questionnaire indicated that the discipline was well developed in some medical schools or institutes, whereas in others the presence of clinical pharmacology was so small as to give real reason for alarm. In part this concern originates from the recognition that many doctors place knowledge of drug therapy high among the subjects that they felt valuable in their training at medical school. Furthermore, attitudes to prescribing instilled during medical training are known to be a major influence in postgraduate life. As clinical pharmacology is so deeply concerned with the training of medical students and postgraduates and the inculcation of ideas of procuring optimal benefits from drugs and cost-effective prescribing, the Symposium urged that medical schools and institutions throughout Member States make proper provision for clinical pharmacology in undergraduate teaching and examination and/or postgraduate instruction.

It was appropriate that the Symposium then turned to consider "Continuing education of general practitioners in clinical pharmacology". Some 70-80% of all prescribing by physicians is undertaken by general practitioners. Analysis of the major influences on general practitioner prescribing finds that the training at undergraduate level has a major effect on prescribing. Other influences include consultants in district hospitals, information from drug formularies and postgraduate courses, but the latter two do not have a long-lasting influence. Much of the impetus for continuing education of general practitioners in clinical pharmacology comes from personal motivation. The latter can be aided by involving general practitioners in clinical pharmacological studies. Indeed, this area of research appears to have been underexplored by clinical pharmacologists. The setting of general practice is particularly favourable to studies such as those of mild chronic disease, e.g. hypertension, studies of the cost-benefit analysis of medicines and the monitoring of adverse drug reactions. There is a need for a greater contact between clinical pharmacologists and general practitioners to allot priorities to collaborative work that is undoubtedly there to undertake. Such work is stimulating to the individuals concerned and the information gathered would be valuable in general medical practice.

Adverse drug reactions in general practice

The Symposium then considered the possible ways of increasing the reporting of adverse drug reactions in general practice. Prescription event monitoring or systems like the Boston Collaborative Drug Surveillance Programme were very good but were probably too expensive for a countrywide system. They also were not adequate to cope with adverse events occurring less often than 1 in 1000. Surveys had shown that only 5-10% of adverse reactions were reported in a spontaneous system, and there were several reasons for this underreporting. Physicians had problems deciding which events to report, they found it too hard work to fill in the forms and regarded the system as too impersonal with no feedback to them. Motivation was improved if physicians reported to a local centre and they received regular informative feedback. Anonymity for the patients was very important

and even with these advantages general practitioners often lost interest after 18 months or so. They were sometimes helped by having a list of events which should be reported (e.g. Stevens-Johnson syndrome or agranulocytosis) but the comment was still occasionally noted by general practitioners who stated that they never saw adverse reactions.

It was generally agreed that there should be no legal obligation on physicians to report on adverse reaction and that they should never be paid for such a report. Several countries where a legal obligation existed found this to be of no help. There should be close collaboration between clinical pharmacologists and general practitioners and there should be more time spent on educating physicians about adverse drug reactions and their reporting. The subject should certainly demand time in the undergraduate medical curriculum in the clinical years of study. Physicians should be asked to be selective in their reporting of adverse reactions. While every event should be reported with a new drug, only severe reactions should be reported for established drugs. Reminders to physicians were often very helpful either in formularies or in the prescription pads. It was important that adverse information about a drug should reach physicians before the media were told.

Patient package inserts (PPI's)

Attention was then directed to the subject of the ideal patient package insert. It was agreed that the pressure for these inserts was considerable and the participants welcomed their introduction. Surveys among the public in France and Switzerland had indicated an overwhelming desire for more information about drugs and other studies in the literature suggested that patient compliance was improved and the efficacy of therapy increased. Concerns that the inserts might confuse patients or increase worries over side effects had not been substantiated. However, it was still not clear if certain patients might be alarmed by the inserts. In France some 500 PPIs had been produced each between 300 and 500 words long. The information they contained must be restricted to the facts and be easily understandable by the patient. The patient needs to know four things:

- how is the medicine expected to help them?
- how should they recognize a problem (adverse effect) and what they should do about it?
- how they should take the drug?
- how is the drug dispensed and how should it be stored?

Regular reference needs to be included in the text telling the patient to consult his or her physician or pharmacist if in doubt.

It was agreed that the insert should be prepared by the pharmaceutical company following guidelines prepared by the licensing authority. The licensing authority would then need to check the insert before it is issued. Concern was expressed that companies should not try to include in the insert every known adverse effect just to satisfy the lawyers. Only common effects should be included and lawyers may need to be educated about this, if necessary by parliaments. It was not clear whether the inserts were aimed at helping the patient to get the most out of their therapy or whether the

inserts were merely there to enable the patient to decide whether to continue with therapy or not. This latter opinion seemed to be a minority viewpoint.

Restrictions on prescribing

Conclusions

Many Member States are limiting the range of medicines that physicians may prescribe, e.g. through various types of restricted lists. The aim of a limited list is to obtain optimal value from unavoidably limited financial resources by selecting from the many drugs available those that are most desirable, taking into account both the risk-benefit ratio and cost. The need for such restriction is understood and appreciated but limiting prescribing may have both positive and negative effects. Compilation and maintenance of such lists requires collaboration between physicians and regulating authorities, and these activities in turn relate to those of the pharmaceutical manufacturers.

The pattern of illness is broadly similar throughout Europe, yet drug utilization studies have revealed marked differences in prescribing habits between Member States. Some of these differences relate to the use of multicomponent drug formulations.

Recommendations

1. The effects of restricted prescribing should be monitored and this exercise should include an estimate of the effects on patient care, the savings made by governments and the effects on the pharmaceutical industry, e.g. in allocation of resources to research.
2. Health authorities and physicians should be encouraged to look critically at pharmaceutical preparations that contain inappropriate or inactive (by dose) components. Multicomponent drug formulations are often irrational and lead to poor prescribing.
3. Physicians should be encouraged to self-audit their prescribing. This is probably most easily achieved by supplying the prescribing physician with an accurate record of his/her recent prescribing profile.
4. When generic substitutes are introduced, their bioavailability should be proven prior to licensing and uniform standards of bioequivalence should be maintained by regular monitoring after licensing.

Restraints on clinical trials

Conclusions

1. Clinical trials should relate directly to medical needs, address validly phrased questions, and should whenever possible be controlled, randomized and blinded. Studies should be analysed on the basis of "intention to treat". Statistical analysis should concentrate more on "confidence intervals" and the "power" of the study. Collaboration with statisticians in planning and conduct is very important e.g. to assess "B risk". Physicians and regulating authorities should be aware of "publication bias", i.e. the selective quotation of clinical trials that reach a particular positive conclusion and

the exclusion of clinical trials that fail to reach such a conclusion, "dose-response bias", i.e. in a comparative trial the use of a reference drug in an inappropriate dose.

2. The question of patients' rights and the manner in which clinical trials should be performed is still left largely to self-audit by the medical profession and the pharmaceutical industry. The fundamental ethical principles that apply to clinical research have not been translated into a coherent set of rules that will ensure that those principles are upheld in any given case. The public will accept that what is legally acceptable must necessarily be ill defined but it will not accept that it remains undefined.

3. It would be impossible to regulate every aspect of clinical research by statute as there are no absolute standards that may be defined in detailed and explicit terms.

4. The burdens and benefits of research on humans should be properly shared, notably in terms of the availability of speedy compensation for persons who may be injured in the course of research on them.

5. The purpose of ethics committees or bodies that perform this function is to assure the public that research is as safe as possible, to elevate standards of ethics and of science, and to protect investigators from undeserved criticism. Such committees may also have undesirable effects, through causing unreasonable delay in or inhibiting research, e.g. by poorly constituted committees. Guidance on the constitution of ethics committees (or equivalent bodies) from a national or supranational source, e.g. WHO, may well be useful. The conclusions of such committees should be binding on an investigator.

6. Clinical trials need also to be conducted in general practice (primary care) since 80% of drugs are used there and many conditions seen in general practice do not present to hospital. While protocols must be scientifically correct, they should be applicable to general practice. Marketing or promotional trials should not be performed in general practice, general practitioners should be motivated to perform studies properly and journal editors must be discouraged from publishing poorly conducted studies. The pharmaceutical industry should be encouraged to share such views and to encourage good communication with general practitioners. Collaboration between hospital physicians and general practitioners should also be encouraged.

7. Clinical pharmacologists need to be more closely involved in all aspects of clinical trials. In particular they should be involved in teaching the fundamentals of the subject to physicians, probably a year or so after qualification. The participants foresaw a time when clinical pharmacologists might need to become involved in assessing priorities for clinical trials because of a shortage of patients. This process should be kept entirely separate from the process of establishing whether a particular country needed a new medicine in a particular therapeutic category (when they already had many medicines of the same category). The advantages of a new drug should be considered in the registration process. The establishment of a "need" clause throughout the Region should not be encouraged although individual countries were welcome to use it.

Clinical trials in general practice

Recommendations

1. Trial requirements should be started clearly in well designed protocol, adherence to which constitutes the proper manifestation of good clinical practice.
2. Serious consideration should be given to the drafting of legislation to cover experimentation on humans where this does not already exist in the legal system of Member States.
3. The details of clinical investigation on humans should be reviewed and approved/accepted by properly constituted local or regional research ethics committees or other bodies that perform that function.
4. Any person who sustains injury as a result of participation in clinical research should have recourse to a system of "no fault" compensation which operates speedily and fairly.
5. (a) Serious consideration should be given to the composition of ethics committees. Their membership should be broadly similar throughout Member States. Most committees contain medicolegal and nursing representation but in addition the desirability of a strong independent nonprofessional or lay membership is stressed. Individuals who hold extremist views are unlikely to help the working of such committees. WHO should give consideration to coordinating and defining opinion and practice, particularly in respect of the composition of ethics committees, for the assistance of Member States.

(b) Ethics committees should recognize that it is unethical to pursue a study of poor scientific quality and should regard the scientific as well as the ethical aspects of studies as being within their remit.
6. (a) Clinical trials need to be conducted in general practice but these should be carefully reviewed and promotional studies avoided. Protocols need to be scientifically accurate but simple to observe.

(b) General practitioners should be motivated to perform clinical trials correctly by close involvement, adequate training and proper supervision by clinical pharmacologists and other interested parties.

(c) General practitioners like other physicians should not receive inappropriate sums of money into their personal bank account and these sums should be available for review by an independent body. Clinical trials in general practice should, however, be paid for with the money being credited to a properly audited "research and development account". The contents of this account can then be used to benefit many aspects of primary health care (e.g. research, education, or equipment).

(d) Clinical pharmacologists should become more involved in clinical trials in general practice both as educators and coordinators. This will have implications for training and staffing of clinical pharmacologists.

(e) While some countries may feel they have to establish a "need" clause in the registration process, the participants did not recommend its universal application in the Region.

Training in clinical pharmacology in medical schools in Europe

Conclusions

The Regional Office for Europe has set up a multinational group to consider the state of clinical pharmacology in Europe. Evidence from a questionnaire indicated great variations in the extent to which the discipline was developed in Europe. Most schools have a separate department of pharmacology but, in some, pharmacology was part of physiology. In similar terms many schools did not possess a separate department of clinical pharmacology, and there is much variation in the number of posts available in different schools and in the number of persons training in clinical pharmacologists.

Recommendation

The discipline of clinical pharmacology should be established in all medical schools and should influence both undergraduate and postgraduate medical training. Teaching of clinical pharmacology in the undergraduate period of training has a strong influence on subsequent prescribing and teaching of this subject in some countries, and this subject should be an important part of teaching in all medical schools/institutes of the Region. Teaching should also extend into the continuing education of physicians in practice.

Clinical pharmacology in primary health care

Conclusions

Of all prescribing by physicians, 70-80% is undertaken by general practitioners. In some countries examination of general practitioners' prescribing habits has found that the major influence is the medical school at which they train. Prescribing habits once established are difficult to eradicate. Other influences on general practitioners' habits include advice for consultants in district hospitals, information from drug formularies and postgraduate courses. The participants recognized that in some countries pressures from the pharmaceutical industry constitute a major influence.

The general practice setting is an underused and potentially very valuable "laboratory" for clinical pharmacology. Studies which are particularly appropriate to general practice are, for example, those of adverse drug reaction monitoring, cost-benefit analysis and study of mild chronic diseases such as hypertension.

Recommendations

1. Recognizing that drug therapy now plays such an important part in medical practice it is essential that all medical schools should have a strong focus for clinical pharmacology, usually in the form of a separate department. Clinical pharmacology should be taught throughout the clinical years of training and clinical pharmacologists should also take part in postgraduate medical education.
2. Clinical pharmacological studies in general practice are underexploited and should receive serious attention.

3. Clinical pharmacologists have an important role in advising on the composition of restricted drug lists. Recognizing that hospital describing influences general practitioner describing, in countries where such lists are made for hospital use consideration of drug prices should relate to the prices charged in general practice.
4. The role of clinical pharmacologists who work in district hospitals - separate from academic institutes - should be recognized by the provision of appropriate posts.

Adverse drug reactions in general practice

Conclusions

General practitioners as well as hospital physicians should be strongly encouraged and motivated to report adverse reactions to medicines. They should report all reactions to new medicines but only severe or unexpected adverse reactions to well established medicines. In the research setting it will usually be necessary to report all adverse reactions. Reporting forms should be kept simple and initial reporting should be to a local (or where accessory regional) authority which will give direct feedback to the physician. The importance of reporting adverse reactions to medicines should be stressed at all stages of medical education, not least to medical students. There need be no legal obligation on physicians to report adverse reactions and no payment should be made to physicians reporting such reactions. Involvement of clinical pharmacologists and other interested parties should be encouraged.

The development of package inserts for patients is welcomed and participants feel that overall this will improve the use of medicines. The portent of package inserts should be limited to facts and be easily readable and understandable by the patient. Patients should be encouraged to refer to health professionals if in doubt. The insert should be prepared by the relevant pharmaceutical company according to guidelines led down by the licensing authority, and subsequently approved by them. The pharmaceutical industry should be encouraged not to include excessive details (e.g. every possible adverse reaction) in the insert, to avoid worrying patients unnecessarily.

Recommendations

1. General practitioners and hospital physicians must be motivated to report adverse reactions to medicines. This should be done by education, by usually reporting to a local (or regional) authority with direct feedback and by good communication. Physicians need not be under any legal obligation to report an adverse reaction and should not be paid directly for any report.
2. Medical education should stress the importance of adverse reactions and their accurate reporting not only during the clinical undergraduate years, but also during the postgraduate period.
3. The development of patient package inserts should be encouraged, with easily readable, understandable and practical comments. Information should be kept to that which is considered useful for the patient. Excessive detail should be avoided (e.g. including every possible adverse reaction).

4. The package insert should be prepared by the pharmaceutical industry and approved by an independent body (e.g. licensing authority).

Annex 1

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