GUIDELINES FOR EVALUATION
OF DRUGS
FOR USE IN MAN

Report of a WHO Scientific Group

WORLD HEALTH ORGANIZATION

GENEVA

1975
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Geneva, 14-18 October 1974

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GUIDELINES FOR EVALUATION OF DRUGS
FOR USE IN MAN

Report of a WHO Scientific Group

A WHO Scientific Group on Guidelines for Evaluation of Drugs for Use in Man met in Geneva from 14 to 18 October 1974. The meeting was opened on behalf of the Director-General by Dr V. Fattoruso, Director, Division of Prophylactic and Therapeutic Substances, who outlined the terms of reference for the present meeting in relation to the Organization’s programme for the promotion of drug quality, safety, and efficacy.

1. INTRODUCTION

Man is continually being challenged by his own creations. Drugs are no exception to this rule. The introduction of large numbers of new drugs during recent decades has caused concern among the medical profession, research workers in the drug field, and the public in regard to both safety and efficacy. But it was not until the tragic effects of thalidomide in the early 1960s that the procedures employed, which left evaluation of the safety and efficacy of drugs largely in the hands of the drug manufacturers and clinicians, were recognized as inadequate. Legislation governing the evaluation of both new and old drugs has now been adopted in many countries.

The manner in which the World Health Organization can contribute to an improvement in drug evaluation has been discussed at various sessions of the governing bodies of WHO. The Seventeenth World Health Assembly (1964) adopted a resolution (WHA 17.39) requesting the Director-General "to undertake, with the assistance of the Advisory Committee on Medical Research, the formulation of generally accepted principles and requirements for the evaluation of the safety and efficacy of drugs" (1, p. 140). A number of scientific groups and meetings have been convened in compliance with this request and their reports have been published in the WHO Technical Report Series (see list of references, 2–11).

The Twenty-fourth World Health Assembly, in resolution WHA 24.56, requested the Director-General to study how best the Organization could cope with its obligations and expand its activities, as required, bearing in mind the need for an overall approach to matters relating to (a) the discovery,
production, and distribution of drugs, (b) the control of drug quality, evaluation of safety and efficacy, and (c) the monitoring of adverse reactions, including dependence-producing properties (I, p. 142).

The Director-General, in his report to the Twenty-fifth World Health Assembly, stated *inter alia*:

To cope effectively with the broad problem that society has to face with the toxic potential of the steadily increasing number of drugs and pollutants, more research is needed to elucidate the basic biochemical mechanisms involved and to supplement it, where feasible, with epidemiological studies in human beings. Continuing review and reappraisal of the relevance of routine tests is also needed to adapt toxicological laboratory testing to the progress of knowledge in order to avoid unnecessary tests and to ensure that requirements for such testing do not give an assurance of safety that may be illusory.

The present Group was convened to consider all aspects of the evaluation and testing of drugs in the light of increasing knowledge and to formulate proposals and guidelines for present and future research in this field. The Group had at its disposal the reports of the previous WHO scientific groups and meetings referred to above, which outline principles and procedures for the evaluation of drugs.

2. GENERAL CONSIDERATIONS

2.1 Introductory Comments

Current procedures for the evaluation of the safety and efficacy of drugs, although greatly improved during the past decade, still leave much to be desired. Therefore, no matter how well performed, it is necessary to emphasize that there can be no guarantee of absolute safety. The WHO Scientific Group on Principles of Pre-Clinical Testing of Drug Safety (2) summarized the situation as follows:

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.

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 to be discussed in this report. Two aspects of the intended therapeutic effects of the drug must be considered. First and most important, the laboratory studies of the efficacy of the drug must be such as to demonstrate that there is a real therapeutic interest sufficient to justify the trial of the drug in man. Second, the intended purpose of the drug is also important, since the possibility of toxic effects may be acceptable
in a drug for treatment of a severe disease whereas the same potential toxic effects
would prevent the trial of a drug for treatment of a relatively minor condition or one
for which other drugs of greater safety already exist (p. 4).

Estimates of the relative safety, the potential efficacy and the mode of
action of a new drug can, to some extent, be predicted for man from the
pharmacology (pharmacodynamics* and pharmacokinetics*) and toxicology
of the new drug in animals and in vitro. Nevertheless, there are inevitable
predictive inadequacies in such studies and these should be recognized.
The WHO Scientific Group on Principles for Pre-Clinical Testing of Drug
Safety (2) commented as follows:

Many pharmacodynamic effects carry over from animals to man, and animal
studies have a relatively high predictive value for such effects. Many toxic effects
may also be predicted from observations made in animals, but, in the present state
of knowledge, there are some important toxic effects that are not predictable from
animal studies, and this is their main limitation. Nevertheless, increasing knowledge
is steadily, if slowly, improving the value of animal and other basic studies as a means
of predicting toxic effects in man. Every effort should be made to build up knowledge
of species differences and similarities in pharmacological and toxicological responses
(p. 5).

The animal studies will vary not only according to the purpose but also
according to the manner of administration of the drug, i.e., oral or parenteral,
local application (dermal, ophthalmic, nasal, rectal, etc.), inhalation
(anaesthetics), aerosols, the duration of use, and whether it is combined
with other drugs. In view of the foregoing, it is not desirable to lay down
formal requirements for pre-clinical evaluation of drugs. The same applies
to the clinical evaluation of drugs. The WHO Scientific Group on Principles
for the Clinical Evaluation of Drugs (4) pointed out that "... 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." (p. 7).

Despite this, it is possible to distinguish in a general way what is good
practice in pre-clinical and clinical evaluation and to offer guidelines,
both for drugs in general and for specific categories of drugs, that will be
useful provided they are subject to frequent review and updating. At present
there are large differences between guidelines provided by various countries.
Internationally acceptable guidelines would reduce wasteful use of personnel
and resources in developing new drugs.

* "Pharmacodynamics" is the quantitative study of the biological and therapeutic
effects of drugs.

* "Pharmacokinetics" is the quantitative study of the absorption, distribution,
bio-transformation, and excretion of drugs.
Definition

The following definition of a drug, proposed by the WHO Scientific Group on Principles for Pre-Clinical Testing of Drug Safety (2), is used in this report:

"A drug is 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." (p. 7).

2.2 Steps in the Development of a Drug

When a compound is found to have interesting pharmacological activity, it is investigated in depth. Before starting this work it is essential to characterize the chemical and physical properties of the new compound. The substance is then subjected to a wide range of pharmacological tests in animals to detect any effects that may be of therapeutic use. Many compounds are rejected at this stage but those that survive are further investigated to determine their pharmacodynamic and pharmacokinetic properties and to assess their toxicity. When adequate data are available, early studies are initiated in man and, if successful, are followed by controlled therapeutic trials. Simultaneously with the pharmacological tests, certain pharmaceutical studies are carried out on the development of the dosage form, assay methods for active and inactive ingredients, and specifications for the ingredients and for the final drug formulation. The usual steps in the development of a drug, in chronological order and indicating concurrent activities, are shown in Table 1.

2.3 Chemical and Pharmaceutical Aspects

It is essential that certain chemical, physical, and pharmaceutical studies on the new compound proceed before the biological testing. If the product on which the initial biological tests are conducted has not been properly characterized, later batches may differ, thus invalidating any testing that has been conducted on the initial material. For the same reason, a decision should be taken as soon as possible on the salt or ester to be used in further studies. In this choice, possible differences in biological effects have to be considered.

Before starting pre-clinical studies, stability determinations should be conducted on the active ingredient or ingredients. When the final pharmaceutical preparations have been developed, extensive stability studies must be conducted on all dosage forms. It is recognized that long-term stability studies need not be completed at the time of the animal studies or at the
<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Synthesis of new chemical or production of new material from a natural source. Identification of the new chemical or characterisation of the new material. Establishment of degree of purity and preliminary stability studies on the compound.</td>
</tr>
<tr>
<td>2.</td>
<td>Biological screening and acute toxicity.</td>
</tr>
<tr>
<td>3.</td>
<td>Pharmacodynamic studies in animals. Development of the pharmaceutical formulations (dosage forms).</td>
</tr>
<tr>
<td>5.</td>
<td>Early studies in man. Completion of long-term toxicity studies in animals. Special toxicological studies as required. Development of pharmaceutical formulations.</td>
</tr>
<tr>
<td>6.</td>
<td>Controlled therapeutic trials. Continuation of special toxicological studies. Completion of stability studies and development of final specifications for the ingredients and formulation.</td>
</tr>
</tbody>
</table>

* The difficulties involved in presenting this complex subject in the form of a small table are recognized. However, it was thought worthwhile attempting to summarize the activities required in the development of a new drug up to the point of registration. Each group of activities, both biological and pharmaceutical, shown at any step would usually be undertaken concurrently.

Stage of the initial studies in man. Stability of the product must be demonstrated for the required duration of storage. Evidence in animals that a drug is safe does not necessarily establish that products of deterioration due to prolonged storage or storage under adverse conditions (heat, humidity, etc.) are non-toxic.

Adequate specifications should be developed for each final dosage form of the new substance to establish the uniformity of the product. Furthermore, it is essential that drugs submitted for evaluation be manufactured under conditions that will ensure the production of consistently uniform batches. These must meet all the specifications that have been established for the product.

The pharmaceutical aspects that affect the evaluation of a drug will be considered by the WHO Expert Committee on Specifications for Pharmaceutical Preparations when it meets in November 1974.
2.4 Application of Statistical Procedures

Appropriate statistical procedures should be applied at all steps of the evaluation of a new drug. It is desirable to have a statistician as a consultant. Biological changes observed must be evaluated for their statistical significance, to assist in determining their relative importance.

3. PRE-CLINICAL STUDIES

3.1 General Comments

Pre-clinical studies can be divided into pharmacological and toxicological. But this division is one of convenience not of principle, because pharmacological and toxicological studies are interdependent and employ similar scientific principles. The studies must be integrated; for example, acute toxicological experiments provide information for the studies of the pharmacologist. These studies in turn will guide the toxicologist in designing long-term studies.

Despite the differences between man and animals, it is often possible to estimate the safety of a new drug and to predict its potential efficacy and mode of action from the results of studies of the pharmacodynamics, pharmacokinetics, and toxicology of the drug in animals and in vitro. A pharmacological profile is an essential prerequisite for the clinical investigator, enabling him to anticipate problems and to design his initial experiments in a rational manner. The content and depth of such studies will vary with the drug and with the results that are obtained as the investigation progresses. The study should be designed to obtain all relevant data to improve understanding of similarities and differences between species in the pharmacological and toxicological responses.

As indicated previously, there is always some element of risk in administering a drug to man for the first time, no matter how exhaustive the animal and in vitro studies may have been. The WHO Scientific Group on Principles for Pre-Clinical Testing of Drug Safety (2) stated:

The best safeguard is to place the investigation of a new drug in the hands of those experienced in pharmacology and toxicology. Any attempt to lay down a rigid plan of testing is not likely to increase the adequacy of this safeguard. A free and intelligent approach to the toxicological problems of a new drug, as a scientific investigation in its own right, is necessary and should not be inhibited by any formal recommendations (p. 4).

Whilst it is desirable that an animal that metabolizes the drug in a similar way to man should be used in pre-clinical studies, this is generally not practicable. Marked species differences between animals should alert
the investigators to the importance of determining the metabolic pattern in man at an early stage so that more meaningful animal studies may be done. Although important differences in biotransformation and other pharmacokinetic properties may explain different reactions in various species, it should be realized that they are not the only cause of such differences. Fundamental species differences in the responses of organs to drugs may be caused by differences in endogenous intermediary metabolism, in the receptors, or in the reaction following receptor binding.

3.2 Pre-Clinical Pharmacology
(Pharmacodynamics and Pharmacokinetics)

3.2.1 Pharmacodynamics

The pharmacodynamic studies should be designed to demonstrate the expected therapeutic effect of the drug and, wherever practicable, its mechanism. In addition, such studies should be undertaken on the main systems of the body to reveal other effects of the drug, desired or undesired. The details of the experimental programme will vary with the type of drug.

Information should be sought that might not only suggest the therapeutic effects but also indicate:

(a) potential undesired effects;
(b) which tissues should be particularly studied morphologically;
(c) which metabolic systems should be studied.

In the pre-clinical studies efforts should also be made to obtain information (pharmacodynamic and pharmacokinetic) that will help the physician to understand and treat overdoses in man.

Specialized studies, such as biochemical pharmacology, add to our understanding of drug action, which in turn contributes to the safe and effective use of drugs.

The use of animals with spontaneous or induced disease may provide therapeutically useful information, but there are difficulties in their use and research in this area is desirable.

3.2.2 Pharmacokinetics

The pharmacokinetic studies include absorption, distribution, biotransformation, and excretion of a drug. Knowledge of these factors is important for the evaluation of the efficacy and toxicity of a drug. These pharmacokinetic studies are important at all stages of drug development and should not be regarded as applying only to studies at the pre-clinical stage.
Typical studies on new drugs involve measurement of drug levels in body fluids and tissues following the administration of single doses by various routes to animals. The purpose of these studies is to estimate the rate and extent of absorption, biotransformation patterns, rate and route of elimination from the body, and localization in tissues. Repeated dose studies must also be done in order to permit adequate definition of the pharmacokinetics of chronic drug administration. This information facilitates extrapolation of animal data to man, discloses metabolic products with therapeutic or toxic effects, and provides the rationale for development of suitable dosage regimens.

3.2.2.1 Assay methods

Pharmacokinetic studies require methods for the assay of the drug and its metabolites in biological fluids and tissues. The specificity and sensitivity of the method must be determined. Useful techniques at present include gas chromatography, gas chromatography combined with mass spectrometry, high-pressure liquid chromatography, and countercurrent distribution. Protein-binding methods, e.g., radioimmunoassay, are also sensitive, although the specificity of such procedures is not always satisfactory. The use of labelled compounds may be of help when it is known that the measured radioactivity in biological samples is associated with a given molecular species. However, too often the measurement of total radioactivity in blood or in tissues is incorrectly taken as a suitable method for describing pharmacokinetics of the drug. Whenever possible a non-radioactive method for the determination of the drug and/or its metabolites in biological samples should be developed to decrease the hazard of submitting normal subjects or patients to radioisotope exposure in clinical pharmacokinetic studies. Newer methods utilizing non-radioactive isotopes are becoming available and should be investigated.

3.2.2.2 Absorption, distribution, and excretion

It is essential to demonstrate the extent to which the drug is absorbed by the route and in the species intended for animal studies. The extent of absorption may sometimes be conveniently estimated by comparison of the area under the plasma concentration/time curve following oral administration with that obtained following parenteral administration. The extent and rate of absorption of a drug will depend upon a number of factors, including the lipid/water partition, the dosage form in which the drug is administered, and the solubility of the drug in the body constituents with which it comes into contact. Physiological factors, such as gastric emptying and intestinal transit time, may also markedly influence the rate
and extent of absorption. Absorption of drugs may also be altered by biotransformation or storage by intestinal flora.

Each drug will be distributed in body fluids and tissues in a particular pattern that varies with time and dose. The distribution of drugs will vary on account of differences in their ability to cross membranes, their binding to proteins or other macromolecules in blood or tissues, and storage in tissues, e.g., adipose tissue. Qualitative and quantitative differences in protein binding also occur from species to species and in certain disease states such as uraemia. Such differences may account for variation in pharmacological or toxicological effects when diseased or different species of animals are studied.

The relationship between the pharmacodynamic and toxicological effects of a drug and its concentration in plasma should be determined whenever possible. Absence of such a relationship suggests the need to consider the formation of an active metabolite, a persistent effect resulting from irreversible binding to the receptors or slow distribution, inaccurate assay methods, differences in the activity of isomers, or other factors that might explain this phenomenon.

Drugs are excreted unchanged and/or in the form of metabolites. The most important organs for the excretion of drugs are the kidneys, liver, and lungs. The extent and rate of excretion of a drug in urine and bile may depend on such factors as lipid/water partition, acid or base dissociation, or molecular weight. In some cases the biliary excretion is followed by reabsorption of the drug and/or the metabolites from the intestine, which results in an enterohepatic circulation. It is of importance to know the route by which a drug is eliminated, since disease of the systems for biotransformation and excretion may alter the level of active substance. The possibility of accumulation of the drug in the body may be revealed by determining the percentage of an administered drug appearing in the excreta during a specified time interval.

3.2.2.3 Biotransformation

The term biotransformation in this report is taken to include any alteration of the drug in the body. Biotransformation of the drug may affect not only the desired activity but also the toxicity, and either property may be enhanced or diminished.

Drug-metabolizing enzymes catalyse processes such as oxidation, reduction, hydrolysis, and synthesis. Although the process of drug biotransformation generally yields products that are more readily eliminated than the parent substance, there are also instances where metabolites accumulate to a greater extent in the body.
(a) Factors affecting biotransformation

(i) Species and individual differences

The rates and patterns of biotransformation of drugs often vary between species, making prediction to man difficult. When these rates and patterns for any drug have been obtained in man and compared with information from other species, extrapolation of toxicological and pharmacological data to man may be facilitated. Differences in drug biotransformation also occur within the same species, which may explain some individual differences in response to drugs. Such differences are largely genetically determined.

(ii) Enzyme induction

The administration of a drug can accelerate its own biotransformation or that of another drug. Drugs can exert this action by increasing the amount of drug-metabolizing enzymes in liver and other tissues, and this phenomenon is referred to as enzyme induction. Enzyme induction occurs in all species that have been investigated including man. It has been shown to occur with drugs of widely different chemical structure and pharmacological activity. Certain other substances present in the environment, such as some insecticides and polycyclic hydrocarbons, can also cause enzyme induction. Exposure of several animal species to insecticides such as chlordane and DDT accelerates the biotransformation of a variety of drugs. Enzyme induction usually results in faster elimination of the drug.

Enzyme induction can have a profound influence on long-term toxicity studies, especially when the drug is administered at a fixed daily dose. If this phenomenon is not recognized, misleading results may be obtained, since the level of active drug in the body may be much lower at the end of the test than at the start.

(iii) Enzyme inhibition

A drug may also inhibit the biotransformation of another drug and thus change the pharmacological action of the latter.

(iv) Age and sex of the animal

The capacities for elimination of some drugs may be low in newborn animals and in young animals of many species. This can result in accumulation and toxicity on repeated administration of doses that would seem acceptable if calculated on a basis of weight or surface area. Similar problems occur in aged animals. Sex differences in the rate of biotransformation of drugs have also been shown in several species.

(v) Saturation phenomena

Many drug-eliminating mechanisms, such as biliary and renal tubular excretion and biotransformation, are capable of saturation. As a conse-
quence, the biological half-life of drugs, e.g., salicylates, may increase with increasing doses. This phenomenon is referred to as "dose dependent" or "capacity limited" elimination kinetics. The elimination rate of a drug should therefore be determined in as widely different dose ranges as possible. In addition, drugs of very different structure are eliminated by the same mechanism. The elimination of a drug may therefore be competitively inhibited by a concurrently administered second drug and cumulative toxicity may result after the repeated administration of "usual" doses. Similar considerations of saturation apply to macromolecular drug binding.

3.2.2.4 Early studies of pharmacokinetics in man

For many years it has been said that pre-clinical studies in pharmacology and toxicology should be carried out in animals whose biotransformation mechanisms are closest to those in man. This desirable ideal has been unattainable because it would have meant that substantial doses of the drug would have had to be given to man before the pharmacological and toxicological profiles had been established in animals. The recent development of improved methods of drug analysis means that there is now the possibility of establishing biotransformation patterns in man using extremely small doses. It is recognized that biotransformation patterns may differ according to dose, but this aspect of drug evaluation has obvious importance for safety and efficacy in both normal and diseased man and deserves exploration and encouragement.

3.2.2.5 The place of pharmacokinetic studies prior to clinical trial

Although pharmacokinetic studies are of undoubted importance in the evaluation of a drug, they are expensive to conduct in both material resources and skilled manpower. It is only in a relatively few centres that exhaustive studies, performed as a routine, are a practical possibility. Correlation of plasma concentration with effect (pharmacological and toxicological) can be of value in choosing doses for the early human studies. The formulation of guidelines for good practice in this area, with particular regard to what is practicable in most countries, would be a useful undertaking.

3.3 Pre-Clinical Toxicology

3.3.1 General comments

The purpose of the toxicological studies is to determine the toxicity of the drug in experimental animals under varying conditions of administration. These tests are generally considered to fall into three classes:
(a) Acute toxicity studies using single administration or a few closely spaced doses.

(b) Long-term studies (chronic studies), which include repeated administration for periods up to one year or even more depending on the intended use of the drug and the animal species to be employed.

(c) Special studies: reproduction (including teratology and effects on fertility and on perinatal development), mutagenicity, carcinogenicity, and dependence liability.

Acute and appropriate long-term toxicity studies must always be carried out before the initial administration to man and before therapeutic trials are conducted. While positive results may be suggestive of potential toxic effects in man, negative data (although valuable) do not give assurance of safety.

3.3.2 The drug

3.3.2.1 Characterization

Before toxicological studies are conducted the drug should be adequately characterized so that it is possible to identify the drug, to determine its stability, and to establish its purity profile. If the characteristics are altered for one reason or another, for example as a result of modification in the method of preparation, it is necessary to assess the effect of this change in relation to the toxicological studies carried out on the original drug (see section 2.3).

3.3.2.2 Physical state

The physical characteristics of the drug, e.g., solubility and particle size, have an important influence on activity. The nature of the vehicle is also relevant.

3.3.3 Animals used

3.3.3.1 Choice of animal

Animal species differ widely in their response to drugs, and the way in which the drugs are absorbed, distributed, metabolized, and excreted. The rat, dog, monkey, and pig are frequently used, especially for chronic toxicity studies, and have the advantage that their reactions are well documented. However, the evaluation of species other than those conventionally used should be encouraged in an attempt to select species whose reactions to drugs are as similar as possible to those of man.
Differences in the response to drugs are also observed between strains. Many of the well-known strains, such as Wistar or Sprague Dawley rats, have undergone great changes in different laboratories, so that these general strain names have little meaning. Accurate records should be kept of the source and derivation of all laboratory animals. In general, it is desirable to use outbred strains in toxicity studies. Except in special cases, e.g., some carcinogenicity studies, there is no need to use inbred strains.

3.3.3.2 Management

Healthy animals are required and animals obtained from uncontrolled sources should be avoided. In recent years, animals largely free of pathogens, called specific-pathogen-free (SPF) or pathogen-controlled animals, have become available in some centres. Evidence is accumulating that for many purposes, and particularly for long-term studies, these animals are superior to conventionally reared animals, and for such studies their use is to be encouraged. At present, mice, rats, guinea-pigs, and rabbits are available, but the rearing of other pathogen-controlled species should also be encouraged.

The drug response of animals is influenced by a variety of factors, such as diet, season, the nature of their housing, environmental temperature and humidity, the presence of infectious diseases, and interactions of the drug with other substances. Hitherto unsuspected impurities, e.g., DDT, polychlorinated biphenyls, and nitrosamines, have been found in some animal diets, and these may change the course of the experiment. An analysis should therefore be conducted for possible contaminants to avoid the use of diets containing unacceptable levels of such substances. The use of insecticides or anthelmintics may also alter some drug responses.

Institutions concerned with the breeding, care, and study of laboratory animals already exist in some countries, and their establishment in others should be promoted.

3.3.3.3 Numbers used

Each study should be designed to include a sufficient number of animals per group to permit a valid estimation of the incidence and frequency of toxic effects. The selection of group size for chronic studies will depend upon the toxicity/mortality data resulting from the preliminary studies and on other considerations, such as interim sacrifices, evaluation of reversibility of adverse effects, and the assessment of other aspects of toxicology, such as carcinogenesis. Wherever feasible, experiments should be evaluated statistically and the numbers of animals used must be in accord with statistical requirements. It is recognized, however, that for a variety of purposes
useful information may be obtained from detailed experiments on a small number of animals. The sensitivity of the test should be stated in reporting the results. Statistical analysis should not blind the investigator to the biological importance of relevant incidental observations, even if not statistically significant.

3.3.3.4 Physiological and pathological state of the animal

Many physiological factors may influence the effects of drugs, such as species, strain, sex, age, endocrine activity, and state of nutrition of the animals, as well as the administration of the drug before, with, or after food. The relevance of these and other factors must be borne in mind by the investigator.

It has been suggested that toxicity studies should include investigations in immature animals. In our present state of knowledge the relevance of these studies to man remains to be assessed, because the stage of development of the newborn animal varies greatly from species to species. A fruitful approach might be to establish in greater detail in man and animals the patterns of enzyme and organ development that are relevant to drug metabolism and toxicity. Information of this nature might enable better prediction of toxicity in infants to be made.

Pathological states may modify the toxicity of drugs. Where information exists regarding significant toxicological changes caused by dietary or environmental factors, and if such problems are prevalent in countries where widespread use of the drugs under test is anticipated, efforts should be made to develop, if possible, experimental models reflecting these dietary or environmental effects. In chronic endemic parasitic infections, e.g., schistosomiasis, where major pathological lesions are induced and an acceptable animal model exists, toxicity studies on such animals may give valuable information relevant to the intended use of the drug in man. However, in general, the use of animals with induced, spontaneous, or genetically determined disease cannot, at this time, be recommended for most toxicity studies since the relevance of data on such animals requires further study.

3.3.4 Problems in the concurrent use of two or more drugs

The problem of adverse reactions arising from the use of two or more drugs has given rise to much concern. In the case of fixed-dose combinations, which may contain two or more drugs, it is necessary to study the toxicity of each of the components individually as well as the combination of the active ingredients in the final product. Where the ratio of the active ingre-
diets in a drug combination has been altered or the dosage increased, a re-evaluation of the new combination should be conducted to determine whether further testing is needed.

3.3.5 Acute toxicity

The purpose of the acute toxicity studies is to define the lethal dosage range of a single administration of the drug or a few closely-spaced doses. These studies are frequently part of the initial pharmacological screening programme. Detailed observations should be made on the effect of the drug upon important functions, such as locomotion and behaviour, respiration, and the production of obvious symptoms, such as convulsions and vomiting. These signs often furnish information on the cause of death; they may be supplemented by autopsy and if necessary by histological examination. The time course of these events may vary considerably between drugs. Therefore, animals included in the acute toxicity studies should be observed for at least two weeks after dosing, or longer if overt signs persist or delayed deaths occur. Routine haematological and biochemical studies have been found to have limited value in acute toxicity studies. The use of different animal species of both sexes and various ages and of several modes of administration provides important though preliminary data on rates and degree of absorption. The volume of solution administered is important, as is also the rate at which intravenous injections or infusions are given.

In general, acute toxicity studies should be carried out in several species, at least two rodents and one non-rodent. These species should include, if possible, those predominating in the pharmacological testing of the drug and those likely to be used in the long-term toxicity and special tests, e.g., reproduction studies. The LD₅₀ for rodents should be determined utilizing a standard statistical method, e.g., probit-analysis, but for non-rodents, which are almost always used in small numbers, an approximate determination will suffice.

If it is expected that the drug will be used in children, it should be studied in both adult and young (weanling) animals. Tests on immature animals are particularly difficult to interpret since the stage of development of the newborn varies greatly from species to species, but it seems difficult to justify omission of such studies if a drug is intended for paediatric use.

The same principle applies when the drug is intended mainly for the treatment of geriatric patients, since it is recognized that this group may show abnormalities in absorption, biotransformation, distribution, and excretion, or may be more or less sensitive to the drug.

Routes of administration should include those by which the drug will be administered.
3.3.6 Long-term toxicity

It is the purpose of the long-term toxicity studies to provide information on the potential toxicity of the drug on prolonged administration, its therapeutic margin in the species tested, whether reversible or irreversible lesions occur, and which organ systems are involved.

The duration of these toxicity tests should be related to the expected duration of the administration to man, as well as to the pharmacological pattern, biotransformation, and the margin of safety of the drug. No universal rule can be formulated for the duration of such tests, but a general guide as to what is currently considered reasonable practice is given in Table 2. However, it should be emphasized that each drug must be the subject of an individual evaluation.

<table>
<thead>
<tr>
<th>Period of administration to man</th>
<th>Suggested period in more than one species of experimental animal</th>
</tr>
</thead>
<tbody>
<tr>
<td>single or a few doses</td>
<td>at least 2 weeks</td>
</tr>
<tr>
<td>up to 4 weeks</td>
<td>13-26 weeks</td>
</tr>
<tr>
<td>more than 4 weeks</td>
<td>at least 26 weeks (not including carcinogenicity studies)</td>
</tr>
</tbody>
</table>

The above table refers to the anticipated duration of the clinical experiment in the development programme of the drug, not to ultimate clinical use.

In the long-term toxicity tests, at least two species of healthy, mature animals, one rodent and one non-rodent, should be used. If sufficient biochemical and pharmacological data are available to suggest which species are most likely to be similar to man in their response to the drug, these species should be selected.

The tests are usually conducted at three different dose levels. Selection of doses should be based upon the pharmacological and toxicological activity of the drug and should not be limited to calculated ratios of the proposed clinical dose or fixed fractions of the LD₉₀. The highest dose should be so chosen that it causes clinical haematological, biochemical or anatomical changes, that is to say, toxic effects, but it should also allow the survival of a majority of the animals. At the least some demonstrable pharmacological effects should be elicited. Certain pharmacological effects of the drug under test may necessitate adjustment of the experimental design to differentiate these effects from true toxic manifestations. The
lowest dose should be close to the desired effective dose of the substance for the species concerned, without causing adverse reactions. Additionally each study should include one or more intermediate dosage levels to evoke incipient toxicity and permit the determination of dose-response relationships. A control group should also be included.

It is useful to compare a new drug with existing drugs of similar clinical use.

As in the case of the acute toxicity tests, the plans for the long-term toxicity studies should be in accord with recognized modern toxicological practice. The age and sex of the animals and the route or routes of administration of the drug will depend upon the expected clinical use of the drug. Systemic effects should result from at least one route of administration.

Drugs that are intended to be administered to man on a daily basis should be given to animals for seven days per week. The omission of one or more days on grounds of convenience is bad practice. The frequency of administration should be adjusted to the drug's half-life in the species concerned if the experimental design necessitates a constant plasma level. However, some drugs require a peak level in the plasma and in these instances no attempt should be made to attain a constant level.

As indicated previously, the active ingredient should be administered by the route or routes intended for human administration. When the drug is administered orally, appropriate measures must be taken to ensure that each animal receives the full intended dose and evidence of absorption should be provided, such as monitoring of the plasma concentration. When the drug is incorporated into the diet, attention should be paid to the stability and to the pharmacokinetic consequences of this method of administration.

If enough evidence exists that the toxicity of the drug might be changed when administered in the form of the pharmaceutical preparation intended for human use, this preparation should be administered as well.

During the conduct of the long-term toxicity tests all animals should be observed for changes in appearance and behaviour, rate of body weight gain, food and water consumption. Eye examinations should be carried out on all animals. Cardiovascular as well as other physiological and pharmacological manifestations should also be monitored where practicable.

Laboratory investigations, such as haematology, clinical chemistry, and urinalysis, should be made periodically in all non-rats and in a sufficient number of rats per group to permit useful statistical analysis. These studies should not be repeated so frequently that they seriously reduce the blood volume of the animals.

All major tissues of all animals that die or are killed should be examined for gross pathological changes. Experience has shown that organ weights have rarely contributed significantly to the interpretation of the toxic effects.
of a drug. However, weighing of organs may be useful in detecting endocrinological effects and may provide information useful in the interpretation of toxic effects upon the kidney and liver when these organs appear macroscopically to be abnormal. Comprehensive histopathological studies, including examination of all macroscopically abnormal organs, should be done in the non-rodents used and in a sufficient number of rodents per group to permit evaluation. The local response of the tissues at the site of drug administration should also be recorded. While pathological lesions occurring after administering excessive doses are considered a valuable indication of toxicity in the animal species concerned, they should be considered as a warning and not as a contraindication for clinical trials. The final decision as to whether or not a clinical study should be undertaken depends upon the type of lesion that has been produced.

Spontaneous changes in haemograms, biochemical values, and anatomical characteristics can occur and should be considered in the interpretation of the results. Control information on all species and colonies used is helpful in explaining biological and procedural variability and may be employed as an aid in interpreting the meaning of these changes. At least some animals at the highest dose level and in the control group should be retained for observation after the end of the administration period; by adding such a recovery period, information is gained as to whether the observed organ lesions are reversible or irreversible.

Unexplained observations during toxicological studies should not be ignored but should be further investigated. The use of electron microscopy, or of molecular biological, fluorescent antibody, histochemical, and autoradiographic procedures may be required.

3.4 Special Toxicological Studies

3.4.1 General comments

Prior to 1962 very little attention was given by most toxicologists and pharmacologists to possible teratogenic, carcinogenic, or mutagenic effects during the evaluation of a new drug. However, this situation changed drastically after the thalidomide experience. At the time, the scientists involved had neither the knowledge nor the techniques available to them to meet this sudden requirement for increased testing for safety. It was necessary to develop additional tests and to improve the procedures in use at that time. Within a few years however, specialists had been trained, research facilities established, and more effective procedures developed to assess at least the potential teratogenic and carcinogenic risks associated with new drugs.
3.4.2 Reproduction including teratogenicity

3.4.2.1 General

It is now realized that drugs may interfere with reproductive processes in other ways than by causing malformation or death of the embryo, for example, by arresting gametogenesis or preventing fertilization. Therefore, reproductive studies are aimed primarily at evaluating possible drug effects on fertility; on the zygote, its transport, implantation and development; on parturition and the newborn, lactation, weaning, and care of the young; on delayed postnatal deviations and especially on the teratogenic potential of the drug. As previously noted in the report of the WHO Scientific Group on Principles for the Testing of Drugs for Teratogenicity (3):

The greatest teratological hazard is generally accepted as occurring in the embryonic period, when tissue differentiation and organogenesis occur. Evidence indicates that developmental deviation can also be induced by adverse influences during the entire gestational period. It is also evident that development in the post-natal period may be diverted in both structural and metabolic terms by agents applied during the pre-natal period. (p. 7).

The word “malformation” does not necessarily connote only structural maldevelopment but may also include functional and biochemical entities. Malformations may be due to a direct effect of the drug on the fetus or secondary to an effect on the mother.

Embryotoxicity means a disturbance of the embryonic and fetal development by dose levels that do not adversely affect the mother. Embryolethality and/or teratogenicity observed only after administering doses that are toxic to the mother should be considered as general toxic effects.

The studies on reproduction are divided into three parts, each of which pertains to a specific phase of the reproductive process. These are (a) study of effects on fertility and general reproductive performance, (b) study of teratogenicity, and (c) perinatal and postnatal study. All three parts may not have to be performed in certain instances, while in other cases special tests may replace or supplement them.

3.4.2.2 Technical

Possible interference by drugs includes effects on: (a) gametes, male and female; (b) mating behaviour; (c) estrous and menstrual cycles; (d) conception rates; (e) uterine and placental function; (f) embryogenesis and development; (g) parturition; (h) lactation and weaning; and (i) delayed postnatal deviations.

No recommendation regarding acceptable species can be made at present. However, at least two species of animal should ordinarily be used, one being a non-rodent, if possible.
Because of their wide use and long history as laboratory animals, mice, rats, and rabbits have been the species of choice for these studies. According to the present state of knowledge, fertility as well as perinatal and postnatal studies should be done in at least one rodent species, e.g., the mouse or rat. However, for teratological studies the use of other animal species, e.g., hamsters, guinea-pigs, ferrets, cats, pigs, dogs, and certain types of primate should be encouraged. Because of the lack of data on the spontaneous malformation rates in colonies of most of these species, a sufficient number of animals should be employed to permit a meaningful assessment of safety. In general, it is practicable to use animals that have a short gestation period and are easily kept in the laboratory in substantial numbers.

Drugs should normally be given at three dose levels, the highest of which either should be subtoxic, i.e., the maximum tolerated dosage, so as not to cause anorexia, sedation, or other adverse pharmacological effects on the mother animals, or should produce only minimal toxicity, such as a decreased body weight gain in comparison with the control group. The lowest dose level should be well below the toxic dose, and should be close to the effective dose in the animals or to the proposed therapeutic dose. Ideally, concurrent controls in these studies should include a group of animals left alone after conception and another group handled in the same way as the experimental group, but not receiving the drug. In practice, the former control group is not usually included, but the second group, which receives experimental handling without the drug, must always be employed.

The proposed route of clinical use should be employed where practicable, but in special cases, e.g., inhalation, it may be necessary to use other routes as well. When clinical administration is to be by the topical route and lack of systemic absorption can be established, reproductive studies need not be made.

It is important that evidence be provided as to whether the drug enters the fetus. It is also desirable that plasma or tissue concentrations in the mother and the fetus be measured, but this is not always practicable at present.

3.4.2.3 Types of observation

(a) Fertility and general reproductive performance

This study provides information concerning drug action on gonadal function of both males and females, estrous cycles, mating behaviour, conception rates, and the early stages of gestation. It also provides information concerning drug action on the entire reproductive process, including teratogenesis, late stages of gestation, parturition, lactation, and weaning. Furthermore, growth, development, fertility, and behaviour of the F₁ generation can also be studied.
The information resulting from this study may serve as a guide for subsequent studies in depth.

(b) Teratogenicity
For this purpose, drug administration should be restricted to the period of organogenesis. In some cases, however, it may be helpful and/or essential to extend the period of administration or to perform additional studies in which the drug is administered only on certain days of gestation.

(c) Perinatal and postnatal study
The purpose of this study is to obtain information on the effects of drugs administered during the last third of pregnancy, the period of lactation and weaning. Effects of the drug on late fetal development, labour and delivery, lactation, neonatal viability, and growth of the newborn should be recorded.

3.4.2.4 Interpretation
Possible sources of error in the performance of teratological studies were summarized by the WHO Scientific Group on the Principles for the Testing of Drugs for Teratogenicity (3) as follows:

In the performance of teratological studies, as in other biological tests, errors can arise if procedures are not followed accurately, and can lead to false conclusions.

Errors may arise from the faulty maintenance of the animal in the laboratory and from the selection of animals in an unsatisfactory state of health. Other factors include poor animal husbandry before the initiation of the experiment, during the period of treatment, and until the termination of the study. Mishandling of the animal, e.g., inconsiderate treatment, may also lead to false results.

The actual treatment of the animal with a drug may result in differences in food intake between the treated and the control animals, thus leading to a greater or a slower growth rate of both the mother and the foetuses.

Selection of unsuitable strains and species of animals, such as those that show a high incidence of spontaneous malformations or those known to be resistant to teratogenic procedures, may lead to unfair condemnation of a drug or to the approval of a drug that has unrevealed teratogenic properties. In such cases the use of a reference teratogenic substance would be helpful.

The use of an inadequate number of control and treated animals can lead to misinterpretations, owing to the occurrence of spontaneous malformations in certain strains and species. The selection of animals for the test and control groups must be randomized to prevent a statistical bias.

The faulty selection of drug doses can lead to error, since they may be too low to permit an adequate evaluation of teratogenicity or so high as to produce other adverse effects. If the doses are too high, foetal death may result, with no opportunity for teratogenic effects to be demonstrated. Apart from the matter of dosage, faulty timing and failure to recognize the sensitive stages of development can result in administration of the drug at a time at which no effect could be expected with a known teratogenic agent.

If the observations are not directed to the proper parameters, certain effects of the test drug may be missed. Thus it is necessary to examine the foetuses in each test.
group for external and internal malformations, including skeletal defects. Another source of error is the failure to allow enough animals to go beyond term to permit the recognition of delayed post-natal developmental deviations. In studies in which post-natal observation is desired, a foster mother must be provided when the natural mother neglects her young or when the milk supply is inadequate. One of the basic errors in the performance of teratological studies is failure to consider available knowledge about the drug's metabolism and pharmacological activity. (pp. 14-15).

In teratologic studies, it is essential to keep accurate records of the number of abortions, stillbirths, and malformations for all species and colonies used. These data provide necessary control information to make possible a more meaningful evaluation of the experimental results.

3.4.2.5 Extrapolation of animal studies to man

The WHO Scientific Group on the Principles of the Testing of Drugs for Teratogenicity (3) discussed the significance of findings in animals. Their comments are as follows:

The predictive value of teratogenic tests is still open to question. One of the difficulties of interpretation is due to the constant interaction between the two different biological systems, the mother and the conceptus. Theoretically, the significance of any teratogenic activity that may be observed can be assessed by taking into account the percentage of malformations obtained, the constancy of the results in several subsequent experiments, and the dose at which the teratogenic effect has been observed.

The value of animal screening is borne out by the fact that all drugs that have been established as teratogenic in man can be shown to be teratogenic in animals. Likewise, drugs shown to be teratogenic in animals may be teratogenic in man under appropriate conditions of dosage and timing. However, generally the doses required to demonstrate teratogenicity in animals are relatively large.

It has been shown that the reaction of the embryo to exogenous agents depends to a large extent upon its genetic constitution. Furthermore, such reaction varies not only between different species but also within a given species from strain to strain and even between individuals of the same strain. The immediate causes of species differences in reaction to teratogenic agents are still largely unknown, but it has been suggested that they could be related to different metabolic pathways or possibly to the formation of noxious metabolites in some species but not in others. (p. 15).

Teratogenicity studies are essential for all drugs that may be given to women of child-bearing potential. However, these studies do not need to be performed if there is absolute certainty that the drug will not be administered to such women.

Whether or not a drug judged to present teratogenic hazard to man may go to clinical trial and eventually be marketed will depend on the degree of risk, the use to which it is to be put, and the availability of other drugs for the same indication.
3.4.2.6 Type of response

It is often possible to show that a positive response in a reproduction toxicity test is dose-related and that a threshold level exists. The effective dose levels can differ widely for the various phases of reproduction.

3.4.3 Carcinogenicity

In spite of extensive research carried out over many years there are still no completely satisfactory methods for carcinogenicity testing of drugs and other chemicals. The methods in use, therefore, represent the best that are currently available, but there is a great need for further research to improve them. The extrapolation of the results of animal experiments to man presents particular problems.

3.4.3.1 Drugs to be tested

The WHO Scientific Group on Principles for the Testing and Evaluation of Drugs for Carcinogenicity (6) drew a distinction between an evaluation of a carcinogenic hazard to man by the ingestion of a drug and testing in animals to elicit any evidence of a potential carcinogenic hazard from the use of a drug. It considered, however, that an “evaluation of carcinogenic hazard to man is essential for all drugs” (p. 8). As a result of the evaluation, it will be decided whether a drug should be tested or not. Evaluation in this context means a review of any existing evidence and of theoretical probabilities. The Group also gave guidance on certain types of drug that should be given high priority for carcinogenicity testing. Those to be tested before they are given to man included drugs chemically related to known carcinogens or that produce metabolites similar to those of known carcinogens, and drugs that damage rapidly growing tissues in relatively short experiments or affect mitosis. The priorities for testing other drugs are less well defined.

3.4.3.2 Methods of testing

The testing of chemicals for carcinogenicity is a very complex procedure, which is influenced by many factors. The WHO Scientific Group on Principles for the Testing and Evaluation of Drugs for Carcinogenicity (6) reviewed the design of long-term tests for carcinogenicity in the light of “experience and advances in knowledge in recent years”. Aspects of carcinogenicity testing have also been discussed recently by the WHO Scientific Group on Assessment of the Carcinogenicity and Mutagenicity of Chemicals (12).
3.4.3.3 Interpretation of results

The interpretation of the results of tests for carcinogenicity was discussed in the report of the WHO Scientific Group on Principles for the Testing and Evaluation of Drugs for Carcinogenicity (6, pp. 19-22) and in the report of the WHO Scientific Group on Assessment of the Carcinogenicity and Mutagenicity of Chemicals (12, pp. 6-12). The following points from these reports are of particular relevance:

(a) As with all chemical substances that give rise to biological effects, it is often possible to show that a positive response in a carcinogenicity test is dose-related. The Group considers that the demonstration of a dose-response relationship in carcinogenicity tests of a drug should be taken fully into account in evaluating the balance of benefit and risk associated with the use of the drug in patients (6, p. 21).

(b) The possible existence of a threshold to the effects of both chemical carcinogens and mutagens should be envisaged (12, p. 12).

(c) The relationship between carcinogenesis and mutagenesis requires further investigation. However, the association between mutagenicity and carcinogenicity of many compounds is sufficiently great to justify the use of mutagenicity tests as prescreening procedures for possible carcinogens (12, p. 12).

(d) It is recognized that there are certain instances of cancer induction that may be secondary to an initial non-carcinogenic effect of a chemical (12, p. 12).

(e) The role of modifying factors, enhancing or inhibiting the effect of carcinogens, must be considered (12, p. 12). [An example of such a modifying factor is pre-existing disease in the test animal or human subject. This topic requires further investigation.]

(f) If there is evidence of a possible carcinogenic hazard from food additives and ingredients of cosmetics, such substances should not be used. This is not necessarily so with drugs, since circumstances exist in which it is proper to use a drug that has been shown to be carcinogenic experimentally. Each drug must be evaluated individually. This Group does not wish to lay down a set of rules for such evaluation—and, indeed, could not do so—but some general guidance on the factors that should be considered is given below.

Some types of response may suggest that long continued exposure to a given carcinogen is required before a positive response becomes evident. Clearly, this would cast doubt on the wisdom of using such a compound as a drug for long periods of time. It is less certain that it should prevent
the use of the drug on a single occasion (or a small number of occasions) in any one individual. Other types of response may suggest that a hazard will arise only in particular circumstances of use—e.g., subcutaneous injection. . . . Such a response should not necessarily preclude all other uses of the drug.

Drugs are used medically for a wide range of conditions from the trivial to the serious, and a given drug may be used for both trivial and serious conditions. Drugs may be given to an individual only once, or several times a day for many years.

Many drugs already on the market have not been evaluated for carcinogenesis. Serious hazards may be associated with drugs available without medical prescription. The Group recommends that any drug that has been shown to be a carcinogen experimentally be used only under strict medical supervision (6, pp. 21–22).

There is good experimental evidence that cancer can be induced in the progeny of animals treated with chemical carcinogens during pregnancy. Similar transplacental induction may occur in human beings (13).

3.4.4 Mutagenicity

3.4.4.1 General

The WHO Scientific Group on the Evaluation and Testing of Drugs for Mutagenicity recommended that all compounds being assessed for toxicity should also be evaluated for possible mutagenic action; it was emphasized, however, that such an evaluation may or may not indicate the need for testing (8, p. 5). Further research is needed before it can be stated that all drugs should be tested for mutagenicity.

3.4.4.2 Drugs to be evaluated and tested

Evaluation may take into account the manner in which the drug is to be used as well as epidemiological evidence and also known structural, biochemical, and pharmacological properties that may cause or be associated with genetic damage. Shortages of manpower and the limited number of specialized research institutions make it impossible to submit all drugs to mutagenicity testing. The following priorities were proposed by the WHO Scientific Group on the Evaluation and Testing of Drugs for Mutagenicity (8, pp. 9–10):

(a) High priority

(i) Compounds that are chemically, pharmacologically, and biochemically related to known or suspected mutagens.
(ii) Compounds that exhibit certain toxic effects in animals, such as:
- depression of bone marrow at tolerated doses
- inhibition of spermatogenesis or oogenesis at tolerated doses
- inhibition of mitosis (e.g., in intestinal epithelium and other rapidly growing tissues) at maximum tolerated doses
- teratogenic effects at maximum tolerated doses
- carcinogenic effects
- causation of sterility or semi-sterility in reproduction studies
- stimulation or inhibition of growth or synthetic activity of a specific organ, cell or virus
- inhibition of immune response at maximum tolerated doses

(iii) Drugs that are often used over a period of years particularly in children and young adults.

(iv) Drugs that are prescribed for a large proportion of the population.

(v) Drugs that are used for general prophylaxis.

(vi) Drugs subject to widespread abuse.

(vii) Drugs that come in contact with sperms in high concentrations, e.g., substances used for sperm preservation and vaginal contraceptives.

(b) Low priority

Many groups of drugs have been in medical use for years with no chemical, toxicological, or other evidence of mutagenic action. A few representative compounds of each chemical group should be tested.

3.4.4.3 Methods of testing

At the present time there does not appear to be any unanimity of opinion in regard to the best procedures for testing drugs for mutagenicity. It has been pointed out that the endpoint of mutagen-detecting assays may be either mutation or one of a variety of events leading to mutation. Although it can be argued that mutation is the most relevant endpoint, the advantages of other endpoints are considerable. For example, tests measuring damage to DNA or repair of damaged DNA are much more sensitive than procedures measuring mutation per se.

A great variety of test organisms and systems have been used in recent years to detect mutagenic substances, included the following:

(a) In vivo cytogenetic analysis in somatic and germ cells.

(b) Host-mediated assays using microbial submammalian and mammalian cells introduced into mammalian hosts.
(c) *In vitro* activation by mammalian tissue preparations with microbial test organisms.

(d) Dominant lethal test, usually in male mammals.

(e) Specific locus test: this method of inducing, detecting, and increasing rates of mutation at several recessive loci in wild type mice needs many thousands of offspring to be raised and examined.

(f) Mutation in mammalian somatic cells *in vitro*: a number of cell lines with suitable phenotypic markers are available and methods for isolation of mutants have been devised.

(g) Mutation in microorganisms and other submammalian systems.

(h) DNA repair studies.

(i) Reaction with DNA.

Detailed accounts of the above methods have been published (14-16). The WHO Scientific Group on the Evaluation and Testing of Drugs for Mutagenicity also considered *in vitro* studies in man (8, pp. 14-15). They can be divided into two categories as follows:

(a) Studies of individuals

(i) chromosome examination in somatic cells

(ii) studies of chromosome aberrations in germ cells, which should be made only in special circumstances

(iii) tests for mutagens in blood and urine.

(b) Epidemiological studies (population monitoring)

Epidemiological studies can be used to detect the mutagenicity of an agent missed in the initial screening, although the many uncontrolled variables are a disadvantage.

(i) chromosome examination of a fetus delivered by spontaneous abortion: the time from conception to detection of abortion alters the results materially and, as in any epidemiological study, it is difficult, if not impossible, to determine the etiology;

(ii) chromosome aberrations among new-born infants;

(iii) sex ratio shift: the human sex ratio is influenced by many factors, so that any shift is difficult to interpret and this method will detect only gross effects;

(iv) marker phenotypes: an expensive procedure that can be expected to detect only gross changes and that suffers from the disadvantage that it is difficult to reach an exact diagnosis, particularly as phenocopies are possible;
(v) somatic cell markers: a variety of somatic cell markers including enzyme activity and chromosome and protein markers, such as haemoglobins, are being developed to detect changes in cells from individuals and from populations; these methods are promising but are in an early stage of development.

Such studies may be limited by medical, ethical, and legal considerations.

3.4.4.4 Significance of results
Two WHO Scientific Groups have made the following comments on this subject:

A positive finding in a species should be considered an indication of potential mutagenic activity in man unless relevant differences in metabolism, pharmacokinetic behaviour and/or pharmacological effects can be demonstrated between the species used and man (8, p. 15).

In vitro mutagenicity tests alone cannot yield definitive results applicable to man. Mammalian test systems are more promising but still require further development and experience (12, p. 12).

As in other areas of toxicological testing, the dose-response relationship is important and should be established whenever feasible.

The interpretation of the dose-response relationship should also take into account the possibility that the mutagenic effect of a compound may be due to two or more different mechanisms, acting, for example, during different phases of the cell cycle, and separate dose-response curves should be established.

It is also important to correlate mutagenic dose-response curves with those of other important biological effects. This is particularly true for the processes involved in absorption, biotransformation, and excretion of the drugs, as well as for their penetration through biological barriers. Efforts should be made to correlate the mutagenic dose-response curves with those of drug concentrations in the target organs (testis, ovary, bone marrow, etc.) and in the cells. Changes in metabolism and excretion due to overloading with drugs, stimulation or inhibition of drug-metabolizing enzymes, and interaction with concomitant drug therapy should be taken into consideration (8, p. 15).

3.4.4.5 Benefit/Risk Assessment
The WHO Scientific Group on Evaluation and Testing of Drugs for Mutagenicity (8), commented on this aspect as follows:

Although a precise benefit/risk assessment applicable to clinical practice is impossible owing to lack of information, the physician is still faced with the problem of having to decide when to use drugs of known and unknown mutagenic potency. Plainly there is no difficulty in deciding to use a known mutagen in serious or life-threatening disease, but mutagens are increasingly being used in diseases that may run a prolonged course, during which the patient may reproduce. Such diseases include psoriasis, rheumatoid arthritis, and other conditions associated with altered immune reactivity. The use of some antiviral and antimicrobial agents may present similar problems.

It is hard to estimate the absolute amounts of expressed damage resulting from mutations, but the hazard can be reduced by various procedures. For example,
where known mutagenic drugs are used in either sex, measures to prevent procreation during and for a few months after treatment are desirable. This practice is already being followed for patients receiving ionizing radiation. Again, where there is a choice of several drugs of known mutagenic potential, the drug with the smallest mutagenic risk for the individual and the population should be chosen.

Finally, it is necessary to take into account the strength of the evidence for mutagenicity, the availability of alternative treatments, the nature of the disease and the status of the patient. (p. 16).

### 3.4.5 Relationship of mutagenesis and carcinogenesis

The relationship between mutagenesis and carcinogenesis was discussed by a previous WHO Scientific Group (II), which commented as follows:

Current theories postulate similarities between the mechanisms of mutagenesis and the mode of action of major groups of chemical and physical carcinogens.

There is increasing evidence that many chemical carcinogens in their carcinogenically reactive form can induce mutations in microbial and some mammalian test systems. But it is impossible to assess whether or not these common properties of many chemical carcinogens and mutagens also point to common sequences of events resulting in a cancer cell or a mutated cell. Furthermore, some potent mutagens do not appear to be carcinogenic in any of the test systems used and certain carcinogens have not been demonstrated to be mutagenic. One major difficulty in the comparison of mutagenic and carcinogenic actions is the use of results obtained from different test systems. Induction of point mutations is reported mostly from studies in microbial systems, whereas chromosomal abnormalities have been observed in tissue culture and, more recently, in vivo. Carcinogenicity, on the other hand, is reported largely from in vivo studies in rodents. A second difficulty arises from the need for metabolic activation of many chemical mutagens and carcinogens. Until recently most in vitro systems used in mutagenesis bioassay have lacked this activation potential. It is thought that metabolic activation converting a procarcinogen into the ultimate carcinogen is analogous to the change from a premutagen to the ultimate mutagen. (p. 8).

### 3.4.6 Dependence liability

#### 3.4.6.1 Introductory remarks

In recent years, concern has increased in a number of countries both among physicians and among the general public regarding widespread non-medical use of drugs and the development of dependence (physical and psychic). During the same period, the danger of the development of dependence from the therapeutic use of drugs, usually from improper prescribing or overprescribing, has received greater attention. WHO has recognized the need for studies in this area and a Scientific Group on Progress in Methodology of Evaluation of Dependence-producing Drugs (I7), which met in November 1974. An earlier WHO Scientific Group on the Evaluation of Dependence-producing Drugs (I7), which met in 1963,
considered the methods then available and appraised their applicability to the determination of dependence as well as their value in predicting the results of permitting a drug to be made available for general use. Since then, there has been a large amount of research in this field, which has produced significant conceptual advances in our understanding of the nature of drug dependence. This research work has also greatly improved the techniques and methods reviewed eleven years ago and has produced new techniques for the assessment of dependence.

3. 4. 6. 2 Evaluation

Physical dependence may be detected by the development of an abstinence syndrome following withdrawal of the drug. The detection of psychic dependence is more difficult.

In its sixteenth report, the WHO Expert Committee on Drug Dependence (18, p. 7) pointed out that evidence for psychic dependence in man is drawn mainly from case histories, subjective statements, and general observations.

Drugs of the following categories should be evaluated for potential dependence liability in man:

(a) drugs structurally related to compounds known to have a dependence liability in man, and/or
(b) drugs acting on the central nervous system, such as analgesics, depressants, hallucinogens, stimulants, and anorexiant.

Since evaluation is a mixture of science and subjective opinion, further studies must be undertaken to obtain better criteria for making a rational decision on whether to undertake testing. The evaluation may result in a decision to perform tests. Some experimental procedures in animals have been developed that may be of assistance in the prediction of the potential for psychic dependence in man. These techniques depend on technical arrangements that permit the animal to self-administer the drug. Information can be obtained on the animal’s response to the drug in regard to:

(a) liking or aversion,
(b) choice, when the drug and alternatives are made available, and
(c) the degree of drive to continue administration.

The Expert Committee concluded that: “These methods are yielding interesting and suggestive data but none has yet reached a level of refinement and reproducibility that would make it acceptable as yielding conclusive evidence of the possibility of man developing psychic dependence on a new agent.” (18, p. 9).
4. CLINICAL EVALUATION

4.1 Ethical and Legal Aspects

The ethical and legal aspects of any testing involving humans in the evaluation of a drug must be accorded continuing attention. Recommendations for the guidance of doctors engaged in clinical research are embodied in the Declaration of Helsinki adopted by the World Medical Association at its meeting in Helsinki in June 1964 (19). All investigators conducting drug evaluation studies should be familiar with this document. In some countries, all experiments on man are subjected to review by independent groups who are responsible for determining whether they are ethically admissible, and this procedure is spreading. Such a review safeguards the welfare of subjects as well as the clinical investigator. It includes the scientific validity and technical aspects of the proposed study, since improperly conducted studies are unethical. Substantial changes in the protocol require further review. The introduction of such a review procedure may provide answers to many of the ethical problems in clinical drug testing.

The WHO Scientific Group on Principles for the Clinical Evaluation of Drugs (4) gave consideration to the ethical aspects of clinical evaluation in their report, but did not take a definite position on the subject because ethical problems are not peculiar to drug research and the membership of the Group was not sufficiently representative to cover general matters of ethics and law. However, it noted the following areas of concern (pp. 17–20):

(a) consent of subjects;
(b) safety of subject;
(c) reward of subjects;
(d) payment of costs;
(e) remuneration of investigators;
(f) compensation for injury;
(g) subjects with limited civil rights (mentally retarded children, psychiatric patients, prisoners).

4.1.1 Drugs for children

The special problems of paediatric drug therapy were discussed at the Second European Symposium on Clinical Pharmacological Evaluation in Drug Control, held in Heidelberg in September 1973 (20). It was pointed
out that the performance of therapeutic trials in children raises many practical as well as ethical problems. These include the lack of adequate methodology, the problem of patient consent, and the lack of clinical investigators who are prepared to conduct such studies. These difficulties may make it impossible in some instances to obtain adequate and well-controlled studies on children. Studies in children should not ordinarily be undertaken until adequate studies of safety and efficacy are available in adults. Nevertheless, it is obvious that drugs likely to be administered to children must be tested in children, but such testing should be done only when there is possibility of benefit to the individual.

4.2 Early Studies in Man

4.2.1 Justification and purpose

The WHO Scientific Group on Principles for the Clinical Evaluation of Drugs (4, p. 8) stated succinctly in its report the justification for and the purpose of the initial studies in man. The WHO Scientific Group on Clinical Pharmacology: Scope, Organization, Training (7, p. 10) has also outlined the aims of and procedures employed in early studies in man:

The aim of early studies of a new drug in man is to find out if it has a potentially beneficial effect. Special training and experience are necessary to conduct these studies in such a way that they yield the maximum information with the minimum risk. The clinical pharmacologist is particularly well qualified to carry out such studies.

Studies of a drug in man must be justified by the demonstration of a potentially useful effect in animals, or by theoretical considerations about its mode of action. The clinical investigator must satisfy himself that these preclinical studies are adequate.

4.2.2 The first study in man

Initial studies in man must necessarily 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; it also provides an opportunity for 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.

Single doses without expected pharmacodynamic or therapeutic effect may be useful for obtaining pharmacokinetic data. Such studies cannot be
assumed to predict what occurs with repeated doses. 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 long-term toxicity tests in animals as would be essential were the drug to be used continuously in each individual for days or weeks.

The clinician and his advisers and the regulatory agency, if required, have the responsibility of satisfying themselves that the preclinical experiments are adequate in scope and they should require a full account of all relevant data.

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.

Communication among investigators should be as direct and rapid as possible to avoid duplication of hazard.

Before the initial study in man, a detailed protocol should be designed by the clinical investigator and the other scientists concerned with the development of the drug. This protocol should contain such items as the type of individual to be studied, the initial and maximum dose to be used, laboratory tests to be monitored for organ system toxicity, and precautions to be observed. To minimize any potential hazards, the first doses are usually given to one subject at a time until sufficient experience is obtained to allow more rapid progression of the study. If specific organ toxicity is suggested by the preclinical studies, the protocol must include laboratory and physiological monitoring of sufficient sensitivity and relevance to provide maximum safeguards for the subjects.

4.2.3 Clinical and laboratory facilities

The requirements for clinical and laboratory facilities 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. This may require complex instrumentation as well as an adequate biochemical laboratory. The investigator must assure himself of the precision of all methods utilized. Facilities to deal with all emergencies must be available.

4.2.4 Clinical and laboratory observations

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

When the drug is first administered to man, arrangements should be made to record the subject's feelings, and the ordinary routine of medical observation (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 should be done as a safety precaution even though animal tests have given no reason to expect these to be altered, for laboratory tests generally provide an earlier indication of malfunction than clinical observation. More information is needed about the usefulness of the observations that are often depended on to detect drug toxicity in these circumstances.

Sometimes it may be desirable to delay or interrupt the clinical programme whilst further animal experiments are done.

4.2.5 Qualifications 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 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.

4.2.6 The clinical pharmacologist

In recent years clinical pharmacology has emerged as a specialty. 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. The functions, scope, and training of clinical pharmacologists have been fully discussed by a WHO Study Group (7).

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4.2.7 Experimental design

4.2.7.1 Choice of subjects

Depending on the objectives of the study, the subjects chosen may be either patients or persons in normal health, due regard being paid to ethical criteria (see section 4.1). Data on absorption, distribution, and excretion as well as evidence of many pharmacodynamic actions may be obtained from subjects in either category, but sometimes a desired effect can be detected only in a diseased subject, e.g., anticancer, antiparkinsonian, or 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 with an independent responsible 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 is 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, due regard being paid to ethical considerations. It should be kept in mind that such volunteer groups may not be representative of the general population.

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

(a) Children (see section 4.2.1). 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) Pregnant women and women of childbearing potential. Women who are known to be or who may be pregnant should not be used for the earliest initial studies with drugs because of the potential risk to the fetus. If, however, drugs are developed that are specifically intended for use in the therapy of pregnant women, the definitive study of efficacy will have to be
performed in them. If the drug is tested clinically before teratology studies have been done, it is prudent to exclude women of childbearing potential.

(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 the purpose and design of the trial have been reviewed by an independent, responsible group.

(d) Healthy volunteers. 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 pressure. This should be taken into account when inviting or accepting such volunteers.

(e) Psychiatric patients and the mentally retarded present special problems.

4.2.7.2 Number of subjects

The number of subjects required before enough can be known about a new drug to warrant embarking on a controlled 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.

4.2.7.3 Dosage and route of administration

To detect the pharmacological effects or the potential therapeutic value of a new drug, gradually increasing single doses 6 may be given until an effect, wanted or unwanted, appears. Experiments should ordinarily be done in different subjects to avoid any possibility of increased hazard due to repeated administration.

The initial dose to be administered to man will be estimated from the \( ED_{50} \) in the most sensitive animal species. It is wise to work up from a small fraction of the predicted effective dose.

In general, an upper limit to dosage should be set in the first experiments, but as experience is gained the dose is gradually increased until some effect is noted. If no response occurs, the explanation should be sought, e.g.,

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6 The single dose may sometimes be given fractionally over a short period.
lack of absorption, rapid biotransfusion, lack of formation of active metabolites.

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 experiment, 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. may be used when appropriate.

4.2.7.4 Duration of administration

The duration of administration in man should not exceed the period justified by the animal toxicity studies (see section 3.3).

4.2.7.5 Pharmacokinetic studies (absorption, distribution, biotransformation, excretion)

Technical facilities for such studies are currently limited and sometimes inadequate. More sensitive techniques for measuring concentrations of drugs and their metabolites have been under development in recent years. Studies of absorption, distribution, biotransformation, 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.

Early pharmacokinetic studies may be particularly useful for demonstrating that the drug is accumulating even before pharmacodynamic effects become apparent.

4.2.7.6 Pharmacodynamic studies

In order to minimize risks in man, it is essential to have methods of detecting pharmacodynamic effects, unexpected as well as expected, as soon as they appear. The most sensitive available techniques should always be employed and these will sometimes demand complex equipment and skills. There is a need for techniques that do not interfere with the integrity of the body (non-invasive techniques) for measuring pharmacodynamic effects. Details may be varied in accordance with the expected effect.
4.2.7.7 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.

However, there is no compelling reason why appropriate controls cannot be used at these early stages. 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 considerations.

4.2.7.8 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.

4.2.7.9 Documentation

Careful and complete records of all studies should be made. The data accumulated in the initial studies should be sufficient to allow a decision on the justification for the controlled therapeutic trial.

4.3 Controlled Therapeutic Trials

4.3.1 Principles

The controlled therapeutic trial has been defined (21) as:

- a carefully, and ethically, designed experiment with the aim of answering some precisely framed question. In its most rigorous form it demands equivalent groups of patients concurrently treated in different ways. These groups are constructed by the random allocation of patients to one or other treatment; such an allocation may sometimes preferably be made within more but smaller homogeneous sub-groups composing the total groups. Sometimes carefully matched pairs of patients may provide the contrast. In some instances patients may form their own controls, different treatments being applied to them in random order and the effects compared. In principle the method is applicable with any disease and any treatment. It may also be applied on any scale; it does not necessarily demand large numbers of patients. It should be designed to promote rather than hinder the traditional method in medicine of acute observation of disease by the clinician at the bedside.
4.3.2 Experimental methods

4.3.2.1 Purpose and method

The purpose of the controlled 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, or other means). 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. 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.

Measurements of plasma concentrations of drugs help decide whether pharmacokinetic variations are responsible for differences in response.

4.3.2.2 Experimental design

(a) 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 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.

(b) 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, and whether they should be without other diseases than the one under investigation.

Comprehensive baseline studies are important in order to exclude those subjects who may be specially at risk. These studies should be assessed in relation to the data obtained in the early clinical and the preclinical investigations.

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.

A question that has arisen is whether data and conclusions of therapeutic trials conducted in, for example, a homogeneous well-nourished population can be assumed to be valid for different ethnic groups and populations subject to endemic diseases or malnutrition. Since it is known that there are important differences in response, re-evaluation of the drug is essential when used under such circumstances.

Research in these areas is desirable since at present little information is available.

(c) 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 the most important, in others joint swelling and pain. 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. The method of assessment must be precise, reliable, and validated between observers. 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 efficacy 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 is now beginning to aid quantitative evaluation of psychiatric signs and symptoms.

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

(d) 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.

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 subdivided (stratified) into appropriate and more homogeneous subgroups, and a random sample withdrawn from each of these for allocation to treatment. The subsample may or may not be proportional to the number of units in the subgroup.

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: (i) to render the subject groups as equivalent as possible in regard to all variables other than the treatment under study, and (ii) 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.

(e) 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 best understood, 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 the symptoms under study, as well as for events that are independent of the treatments. The placebo is an important tool for distinguishing between a true therapeutic or adverse 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.

The following techniques are in common use:

(i) Double-blind and single-blind techniques. The expression "double-blind" 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 trial is almost always less satisfactory than one using the double-blind technique, and the slight gain in convenience hardly compensates for the potential loss of rigour in the study.

(ii) 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 or in 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.

(iii) **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.

**(f) 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 requires one clear-cut endpoint; it is difficult to reach a decision by 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 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 clinically important.

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.

(g) Fixed dose or variable dose

Therapeutic trials are often performed by using only one dose of a drug. This is satisfactory where it is reasonably certain that the dose 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.

(h) Testing multiple therapy, including fixed-dose combinations

The testing of multiple drugs may sometimes be a valid primary objective.

This may be done with a fixed-dose formulation, or the drugs may be administered separately. It is essential that there be a scientific basis for the combination of the drugs and the selection of the doses. Generally the trial should include a comparison with the ingredients given separately.

Special precautions must be taken in the testing of drug combinations to consider individual toxicity, biochemical interaction, and interaction in the disease state under study.

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

(j) 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, poses 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 drugs; 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 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.

(k) 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.

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.

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.

4.3.2.3 Statistics

The planning, execution and analysis of a therapeutic trial demand statistical ways of thinking and statistical techniques. Therefore the statistician should be involved at all stages.

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 of the observed (or greater) magnitude between two (or more) groups of patients 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.

4.3.3 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 rationalization 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.

Much misleading information on the therapeutic indications of drugs derives from the confusion frequently made between statistical significance and therapeutic importance. The statistical analysis is to assess the probability that a given effect occurs, but it does not establish if the effect is of

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benefit to the patient. Similarly, in the final analysis we must be concerned with therapeutic effects, not merely with changes in biochemical and other parameters, e.g., morbidity and mortality of diabetes with hypoglycaemic drugs, and coronary heart disease with hypolipidaemic drugs.

Throughout the testing of a new drug, contact should be maintained with the preclinical investigators; and further animal experiments should be done, when indicated, to elucidate events observed in man.

4.4 Pharmacogenetics

Genetic control of responses to drugs is of two principal kinds:

(a) what is ordinarily recognized as a biological variability, i.e., the familiar normal distribution curve; this is the result of multifactorial or polygenic inheritance;

(b) non-continuous or discrete variability due to a single gene with mendelian inheritance that may result in dramatic, even all or nothing, differences in response, e.g., glucose 6-phosphate dehydrogenase (G6PD) deficiency and haemolysis, slow and fast acetylations, suxamethonium sensitivity, and malignant hyperthermia.

Clinically important differences in both areas may occur between populations and thus have a bearing on international acceptance of data. In spite of the obvious importance of this subject, knowledge has not progressed as rapidly as is desirable.

4.5 Bioavailability

Plainly it is not sufficient merely to put a drug into a formulation. It is also necessary to ensure that is will leave the formulation and reach its site of action in sufficient concentration. The WHO Scientific Group on Bioavailability of Drugs (II) pointed out that:

Patients vary greatly in their response to a drug. This variability depends upon factors such as dose, severity of disease, rate of drug metabolism and excretion, and other pharmacokinetic factors. However, an important and often unrecognized source of variability is the bioavailability of the drug from the dosage form being used, i.e., its time course and extent of absorption. (p. 6).

Problems connected with bioavailability arise with formulations of all kinds, particularly in the use of oral and topical preparations.

[Bioavailability] is determined by measuring either the time course and extent of drug absorption into blood (plasma) or its excretion into urine, in comparison with the absorption or excretion of a reference formulation of the same drug, such as an intravenous solution, an oral solution, or a suitable solid oral dosage form.
Bioavailability studies can be conducted either in normal human subjects or in patients receiving treatment with the drug under study. These studies need to be carefully designed to take into account ethical, medical, biopharmaceutical, analytical, and statistical considerations.

More trained personnel and more research are required in pharmacokinetics and biopharmaceutics to improve our understanding of the factors that determine bioavailability and to develop in vitro and animal tests that can be used to predict or control the bioavailability of drugs. (p. 17).

The bioavailability of formulations of the same drug from different sources may vary and must be evaluated in the light of their clinical importance. New drug delivery forms, e.g., controlled release formulations, require careful bioavailability studies.

Clinical investigators should recognize that if they alter the formulations to meet double-blind conditions of their therapeutic trials, they may also alter the bioavailability of the standard preparation and so invalidate their results. It is suggested that all clinical trials should be conducted with the formulation that may ultimately be approved for general use. This is often impracticable, but the difficulty may be overcome if bioavailability studies are performed on each formulation used.

5. POST-REGISTRATION SURVEILLANCE

5.1 General Comments

It has been recognized for many years that the therapeutic trials that are adequate to justify registration of a drug for general use are inadequate to reveal uncommon adverse reactions. For this reason national centres for monitoring adverse reactions have been set up in many countries and WHO has played a coordinating role. A similar problem exists in relation to therapeutic efficacy. This is because the patients treated form a relatively small group, which is usually rather homogeneous, and also because the clinicians have a particular interest in the disease and its treatment.

It is obviously desirable to establish what can be achieved with a drug when used under ideal conditions. But it is unrealistic to expect such good results when the drug passes into general use for treating patients who may of a kind not included in the therapeutic trials, who may also be suffering from other diseases and taking other drugs, and who are under less close supervision.

It is impracticable and undesirable to delay general use of a valuable drug until all possible effects become known. Therefore, the development of methods for monitoring both safety and efficacy after registration is a matter of great importance.
5.2 Monitored Release

In the case of certain drugs intended for the treatment of important diseases or having unique properties, the data available may not be sufficient to permit release for general use. Despite this a drug may appear likely to have some special advantage for certain patients. Under these conditions, it may be desirable to release the drug on a restricted basis with special arrangements for monitoring patients. This has been termed "monitored release". It has been described in the report of the Symposium on Clinical Pharmacological Evaluation in Drug Control, Heidelberg, 1972 (22) as follows:

In some special cases, it has proved useful to allow a limited availability (monitored release) of drugs so as to ensure that extensive additional scientifically based information is obtained rapidly, on the basis of which a decision as to restriction or full general release can be taken.

It is possible that this principle of monitored release might be applied more widely to certain drugs, which, even following general release, would be identified as still being subject to post-registration surveillance until a final evaluation of "real-life" efficacy and toxicity could be made. Since this suggestion presupposes the development of an acceptable methodology, research on suitable surveillance methods should be encouraged.

5.3 Monitoring of Adverse Reactions

Many countries have now established national monitoring systems for adverse reactions along the lines recommended by WHO meetings (see ref. 5 and 9).

The principal objectives of monitoring for adverse reactions are to detect such reactions, to diminish the time necessary to recognize them, and to determine their importance in relation to the therapeutic use of the drug.

The main activities of national centres should include:

(a) The collection of data on adverse drug reactions derived from such sources as reporting by individual practising doctors, comprehensive monitoring in hospitals, and systematized collection of data on defined populations. The systematized monitoring of populations and other sources of adverse drug reaction data (e.g., health statistics and drug utilization data) need to be further developed.

(b) The analysis of data on adverse reactions. The effectiveness of this analysis will be dependent upon the quantity and quality of the reports provided, and upon the system for storage, linkage, and methods of analysis.
The quality of reports can be improved by developing methods for validation. When the number of adverse reaction reports is large, methods should be developed to determine which reports or groups of reports require further investigation. Special attention should be paid to new drugs.

(c) The support and promotion of specialized and comprehensive monitoring centres and systems, which can provide additional data and may be especially useful for the investigation of drug safety problems.

It is clear that all activities of the national centres require continuous research and development. The problems involved are sufficiently difficult and important to require methodological, epidemiological, clinical, and laboratory investigation. It should be one of the primary responsibilities of the national centres to promote this type of research.

Collaboration between national centres through the international system is therefore essential. The WHO programme for drug monitoring should assist national centres by (a) developing systems for recording and processing data for comparative and investigative purposes, (b) promoting the establishment of national centres and (c) supplying information to national centres and aiding them in meeting their responsibilities.

It is desirable that validated data on adverse reactions be made available to the health professions.

5.4 Monitoring for Efficacy

Factors of importance in therapy include the knowledge and experience of the doctor, the completeness of the information available to him, his motivation to use it, his diagnosis, the closeness with which he follows the prescribing recommendations, the instructions and supervision he gives the patients, the doctor-patient relationship, patient comprehension and compliance, and the occurrence of adverse effects.

Whilst the methodology for monitoring adverse reactions is comparatively well developed, there is a serious lack of suitable methods for monitoring efficacy. It is important to develop such methodology, preferably on an international basis.

5.5 Information from Poisonings and Overdosage

Many countries have established centres for collecting and distributing data on accidental or deliberate overdose or poisoning and some of these also provide advice on treatment. Such poisoning is not restricted to drugs but includes household chemicals of all types. In such cases, clinical observations and laboratory tests on the patients can provide valuable data. International coordination is useful, especially with the rarer poisonings.
5.6 Continuing Evaluation

It is rare for the full information necessary for the safe and effective use of a drug to be available when it is registered. Evaluation and experimentation must therefore be continued after registration.

5.7 New Indications for Registered Drugs

Where a registered drug is thought to be of use for a new indication, the scientific data in support of this should undergo review by the regulatory authority.

5.8 Information for and Education of the Physician

However good the post-registration surveillance systems, they will not contribute directly to safer and more effective therapy unless physicians are continuously provided with accurate, unbiased information on drug therapy. Informational sources to prescribers are generally inadequate and should be improved.

In addition, education of the physician in rational drug therapy is widely believed to be insufficient, both in the undergraduate period and throughout his professional life. Action in this area is also needed.

6. FUTURE RESEARCH NEEDS AND FURTHER ACTIVITIES

6.1 Research

The Group considered that the development of efficacious and safe drugs requires research in the following areas:

1. Study of pharmacological and toxicological differences between animal species and strains and their relevance to man.
2. Use of new or seldom-used species of test animals.
3. Development and utilization of animal models with spontaneous or induced disease for pharmacological and toxicological tests.
5. Influence of environmental, nutritional, and genetic factors on pharmacological and toxicological testing and their relevance to man.
6. Drug action at different stages of the life cycle of the experimental animal, e.g., newborn, juvenile, aged animals, and relevance to man.
(7) Short-term animal or in vitro tests for carcinogenicity.

(8) The possible existence of a threshold level for the effects of both chemical carcinogens and chemical mutagens.

(9) Development of techniques that do not interfere with the integrity of the body (non-invasive techniques) for measuring physiological functions.

(10) Improvement of methods for conducting international therapeutic trials, including problems of defining diseases and of genetic differences in populations.

(11) Methods of post-registration surveillance for therapeutic efficacy.

(12) Development of methods to be used by national and international centres to collect systematized data on large populations in order to determine whether animal studies on adverse effects, carcinogenesis, mutagenesis, and teratogenesis are relevant to man.

(13) Studies on the methodology of re-evaluation of drugs when they are introduced to population groups with significantly different ethnic characteristics, nutritional states, or prevalence of serious endemic diseases.

6.2 Further Activities to be undertaken by WHO

The Group proposed that WHO should undertake the following activities:

(1) The preparation of guidelines for drug evaluation (preclinical and clinical) in particular pharmacological or therapeutic areas. Such guidelines could assist in the mutual acceptance of the results of testing undertaken in different countries.

(2) Initiation and coordination of studies on the ethical problems raised by clinical drug evaluation.

(3) Dissemination of the results of post-registration surveillance for safety and efficacy in order to assist health professions and regulatory bodies in drug evaluation.

(4) Discussion of the differences in the importance attached to effects observed at the highest dose levels in carcinogenicity studies as compared to general toxicity studies with a view to determining whether research should be undertaken to establish valid reasons for this difference.

(5) Study of the possibility of promoting regional cooperation and development of facilities for drug evaluation, which are inadequate in some parts of the world.
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