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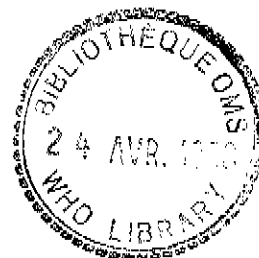
SCIENTIFIC GROUP ON PRINCIPLES FOR
THE CLINICAL EVALUATION OF DRUGS

Geneva, 13-18 November 1967

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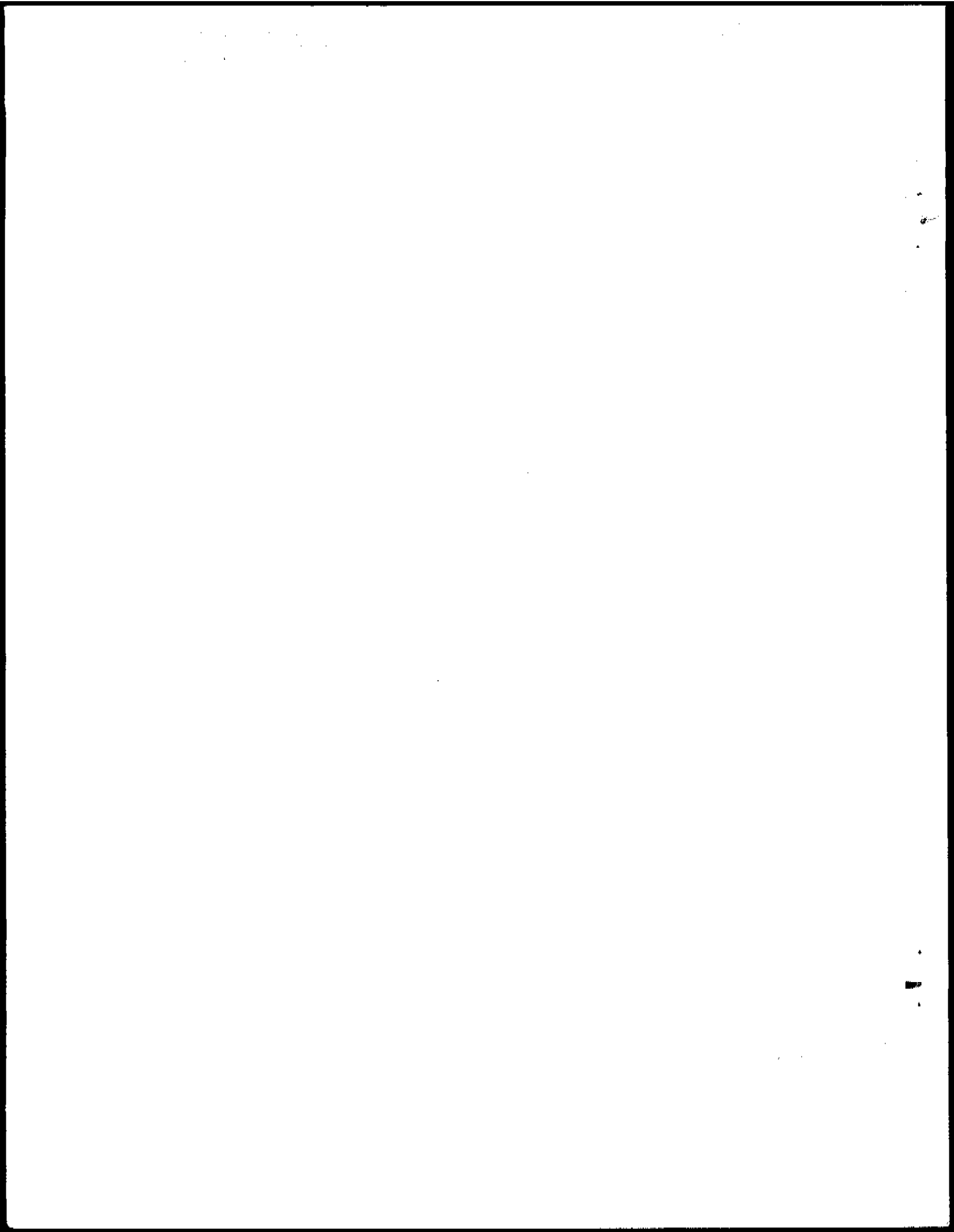


REPORT TO THE DIRECTOR-GENERAL

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WHO SCIENTIFIC GROUP ON PRINCIPLES FOR THE CLINICAL EVALUATION OF DRUGS

Geneva, 13-18 November 1967

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PRINCIPLES FOR THE CLINICAL EVALUATION OF DRUGS

Report of a WHO Scientific Group

The WHO Scientific Group on Principles for the Clinical Evaluation of Drugs met in Geneva from 13 to 18 November 1967. The meeting was opened, on behalf of the Director-General, by Dr L. Bernard, Assistant Director-General, who outlined the WHO programme related to the promotion of drug safety, with particular reference to preceding publications of the Organization.

Dr M. Finland was elected Chairman, Dr P. Deniker Vice-Chairman, and Dr C. T. Dollery nominated as Rapporteur.

1. INTRODUCTION

In recent years widespread concern about the safe use of drugs¹ has been developing amongst medical and other scientific workers and the general public. The development and surveillance of drugs affect the welfare and rights of both the individual and society, and encompass scientific, ethical and legal matters of extraordinary complexity. These factors may at times lead to conflict, and the goal of the responsible parties must be a judicious balance of these needs and values. The ways and means by which WHO can contribute to the promotion of the efficacy and safety of drugs have been discussed extensively in various sessions of the governing bodies of the Organization. As a result, the Seventeenth World Health Assembly (1964) adopted a resolution requesting the Director-General, *inter alia*, "to undertake, with the assistance of the Advisory Committee on Medical Research, the formulation of generally acceptable principles and requirements for the evaluation of the safety and efficacy of drugs".² In compliance with this request several meetings of experts have been convened by the Organization and their reports published.³

The present Group was convened to review and to formulate some principles for the clinical evaluation of drugs, whether new or old, and whether used for a new indication or in a new physical form or combination.

2. GENERAL CONSIDERATIONS

For the investigation of drugs, planned scientific studies in man are always necessary. It is not always recognized that it is unethical to introduce into general use a drug that has been inadequately tested. The ethical problem is not solely one of human experimentation; it is also one of refraining from human experimentation.

¹ A WHO Scientific Group on Principles for Pre-Clinical Testing of Drug Safety defined a drug as "any substance or product that is used or intended to be used to modify or explore physiological systems or pathological states for the benefit of the recipient". (Wld Hlth Org. techn. Rep. Ser., 1966, 341, 7).

² Resolution WHA 17.39 (Off. Rec. Wld Hlth Org., 1964, 135, 17).

³ Principles for the Pre-Clinical Testing of Drug Safety: Report of a WHO Scientific Group (Wld Hlth Org. techn. Rep. Ser., 1966, 341); Principles for the Testing of Drugs for Teratogenicity: Report of a WHO Scientific Group (Wld Hlth Org. techn. Rep. Ser., 1967, 364). The report of a WHO Scientific Group on the Evaluation of Dependence-Producing Drugs (Wld Hlth Org. techn. Rep. Ser., 1964, 287) is also relevant to this subject.

It must be realized that adherence to ethical and humane principles as well as to economic and technical considerations will sharply limit the number of subjects and the number and quality of organized studies in man as compared with those in animals. Because of these restrictions it is essential not to waste human and economic resources in carrying out scientifically inadequate studies, the validity of which will later be questioned.

In initial trials of any new agents, the investigator must be genuinely open-minded concerning the possibility that the drug is worth a trial and that it may be as good as, or perhaps better than, one or more of those already available. Strong convictions for or against its value in the treatment of a disease can render it unethical for him to use or withhold the agent under trial or to use a placebo; in this case he should not undertake the investigation.

The fact that a trial has been proposed implies that the investigator must have formed some opinion about the value of the new drug, but he must be able to divorce his views from the conduct of the trial.

As was pointed out in the report of a WHO Scientific Group on Principles for Pre-Clinical Testing of Drug Safety,¹ "in this context there can be no absolute safety. The administration of biologically active substances to human beings must always be accompanied by some element of risk that cannot be avoided by the most careful and exhaustive scientific study of the drug before it is introduced."

The report continued: "Any situation, including the introduction of new drugs, that may involve some hazard to an individual or to a community should be judged from an evaluation of the balance between benefit and risk. This balance implies that the therapeutic aims of the drug be considered in relation to the possible risks demonstrated by the early studies", i.e., the studies on animals that were the subject of that report. Similar judgements must be exercised throughout the procedures for clinical testing discussed below.

Before drugs are used in general medical practice, it is important to study their comparative therapeutic efficacy and toxicity. Any hazards that may arise from interaction with other drugs, domestic remedies, alcohol or food should be considered, and investigated where indicated.

The initial trial of a new drug in man will involve a small number of subjects under close clinical and laboratory supervision by experienced investigators. If the results are considered to justify it, the studies will then be extended to larger numbers, but this will pose additional difficulties in ensuring close and adequate supervision.

The subjects of such studies may be healthy volunteers, consenting patients, or sometimes even patients whose consent has not been sought because it was not in their interest to do so or because they were not competent to give it (see section 4.1.).

Because the procedures involved in the testing of new drugs vary widely, e.g., (the tests for a general anaesthetic, a dermatological, a psychotropic, or an antimicrobial agent), because the methods used are continually being improved, and because "facilities, attitudes and legal restrictions vary widely from country to country",² only general principles can be offered in this document. Indeed, any attempt to lay down rigid requirements for clinical evaluation of widely differing drugs would fail to achieve its objective and would hinder the advance of therapeutics.

¹ Wld Hlth Org. techn. Rep. Ser., 1966, 341, 4.

² Wld Hlth Org. techn. Rep. Ser., 1966, 341, 19.

Besides the problem of testing new drugs there is a need to re-evaluate many established or commonly used drugs. Many of these have never had adequate and comprehensive testing (enzyme induction, protein binding, interactions, etc.) and judgements of their safety and efficacy rest as much on intuitive reasoning as on acceptable scientific evidence.

Studies of drugs in man are considered under two main headings here:

(1) Initial studies

(a) pharmacological studies (including absorption, metabolism, etc.) on small numbers of healthy volunteers or patients, or both;

(b) wider use in patients under close supervision in order to establish whether the drug has any potential therapeutic use and to obtain data (range of dosage, patient selection, etc.) to allow design of a formal therapeutic trial should that seem justifiable.

(2) Formal therapeutic trials

Formal assessment of therapeutic merits, that is, of efficacy in relation to safety, and comparison with those of existing therapy, if any.

Drug investigations other than formal therapeutic trials may reveal important therapeutic or toxic effects of new agents, particularly if the course of the disease or symptom is accurately predictable in the absence of treatment. The formal therapeutic trial, however, provides a quantification of the comparative efficacy and toxicity of new and standard treatments, and of placebos, when these are included.

In addition, as drug therapy becomes more effective, it becomes more difficult to justify trials of new treatments that might possibly be less effective or more toxic than those currently used, especially if they involve withholding existing well-tried agents. For these reasons, it is a duty to increase the sensitivity and selectivity of the techniques of measurement (clinical, physiological, pharmacological, biochemical, statistical) to obtain the maximum of information from the minimum of subjects.

After a new drug has been introduced into general medical use, it is desirable to set up a monitoring system to detect any rare adverse reactions that may not have occurred amongst the necessarily limited numbers involved in the formal therapeutic trials.

3. INITIAL STUDIES IN MAN

3.1 Justification and purpose

Any studies with a new drug in man must be justified by an analysis of the rationale underlying the drug's development, by the preclinical data, and by the specific medical needs that it is hoped the new drug will meet.

The main purpose of the initial studies in man is to find out whether the drug has a pharmacological effect that may be useful in therapy. The range of dose must be established and special attention given to drug toxicity.

It is desirable to combine early studies at low doses with chemical or radiochemical measurement of absorption, distribution, protein binding, metabolism and excretion. Special care is needed if the metabolic disposition in man proves to be very different from that observed in any animal species used for preclinical pharmacological and toxicological work.

Once a potentially useful therapeutic effect has been observed information must be accumulated on dosage, side-effects, and therapeutic indications.

3.2 Prerequisites

3.2.1 Results of preclinical testing in animals

Initial studies in man must necessarily at first be based on tests in animals. Where possible, the clinical investigators should personally meet the responsible scientific staff who carried out the animal tests. This facilitates understanding by allowing the preclinical workers to explain the animal data to the clinicians, who may not be fully familiar with some of the tests and the reasons for their choice, and the clinicians to explain to the laboratory workers the clinical situation in which the drug is to be tested. Discussion should include the way in which disease might influence the action of the drug.

Sometimes single doses without pharmacological or therapeutic effect may be useful for obtaining pharmacokinetic data. At other times, a single dose or a brief period of administration may be sufficient to determine pharmacodynamic or therapeutic potential, as in the case of local or general anaesthetics. In these situations, the clinician need not demand such extensive toxicity tests in animals as would be essential were the drug to be used continuously in each individual for days or weeks.

Circumstances are so various that no comprehensive guidance can be offered. The decisions on how much animal testing is sufficient must be decided in each case.

The clinician and his appropriate advisers have, however, the responsibility of satisfying themselves that the preclinical experiments are adequate in scope and they should request a full account of all relevant data. The chemical formula of the drug (where known), relevant physicochemical properties and information about the purity and stability of the drug should be provided. In his turn, the clinician must make all his data available, in confidence, to the preclinical workers. Information exchanged among investigators should not be divulged without their permission, except insofar as required by law.

The amount of information that can be provided on the mechanism of action of a drug and on its absorption, distribution, metabolism and excretion must depend greatly on the state of current knowledge in the areas concerned, and the clinician will take this into consideration when assessing whether the animal data provided are adequate.

Prior to the first administration in man, attempts should be made to find out how and where the drug acts. This may increase the reliability of pharmacological and toxicological predictions for man.

Close collaboration between the preclinical and the clinical workers is particularly important in assessing the first results of administration in man; sometimes it may be desirable to delay or interrupt the clinical programme whilst further animal experiments are done.

At this stage, communication among investigators should be as direct and rapid as possible to avoid duplication of hazard. To achieve this goal, responsibility for disseminating information should be assigned to a specific individual or group.

3.2.2 Clinical and laboratory facilities

The requirements for these will vary greatly according to what is being attempted. The clinician has a duty to supervise closely, to record, and to measure the functions that may be affected by the new drug. For example, preparations applied to the skin may be absorbed into the blood and so, in addition to observing changes in the skin, it is necessary to seek

evidence of absorption, which may be provided by detection of the drug or its metabolites in blood or urine and/or by its systemic effects. Testing a preparation for use in, for instance, cardiac arrhythmias will demand complex instrumentation as well as biochemical facilities.

All changes reported by or detected in the subject should be assumed to be due to the new drug until they have been otherwise explained with reasonable certainty.

3.2.3 Clinical and laboratory observations

Investigators should not only try to detect changes that may be predicted from the results of the animal experiments but should be on the alert to detect the unexpected.

When the drug is first administered to man, arrangements should be made to record the patient's subjective feelings, and the ordinary routine of medical practice (temperature, pulse, respiration, urine, bowel function) must be maintained. In many cases, it may be thought necessary not only to increase the frequency of these routine observations but to adopt more sensitive or extensive techniques. Regular examination of the peripheral blood and of hepatic and renal function may be added as a safety precaution even though animal tests have given no reason to expect these to be altered, for laboratory tests will provide an earlier indication of malfunction than will clinical observation. More information is needed about the usefulness of the regular tests for drug toxicity that are often carried out in these circumstances.

In general, initial clinical studies should be undertaken only where close observation and supervision are possible. Where systemic actions are anticipated, a clinical laboratory equipped to measure a wide range of physiological variables and supported by facilities for biochemical and for pathological studies (e.g., biopsies of bone marrow, liver, etc.) is required. Naturally, the minimum facilities will depend on the nature of the studies that are being made and on the local circumstances. But it must be stressed that the clinical worker should make every effort to collect all relevant information.

3.2.4 Qualification of the investigator

The clinical investigator of a new drug should be experienced in the specific disease for which the drug is intended. Ideally he should also be skilled in the design and practice of scientific clinical investigations in man and in the principles of pharmacology and of statistics. It is, of course, rare to find all these qualities combined in a single worker. The initial studies in man will, therefore, more often be done in consultation with other appropriate experts or by a group of workers. It is, however, important that each worker in such a group should have at least some broad knowledge of his colleagues' disciplines; in particular, the statistician should, whenever possible, have had training in medical statistics.

3.2.5 The clinical pharmacologist

In recent years, the new specialty of clinical pharmacology has developed. Clinical pharmacologists have usually been trained in both pharmacology and clinical medicine and may have special interest in the methodology of experimental design. They naturally specialize in a particular area of pharmacology or disease for their personal research but have sufficient interest in general pharmacology to function as advisers to, or to collaborate with, other clinical investigators. They may organize hospital-wide systems for monitoring adverse reactions to drugs and arrange teaching programmes in therapeutics.

Clinicians who were not "clinical pharmacologists" in the modern sense have been responsible for most of the therapeutic advances of the past and they will continue to make

major contributions. Nevertheless, the clinical pharmacologist can play a special and useful role in drug evaluation.

3.2.6 Facilities for clinical pharmacology

At present, most clinical pharmacologists are attached to a section of the department of medicine or other clinical department, or have a joint appointment in both a department of pharmacology and a department of medicine. As the organization of universities and of patient care varies widely in different countries, it is not possible to make a general recommendation about the administrative position of a unit of clinical pharmacology.

A clinical pharmacology unit should have direct access to patients and adequate laboratory facilities. Personnel may include one or more clinical pharmacologists, pharmacologists, and biochemists specializing in drug metabolism. It may be possible to arrange a system of shared appointments between departments, but it is better if all the personnel required form part of the clinical pharmacology unit. A clinical pharmacology unit will require adequate technical support and its existence will probably create extra work in other sections, such as the pharmacy and medical records department.

Special attention was devoted to clinical pharmacology because it is a new discipline. The Group recommends that consideration be given to organizing clinical pharmacology units in order to improve facilities for clinical evaluation of drugs and to train more personnel in this discipline.

3.3 Experimental design

3.3.1 Choice of subjects

Depending on the objectives of the study, the subjects chosen may be either patients or healthy subjects. Data on absorption, distribution, metabolism and excretion as well as evidence for many pharmacodynamic actions may be obtained from either, but sometimes a desired effect can be detected only in a diseased subject, e.g., anticancer, antiparkinsonian, and antimicrobial effects. Similarly, exploration of the modification of drug action by disease, e.g., hepatic or renal insufficiency, can be carried out only in patients with the disease.

The decision whether to test the drug on healthy volunteers, volunteers with a disease other than that under investigation, volunteers with the disease under investigation or, rarely, patients who are not consulted (e.g., those with advanced mental disease) should be taken after discussion by an informed group and not by the experimenter alone. The choice will depend on a wide variety of factors, especially the likely hazards. If these are thought to be substantial, it may be preferable to choose a subject who could possibly derive personal benefit from the drug rather than one who could not. This reasoning sometimes leads to the selection of patients who are resistant to current therapy. Whilst this may be justifiable at the outset, it should be remembered that a useful drug may be lost if it is abandoned after being tested solely on patients who have failed to respond to existing drugs.

If it is decided not to accept such patients as subjects, volunteers may be invited from amongst apparently healthy groups, or occasionally from patients with another disease, but due regard must be paid to ethical obligations, technical factors, and the attitudes of the society concerned. It should be kept in mind that such volunteer groups may not be representative of the general population under consideration.

A number of problems arise in regard to the use of the following subgroups as subjects:

(a) Children. In general, new drugs will be evaluated initially in adults. Therapeutic trials will also be first attempted in adults in most cases, but occasionally unique paediatric problems will require that the first trials for efficacy be performed in children.

(b) Women of child-bearing age. Women who are known to be or who may be pregnant should preferably not be used for the earliest initial studies with drugs because of potential risk to the foetus. If, however, drugs are developed that are specifically intended for use by pregnant women, the first clinical study of efficacy will have to be performed in them.

(c) Mortally ill patients. It is inadvisable to conduct the earliest human investigation of a new drug in patients who are mortally ill, since toxic or therapeutic effects may be masked by the precarious physiological state of the subject. If, however, drugs are to be tested for their effects on disease states obtaining only in the mortally ill, clearly clinical trials will be relevant only if performed in such patients. If a seriously ill patient is mentally competent and wishes to volunteer for a "non-therapeutic" experiment, he should be allowed to do so, provided that purpose and design of the trial have been reviewed by a group acquainted with the circumstances.

(d) Volunteers in special situations. There is a risk that persons who are in a position of dependence (e.g. students or prisoners) and are asked to volunteer for studies might feel that they are subject to undue pressure. Special care is therefore needed in accepting volunteers in these situations, and review of the purpose and design of the trial by groups of physicians and other medical scientists is desirable.

(e) The psychiatrically ill and the mentally retarded. See section 4.1.

3.3.2 Number of subjects

The number of subjects required before enough can be known about a new drug to warrant embarking on a formal therapeutic trial will vary greatly according to circumstances. Sometimes it will be influenced by the fact that the new drug is closely similar to existing drugs. It will always be influenced by the results of the first experiment.

3.3.3 Dosage and route of administration

To detect the pharmacological effects or the potential therapeutic value of a new drug, gradually increasing single doses¹ may be given until an effect, wanted or unwanted, appears. Experiments should ordinarily be done in different subjects to avoid any possible increased hazard of repeated administration.

The predicted effective dose may best be calculated from animal studies on the basis of body weight, surface area, plasma concentration, or even better from factors in drug metabolism, distribution and excretion.

In the initial administrations to man it is usually wise to work up from a small fraction of the predicted effective dose: the pharmacologist may predict an effective dose for man on the basis of animal experiments, but the clinician must not accept this without full consideration of the physiological differences between man and animals.

¹ The single dose may sometimes be given fractionally over a short period.

In general, an upper limit to dosage should be set in the first experiments, but as experience is gained a gradual increase is allowed until some toxic effect is noted or until the therapeutic dose response curve has been adequately defined. If no response occurs, the explanation may lie in blood-protein binding, tissue binding, or in other factors of distribution, metabolism or excretion of the drug, or in tissue tolerance.

In general, prediction from animals of what effect a drug will have in man is more reliable than prediction of the dose at which this effect will appear; in other words, species differences are more often pharmacokinetic than pharmacodynamic.

The route of administration should be selected on the basis of knowledge of the drug and of its intended use. For reasons of safety and convenience, oral administration will commonly be preferred for the initial administration, although the superior control afforded by the intravenous route, or its relevance to the purpose for which the drug is intended, may render it preferable in special cases. Other routes, topical applications, inhalations, etc. will be used when appropriate.

3.3.4 Duration of administration

There is no firm scientific basis for selecting any particular period of time for chronic toxicity tests in animals as being necessary before studies may be done in man. Indeed the induction of drug metabolizing enzymes or tissue tolerance may mask toxicity in prolonged studies.

By using a wide range of dosage, appropriate species and larger groups of animals, the important information may be obtained in weeks or months. Except for questions involving certain aspects of reproduction, genetic effects, or carcinogenesis, toxicity testing seldom needs to be prolonged beyond a few months.

As a guide, the Group suggests that a single administration of a new drug to man may be justifiable after only a few weeks of well planned and carefully executed animal toxicological studies. On the other hand, a drug should not be administered to man for long periods without three to six months of such studies.

3.3.5 Pharmacokinetic studies (absorption, distribution, metabolism, excretion)

Technical facilities for such studies are currently limited and generally inadequate. Development of more sensitive techniques for measuring concentrations of drugs and their metabolites is much needed.

Studies of absorption, distribution, metabolism and excretion contribute to the safer conduct and more efficient design of human drug studies, allow accurate dosage schedules to be reached at an earlier stage, enhance prediction of the effect of disease on the action of the drug, and allow the preclinical scientist to devise more informative laboratory experiments.

In the earliest human studies of most drugs, a pharmacodynamic activity will not usually be seen with the small doses employed, and with some drugs, e.g., antimicrobials, certain effects may be seen only after a period of continuous use. In these cases, early pharmacokinetic studies may be particularly useful.

3.3.6 Pharmacodynamic studies (biological and therapeutic effects)

In order to minimize risks in man, it is essential to have methods of detecting pharmacodynamic effects, unexpected as well as expected, at their earliest appearance. The most sensitive available techniques should always be employed and these will sometimes demand complex equipment and skills.

Details may be varied in accordance with the expected effect and no further discussion would be useful here.

3.3.7 Controls

When a single dose of a drug is given to man for the first time, the principal aims are: to determine whether it can be given safely, to observe a pharmacodynamic action, and to examine its pharmacokinetics rather than to perform a controlled therapeutic experiment. This means that, generally, the control is the subject's state before the administration.

There is no place, at this stage, for a controlled comparative experiment. However, sometimes it may be profitable to keep from the subject any knowledge of the actual moment of administration of the drug. This will obviate the effects of psychological changes on, for example, the cardiovascular system, which may be produced by the knowledge that a new drug has just been given. It must be stressed, however, that considerations of ethics and safety are paramount and nothing may be done, however desirable scientifically, if it is likely to prejudice these.

When the initial studies are well advanced, it may be appropriate to introduce controls, such as use of placebos, to determine whether the changes that have occurred are in fact the result of the drug. This need not increase the hazard.

3.3.8 Interactions

During the initial studies in man it is desirable, whenever possible, to ensure that a subject receives only the experimental drug. Investigators should bear in mind the complicating effects of other drugs, whether prescribed or not as well as those of household remedies, alcohol, caffeine, nicotine, food, etc. However, as the studies widen, patients will inevitably receive the new drug at the same time as they take other drugs.

Plainly, it is impossible to demand that interactions with all possible drugs should be studied in animals. Two types of interaction should, however, be considered for laboratory study prior to human trial:

- (a) interactions between the new drug and other drugs especially likely to be taken concurrently by patients with conditions that the new drug is designed to treat;
- (b) interactions known to occur in the case of other drugs that are chemically related to the new drug or whose behaviour in respect to metabolism, protein-binding, etc., is similar to that of the new drug.

A WHO Scientific Group on Principles for Pre-Clinical Testing of Drug Safety has recommended a study of interactions of formulations containing more than one drug and "when the initial trial in man requires the new drug to be given in addition to concurrent therapy".¹

A number of important mechanisms of drug interaction are known and should be considered:

Drugs may be bound in the gut lumen and so rendered inactive (e.g., binding of tetracycline by aluminium or calcium salts). Changes in bacterial flora may also alter drug absorption.

Absorption may be increased if breakdown in the gut mucosa is inhibited (e.g., certain sympathomimetics in foods and some sympathomimetic drugs in the presence of monoamine oxidase inhibitors).

Drugs that are strongly bound to plasma proteins may displace other protein-bound drugs and so cause a temporary increase in the free (active) portion in plasma (e.g., clofibrate may displace dicoumarol).

¹ Wld Hlth Org. techn. Rep. Ser., 1966, 341, 15.

Drugs may interact at the receptor by combining with it or competing for it. In other instances, drugs with closely related pharmacological activity may enhance each other's effects (e.g., alcohol, barbiturates, phenothiazines, and narcotics). Some drugs counteract another's therapeutic effects (e.g., imipramine counteracts the effect of guanethidine).

Drugs that are metabolized by microsomal enzymes may be metabolized more rapidly as a result of enhanced enzyme activity induced by another drug (e.g., more rapid metabolism of dicoumarol after barbiturates).

Drugs may compete for excretory mechanisms in the kidney or liver, causing delayed elimination (e.g., probenecid and penicillin).

Interactions between drugs may produce an abnormal host-parasite relationship (e.g., effect of agents altering gut motility or flora in amoebic infection).

Drugs may also interact with other therapeutic devices (e.g., sympathomimetics in patients with artificial cardiac pacemakers).

3.3.9 Documentation

Careful and complete records of all studies should be kept. Data relevant to safety and efficacy should be shared with the sponsor of the drug and other investigators in the most rapid and effective manner.

The data accumulated in the initial studies should be sufficient to allow a decision on the justification for formal therapeutic trial. Throughout this period contact should be maintained with the preclinical scientists, and further animal experiments should be requested, when indicated, to elucidate events observed in man.

4. ETHICAL AND LEGAL ASPECTS¹

The problems of ethics and law in human experimentation are ever-present in drug evaluation, but they are not peculiar to this field, and a detailed exposition of the problem has not been attempted in this report.

Research in man has ethical implications that play an important part in the planning and execution of experiments. Good research should have a secure moral basis.

Repeated contact between groups of competent investigators would be helpful in clarifying these questions, and would assist in the organization of any review or supervisory process. To evaluate ethical questions it is important to understand the objective and nature of the research.

It is possible that rigid, legalistic interpretations of codes and regulations may hinder the orderly and rational introduction of new therapeutic agents. Review of the purpose and design of the trial and of preliminary data by local research committees composed of physicians and experienced medical research workers ("peer groups") may actually be more effective than laws in protecting both the patient and the investigator. The Group hopes that such reviews will become more widespread in the future. Where there is an official agency that approves studies on healthy volunteers or on patients, it is important that it should be composed of medical scientists - for instance, a committee of a medical research council.

¹ For convenience, these aspects are discussed here in relation to both initial studies and therapeutic trials.

In some countries there are substantial restrictions on the use of animals for research, and in others, the introduction of such restrictions has been proposed. While strongly in favour of measures to ensure the humane treatment of animals, the Group is very concerned about any measures that might slow therapeutic advance.

4.1 Consent of subjects

Subjects must usually be informed of the nature and purpose of the trial and of the potential risks and benefits. A fair presentation of the major issues should be given, but not an excessively detailed and technical discussion which might simply confuse the subject. A written record of the subject's consent is ordinarily desirable, although it need not contain an account of the full discussion required to acquaint the subject with the hazards and goals.

Insofar as consistent with the patient's best interests, his freely-given consent should be obtained, if at all possible, and, in case of legal incapacity, consent should be procured from the legal guardian. For patients with major psychoses or severe mental retardation, some special procedure may have to be employed, such as consultation with the physician in charge, expert consultants and with the family or official custodians. The procedure may vary in different countries.

At times, the physician may judge that to seek informed consent would be either impossible or not in the best interests of the patient; in such instances the patient's interests will be safeguarded by consultation with a review group of physicians and other medical scientists (peer group).

4.2 Safety of subjects

There is little risk of serious danger when clinical investigation is conducted by competent investigators with adequate facilities and there is close supervision of subjects. However, it is essential that in the planning of studies provision be made for dealing with untoward effects in the subjects. The subject's welfare must always take precedence over the purpose of the investigation. If there is any suggestion of significant harm to a subject, administration of the drug should cease immediately and appropriate remedial measures should be taken.

4.3 Reward of subjects

In some places, subjects may be rewarded for participation in research, sometimes to encourage participation and at other times as an incidental reward. To ensure that rewards do not induce subjects to submit to unreasonable hazards, persons not involved in the research should review the protocol and decide the advisability of the study independently of considerations of reward.

4.4 Payment of costs

When a trial is conducted during the course of medical treatment, costs in excess of routine medical expenses should be paid by research grants from the sponsor of the drug, government or other sources.

4.5 Remuneration of investigators

Many investigators engage in drug research without extra payment for their efforts. Nevertheless, if research interferes with a physician's usual professional duties, payment may be made to him, or to the institution for which he works or where the investigation is performed. It may also be necessary or desirable to pay professional personnel (doctors,

nurses, etc.) for time spent outside their regular working hours in making reports, filling out forms, etc. Research review groups should be informed of any personal payments made.

4.6 Compensation for injury

There has been a failure to consider the needs of human subjects who are injured in the course of an ethically irreproachable human experiment. It is not possible under common law to absolve the investigator from liability for negligence; nor should he be so absolved. Liability for negligence remains a useful check on the incompetent or unscrupulous investigator. However, injuries or mishaps with medical consequences may occur during the course of research in which there is no question of negligence.

There is need for some process, such as an insurance system, that will pay for medical care, where necessary, and provide appropriate compensation when research subjects sustain injury or death during investigation, regardless of possible negligence and without prejudice to liability. The cost of this protection should be considered part of the basic cost of the conduct of the clinical investigation.

5. FORMAL THERAPEUTIC TRIALS¹

This section is concerned with the stage following a decision that a drug has sufficient therapeutic potential in relation to its safety to deserve a formal scientifically designed trial to determine its usefulness and/or to compare it with existing therapy. A short list of publications providing more detailed guidance on the design and conduct of therapeutic trials is given on page 23.

5.1 Purpose and method

The purpose of the formal therapeutic trial is to determine whether a drug has a useful effect in treating or preventing disease and to evaluate it, in terms of efficacy and toxicity, in relation to other therapy (whether this is by drugs, surgery, psychotherapy, diet, etc.). It is designed to ensure that the comparisons made are as precise, informative, and convincing as possible.

A therapeutic trial is usually begun with the intention of deciding whether a new drug has more (or less) value than the current standard treatment. Frequently, however, the investigator should try to do more. He should try to determine why certain patients respond to a treatment and why others do not. What are the features in the patient that lead to this result? This is a much more difficult problem to solve. It may call for the recording of much information about each patient before the trial starts. At its conclusion, it may then be possible to determine the characteristics of those patients who showed a favourable response in comparison with those who did not. The task will, of course, be much easier if the investigator can have in mind initially some particular characteristics that may conceivably affect the outcome. He will then be saved a wide and roving inquiry.

5.2 Experimental design

5.2.1 Formulation of questions to be answered

The first step in the design of a therapeutic trial is the formulation of the questions that it is hoped to answer. It is wise to limit the number of questions and to make these few absolutely precise. This has the disadvantage that the answers are limited to specific

¹ The principles enunciated in this section also apply, in general, to prophylactic trials.

questions and are unsuitable for generalizations. On the other hand, if the questions are made too complex, the investigator will be unable to draw any firm conclusions at the end of the trial; he will be faced with a number of inconclusive answers, each based upon too few observations.

In short, the exact aim of the trial should be thought out in detail before it is begun. This will involve such points as the accurate description of the patients to be included in the trial, the treatment(s) that they are to be given, and the measurements that are to be made to reveal the progression of their illness and the effects, if any, of the drug.

5.2.2 Selection of patients

In this connexion, the investigator will need to consider such questions as accuracy of diagnosis and severity of disease in patients to be admitted to the trial, whether the patients have a history of therapy that might modify the course of their illness and thus, possibly, confuse the issue of the trial, whether they should be limited to defined ages (e.g., excluding the very young or old), whether they should be without other diseases than the one under investigation, and so on.

The criteria must not, of course, be made so rigid as to limit unduly the patients available for the trial, nor to make the answer to the trial so narrow as to be of little use in medical practice.

5.2.3 Choice and measurement of variables

The choice of variables to be measured will depend upon the disease. In some, for instance, the status of the heart will be of dominating importance, in others joint swelling and pain, and so on. The methods of measurement must remain unchanged throughout the course of the trial. Any criteria of assessment of the patient's condition must similarly remain unaltered. Clear definitions of methods, criteria, times of measurement, and clinical assessment must be agreed upon before the trial starts. Such methods, criteria and time schedules should be adhered to as closely as possible. Every departure from the rules lowers the efficiency of the trial.

In the field of psychopharmacology, where the variables involved make objective measurements either difficult or irrelevant, a scoring system for the evaluation of the symptoms may prove of value. The use of newer techniques and instruments may in time aid quantitative evaluation of psychiatric signs and symptoms.

It is axiomatic in any trial that the same care and precision in measurement be applied to all groups whether treated with a new drug or not.

5.2.4 Construction of groups and stratification

Methods of allocating patients to different groups, or of assigning different treatment to different patients, are subject to both conscious and unconscious bias if they depend on a physician's choice. Some method of random allocation is essential to avoid this danger. Commonly, this is achieved by the use of tables of random numbers, where each digit or each combination of a given number of digits has an equal probability of selection.

¹ The trial may, of course, run into unanticipated difficulties that require fundamental changes in the methods of measurement or of the criteria of assessment; in such cases, the experiment will usually have to start again and the previously collected data will be discarded.

If relevant background information on different variables in patients is available, "stratification" of such information may increase specificity of comparisons and conclusions. In other words, the original sample of patients may be sub-divided (stratified) into appropriate and more homogeneous sub-groups, and a random sample withdrawn from each of these for allocation to treatment. The sub-sample may, or may not be, proportional to the number of units in the sub-group.

Special tables of random permutations of small numbers exist, and may be needed to provide groups of equal size when a rare condition is studied.

The purpose of randomization is twofold: (1) to render the subject groups as equivalent as possible in regard to all variables other than the treatments under study, and (2) to provide scientific justification for the application and interpretation of statistical tests of probability and significance.

The treatments frequently need to be disguised, in order to render the trial "blind". Coding of treatments is best done on an individual basis, with separate letters or numbers for each subject, so that if for any reason (such as suspected harm to the subject) it is necessary for the investigator to know which treatment has been used in a particular case, the identity of the medications being given to other subjects is not automatically revealed.

It is sometimes inevitable that patients have to be withdrawn from the treatment allotted to them. For example, some may suffer severe reactions to a drug, use of which cannot therefore be continued. Such patients must, however, continue to be counted as a part of the trial, as their omission would lead to a biased comparison.

5.2.5 Control by standard treatment or by placebo

For quantifying the therapeutic and toxic effects of a new drug, there are two usual standards of reference. One is the placebo, and the other is the drug (or drugs or other forms of therapy) generally accepted as the best treatment already available. The decision whether to include only the placebo, only a standard drug, or both, will depend on the nature of the disease, the drugs already in use for the disease, the state of the relevant experimental methodology, and the goals of the study. Placebos may be crucial to the interpretation of an investigation in which the performance of a new drug appears similar to, or inferior to, the standard medication. Even here, however, the use of placebo controls is not mandatory; the establishment of dose-response curves for the new and the standard drugs may obviate the need for a placebo and will indeed provide a clearer picture of the status of a new drug than a placebo-controlled experiment with single dose levels of new and old drugs.

The placebo is a control for two types of phenomenon. One, the best known and appreciated, is the effect of suggestibility, personality, attitudes, anticipations and other biases on the part of the patient, investigator or observer. These biases may be in the direction of augmenting the benefit of treatment or of diminishing it, of concealing side-effects or of reporting or displaying ill-effects that are unrelated to treatment.

In addition, the placebo provides a vital control for spontaneous changes in the course of the disease or in the symptoms under study, as well as for events that are independent of the treatments under study. In the absence of a period of study with, or of a group of patients receiving, no treatment of any kind (including placebo), it is impossible to determine the relative contribution of spontaneous changes in the disease and other events independent of treatment to the over-all placebo "success rate" or "toxicity rate". In most instances, however, this distinction will not be important to the investigator, and the placebo will remain an important tool for distinguishing between a true pharmacological effect and both the psychological effects of taking medication and the fortuitous changes associated with the passage of time.

The placebo should be as similar as possible to the active treatment in appearance, taste, etc. Some have suggested the use of placebos containing drugs that will mimic the side-effects of the active treatments. The difficulty of producing such "active placebos" and the impossibility of reliably predicting what positive or negative effects they will have render their use inadvisable, scientifically as well as ethically.

Double-blind and single-blind techniques. The expression "double-blind" (sometimes "double blindfold") is used to describe a trial in which the nature of the treatment being received by a subject at any time is unknown to both subject and observer. This precaution gives protection against the preconceptions and anticipations of both, and is often required to render the trial valid and the data interpretable.

Provision must always be made to enable the observer to find out immediately what the drug is, if it should be in the patient's interest to do so. The double-blind technique, properly conducted, is in no way unethical.

The term "single-blind" refers to a trial in which one participant, usually the subject rather than the observer or investigator, is unaware of the treatment he is receiving at any specific time. Such a control is almost always less satisfactory than the double-blind technique, and the slight gain in convenience hardly compensates for the potential loss of rigour in the study.

The term "triple-blind" has a variety of meanings, none of which is particularly useful or relevant to clinical trials.

Within-patient comparisons. It may sometimes be advantageous to use a subject "as his own control", i.e., to expose him to the various treatments under study and compare the responses to these treatments. Such a technique is efficient only if there is less variation within subjects at different times than between subjects (e.g., in chronic arthritis and Parkinson's disease). If this is not the case, the within-patient comparison (or cross-over trial) can be wasteful and misleading. If, for example, a patient with pneumonia is being treated with an effective antibiotic, it is pointless to stop this treatment after a few days and change over to a test drug; the patient will have changed so much since the initiation of therapy that it will be better to give the second treatment to another patient at the start of his illness.

Concurrent or retrospective controls. In between-patient comparisons, the patients in the group receiving the treatment under test and those in the control group are generally best allocated concurrently. By doing this, known and unknown fluctuations in the disease, the environment and the type of patient admitted are more likely to be equally represented in each group.

If patients treated in the past are used as controls, the likelihood that the treated and the control groups will be equivalent is much less.

Concurrent controls are particularly important where the natural history of diseases or symptoms is likely to be inconstant and where changes in the kind of patient to be selected, or in the environment, frequently occur - but where the prognosis is fairly constant, retrospective controls may be acceptable and may, indeed, be the only kind that are ethically permissible.

5.2.6 Fixed-sample and sequential trials: sample size

When a therapeutic trial is undertaken it is necessary to ensure that the decision to terminate it should be uninfluenced by the observer's preconceptions of what he thinks the result might be or ought to be. One way of achieving this is to decide in advance that a

certain number of patients shall be treated, i.e., the fixed-sample trial (a variant on this is to treat all suitable patients presenting within an agreed period of time).

Alternatively, results may be analysed sequentially, i.e., as they appear. The advantage of sequential analysis is that, on average, fewer patients are needed than where the analyses are done after a predetermined number of observations. This has ethical implications in serious disease. A disadvantage of the technique is that the decision on the outcome in the individual patient has to be taken on one clear-cut endpoint and not on assessment of multiple variables. In addition, the confidence limits of the differences may be very wide, because the trial may end after only a small number of patients have been studied. Sequential analysis is a relatively new technique and it requires sound statistical knowledge if it is to be used appropriately.

Even with a fixed sample the investigator may wish to analyse his results from time to time as they accumulate. This may well be helpful, but he should realize that such analysis invalidates ordinary tests of significance, and it cannot be used as an alternative to sequential analysis.

It is frequently difficult to decide how many patients to include in a fixed-sample trial. An answer to this question is impossible unless there is some indication of the size of the difference that is expected and that would be considered significant.

Generally the clinician and the statistician should consult together on these two points. When they have also taken into consideration the number of patients likely to enter the trial within a reasonable time and the precision with which clinical differences can be measured, the statistician can help the clinician to choose a number that offers reasonable hope of achieving the objective.

5.2.7 Fixed dose or variable dose

Therapeutic trials are often performed by using only one dose level of a drug. This is satisfactory where it is reasonably certain that the doses can be high enough to be both effective and non-toxic regardless of individual variation, as is the case with some anti-infective drugs, and where there is reason to believe that the trial design is capable of detecting the expected changes.

However, in clinical practice it is often essential to adjust the dose of a drug to suit the individual patient, e.g., in hypertension, or in using some antibiotics in the presence of renal disease. Where this is so, provision for individual adjustment can be made in the therapeutic trial. Such provision complicates the design and conduct of the trial, but it is essential if the results are to be relevant to general clinical use.

Sometimes two fixed doses of the drug are tested. This can be valuable because, in the event of a difference appearing, it gives information both about the drug and about the sensitivity of the trial design. However, it may increase the size of the trial to a point where it becomes impracticable.

5.2.8 Pharmaceutical formulation

Any change in the manufacturing process or in the pharmaceutical formulation of a drug may greatly influence its biological properties. Repetition of some of the earlier studies may be necessary.

5.2.9 Testing multiple therapy (combinations)

The testing of multiple drugs may sometimes be a valid primary objective. Combinations of drugs may be designed to achieve lower individual doses, to minimize toxicity (e.g., antihypertensives and diuretics), to potentiate or to activate one agent by another (e.g., acidifying drugs and mandelic acid), or to minimize solubility problems. The prime purpose of a single drug may necessitate its administration alongside other known or new drugs (e.g., corticosteroids in infectious shock).

Special precautions must be taken in the testing of multiple drugs to consider individual toxicity, biochemical interaction, and interaction in the disease state under study. Trials must be so designed that they do, in fact, answer the principal questions.

Comparative studies of drugs with non-drug therapy (e.g., comparison of a drug with diet and rest in peptic ulcer, or of electrical stimulation with a cholinergic drug in bladder atony) involve the same principles.

5.2.10 Multi-centre trials

Many diseases are seen relatively infrequently by any one investigator. An advantage of a multi-centre trial is that sufficient patients can be admitted and treated in a relatively short time. It may also have the advantage of revealing the consistency with which an answer to a problem is reached. To learn that a drug has (or has not) value in the hands of six investigators can be more illuminating than the same result in the hands of one worker, whatever his statistical test of significance may indicate. This advantage will be reaped only if all investigators adhere strictly to the experimental design of the trial and if each centre contributes enough patients to allow separate analysis by centre. It is sometimes very difficult to ensure the required uniformity, e.g., that all observations, measurements, interpretations, etc. are systematically and similarly made. For this reason, a central organization is essential to supervise the various centres during progression of the trial and to keep them informed of what is going on in other centres.

5.2.11 Duration of the trial

A short trial, e.g., the treatment of an acute illness over a few days or weeks, is relatively easy to carry out. On the other hand, a trial lasting many months or even years, e.g., treatment of a chronic disease, raises many problems. For example, it may be imperative in the course of time to change treatments for patients who do not respond to the new drug; during the trial a yet newer treatment may be introduced making it impossible to continue the trial of the first drug; in the course of time, so many patients may be lost to sight as to make the results with the remainder of doubtful value. It follows that the investigator should think carefully of all these problems and how they may be solved before he embarks upon a trial that must necessarily be prolonged.

Long-term studies are obviously necessary to evaluate drugs that are intended for treatment or prevention of chronic disease.

5.2.12 Documentation

Before a therapeutic trial is begun, a written statement should be prepared setting out in detail the question(s) being asked, the treatment(s) to be used and the measurements that will be required. This statement should incorporate information about the patients to be admitted and how they will be allocated to the different treatments. The method of making measurements must be laid down and the times at which they will be made must be specified. In all this the medical statistician should be closely concerned. In some matters laboratory staff should also be consulted, since additional work may be created by tests for toxicity or drug analyses.

Following this statement of the whole project, it will be necessary to construct forms upon which all the data of the trial will be recorded. Care here is of the utmost importance. Attention must be given to such matters as patient identification, the treatment administered to each, and the measurements and clinical assessments that will be made at defined intervals.

Skilful design of this form will save much time both in the recording and in the subsequent analysis of the data. It may be necessary to construct the form so that the data can easily be transferred to punch-cards and sorting machines or to a computer.

Presentation of results. In the publication of the results of the trial the question(s) asked and the answer(s) obtained should be clearly stated. Sufficient details should be given, both of the data derived from the trial and of the methods used to obtain them, to enable other workers to appreciate their validity and, if they wish, to repeat the investigation and check the results.

5.2.13 Statistics

The planning, execution and analysis of a therapeutic trial demand statistical ways of thinking and statistical techniques. If a statistician is involved, as consultant or as one of a team, he should preferably be a medical statistician. He should be able to assist in the design of the trial so that comparisons of the various treatments will be made as precisely and as efficiently as possible and with minimal disturbance from other factors that may influence the clinical response.

Often, however, it is not sufficient for the statistician to be involved solely in the original design of the trial and in the final analysis of its results. During the course of a trial many problems may arise, small or great, that demand immediate attention and, possibly, some modification of the original design. These problems may well have statistical implications and the advice of the statistician should be sought as they arise and not after the event, when it is too late to take action.

In the final analysis of the results, one treatment will be contrasted with another. A formal test of statistical significance may then be required. It is important that the clinical investigator understand the meaning of this test. It tells him how often a difference between two (or more) groups of patients of the observed (or greater) magnitude would have arisen by chance. If the difference is unlikely to have arisen by chance, the investigator is in a position to conclude that it is due to the drug he is testing. The better the design and conduct of the trial, the surer he can be of that conclusion.

5.3 Evaluation of results

Where a conclusion is reached that a therapeutic effect has probably been achieved, it is necessary to consider this in relation to independent studies from other centres, if any. If the conclusions of these centres are similar, there can be greater confidence in the results.

If the conclusions differ, then an explanation should be sought. If there is a good reason from knowledge of the mechanisms of drug action and disease to expect a given result, this is of help in deciding which conclusions to adopt, but where mechanisms are ill understood, the rationalizing of empirical, but contradictory data may have to wait until more is known about the drugs and the disease.

Where a comparative trial of two or more drugs has been done, the final evaluation involves a consideration of efficacy in relation to adverse effects of each. Such comparisons can be difficult where adverse effects differ in kind and not solely in severity or frequency.

6. MONITORING OF ADVERSE REACTIONS¹ TO DRUGS AFTER GENERAL RELEASE

The Group recognized the need to establish monitoring programmes for adverse reactions to drugs at the stage when they are released for general use. Therapeutic trials, no matter how extensive, cannot be expected to reveal all serious adverse effects if such effects occur infrequently, or if the population involved in those trials differs substantially from the general population with respect to such factors as age, sex, race, pregnancy or previous exposure to the drugs. For example, hypersensitivity reactions are still unpredictable. Furthermore, the frequency of even the more common reactions may not be known with precision at the time when a new drug is introduced into general medical usage. However, this is a complicated subject that is largely outside the scope of the present discussions.

Drug monitoring systems are being developed in a number of countries. However, the methods of obtaining, recording and assessing reports of adverse drug reactions are in an early stage of development and require more intensive methodological research to improve their efficiency. It is desirable that efficient systems be established wherever possible. With a smoothly functioning and large network, the delays in recognizing infrequent reactions should be shortened. Such programmes should be organized in such a way as to ensure that they operate in accordance with established ethical principles in regard to the confidential nature of case reports.

Two general approaches to the reporting of suspected drug reactions have been proposed. The first and most commonly used method is to rely on voluntary reports from practising doctors and hospitals directly to drug monitoring centres. The second method is to use epidemiological techniques aimed at systematic coverage of separate hospitals, representative samples of the physician population, etc. The relative utility of these two methods, used separately or in combination, is a subject that deserves study.

Clinical monitoring of adverse reactions to drugs may be supplemented by evidence of such reactions obtained from tissue specimens at autopsy and biopsy. Further systematic development of this type of monitoring is desirable.

Panels of clinicians and pharmacologists should be established to review case histories of suspected reactions and to assess their significance.

The existence of specialized centres for the treatment of poisoning provides an important source of information about drug toxicity. Arrangements for exchange of information between these centres would be of value in the rapid and effective accumulation of data on therapeutic risks.

The role of WHO in monitoring adverse reactions to drugs has been outlined elsewhere.²

¹ An adverse reaction to a drug is defined as one that is noxious, unintended, and occurs at doses normally used in man.

² Off. Rec. Wld Hlth Org., 1966, 148, Annex 11.

7. CONCLUSIONS

The Group was convened because of the growing concern about the safe introduction of effective drugs into medical practice.

The clinical introduction of drugs that have been developed on the basis of work in animals requires carefully planned scientific investigations in man. Such studies are complex and involve a number of disciplines, including clinical medicine, clinical pharmacology, pharmacology and toxicology, biochemistry, and medical statistics.

The initial studies of a new drug are made in a small number of individuals under close supervision. Then, if it appears that the drug has therapeutic potential a formal therapeutic trial is begun.

Carefully designed therapeutic trials provide by far the most satisfactory means of measuring the advantages and disadvantages of a drug in comparison with existing treatments.

Attention is directed especially to the following points:

1. More and better trained personnel as well as improved laboratory facilities are needed to improve the evaluation of drugs in man. As one method of achieving this objective, consideration should be given to forming more clinical pharmacology units in medical centres. Attention should be given to developing better techniques for measuring absorption, distribution, and excretion of drugs and their metabolites, and for the detection of toxic effects of drugs.
2. Where it is impracticable to establish clinical pharmacology units, consideration should be given to the inclusion of therapeutic research in specialized units or centres, equipped for thorough investigation of diseases that are important in particular areas of the world.
3. The problems, both ethical and technical, of drug evaluation are so complex that investigators should discuss the plan of the investigation with other physicians and experienced medical research workers before embarking on the initial investigation of a new drug. This is best done with a local medical and scientific committee rather than by an official control organization.
4. In drug studies, however carefully conducted, some subjects may suffer ill health or injury where there is no question of legal liability for negligence. In these circumstances, there should be some method of compensating the subjects concerned. The method of compensation will vary from one country to another.
5. Prompt dissemination of all relevant information about new drugs among all investigators concerned, either in the same or in other countries, is essential and should be made an integral part of any investigation.
6. Monitoring of adverse reactions to drugs in widespread use is still at an early stage of development. Much research is needed to improve it. Special attention should be given to the elaboration of methods that will provide not only early warning of drug-related toxicity, but also incidence figures that can be used to quantify the risks associated with the use of a drug.

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