Safety requirements for the first use of new drugs and diagnostic agents in man

Geneva, 1983

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A review of safety issues in early clinical trials of drugs

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NOTE ON CIOMS

THE COUNCIL FOR INTERNATIONAL ORGANIZATIONS OF MEDICAL SCIENCES (CIOMS) is an international nongovernmental scientific organization established jointly by WHO and Unesco in 1949. Through its membership, CIOMS is representative of a large majority of the biomedical scientific community. In 1983 there are sixty-five international member organizations, representing a large proportion of the biomedical disciplines, and twenty-seven national members, representing national medical academies of sciences and medical research councils. The main objectives of CIOMS are: to facilitate and to promote international activities in the field of biomedical sciences especially when the participation of several international associations and national institutions is deemed necessary; to maintain collaborative relations within the United Nations and its specialized agencies, in particular with WHO and Unesco; and, to serve the scientific interests of the international biomedical community in general.

The main fields of activities include:

Bioethics — particularly research involving human subjects, and the protection of prisoners against torture and maltreatment;

Drug Development and Use — medical, social and economic implications;

International Nomenclature of Diseases — internationally agreed and recommended names and definitions for every disease;

Biomedical Research Involving Animals — international guiding principles;

Health Manpower Development — promotion of study on health services and health manpower development in relation with primary health care.

The methods used by CIOMS for achieving its objectives are the organization of ROUND TABLE CONFERENCES on subjects that are both topical and of international significance and the preparation of INTERNATIONALLY AGREED GUIDING PRINCIPLES. The conferences provide international forums for the exploration not only of the scientific and technical aspects of new developments in biology and medicine but also of their social, ethical, administrative, and legal implications.

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BACKGROUND

The Council for International Organizations of Medical Sciences (CIOMS) is an independent, international, non-governmental, scientific organization established in 1949 under the auspices of the World Health Organization (WHO) and the United Nations Educational Scientific and Cultural Organization (Unesco). In 1978 a CIOMS Round Table Conference on Trends in Drug Research and Development agreed that CIOMS could provide an effective forum to facilitate discussion of policy matters between the pharmaceutical industry, regulatory authorities and academic experts. With this encouragement CIOMS is developing a programme on Drug Development and Use.

To further this programme, a small advisory group met at the CIOMS offices in Geneva in December 1980 (Dr. Z. Bankowski, Executive Secretary, CIOMS; Professor C.T. Dollery; Dr. J.F. Dunne, World Health Organization; Professor F. Gross; Dr. L. Werko; Professor G. Zbinden). This group resolved to set up two working parties to study the "Safety Requirements for the First Application of New Drugs and Diagnostics in Man". These working parties met in Geneva and in London during 1981 and their joint report was then circulated amongst a number of international experts for comments.

This document is an edited version of the working parties' report taking into account the comments received. Its aim is to outline a basis for assessing preclinical safety requirements for early drug studies in man that is simpler and more rational than some of the existing national regulations. The peoples of the world have much to gain by facilitating the development of new therapeutic agents provided that safety is not compromised.

The report is motivated by the belief that simplification and flexibility at the preclinical stage is possible without impairing safety provided that the standards maintained in clinical studies are high. It will now be distributed as a consultative document to ministries of health, medical research councils, medical faculties, relevant non-governmental organizations, research-based pharmaceutical companies and medical journals.

Comments on this review are welcome and should be directed to:

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INTRODUCTION

New drugs which are more effective and safer than existing ones are still urgently needed for many types of human disease. Despite the burgeoning research effort in the biological sciences there is evidence that the pace of innovation in drug therapy has slowed. In part this reflects the greater degree of difficulty inherent in trying to improve on an existing drug, rather than to discover the first therapeutic agent in a field where none has existed before. Furthermore the pathological processes now being tackled are more difficult to reverse, than was the case for the deficiency diseases and acute bacterial infections which were the subject of some of the early therapeutic triumphs. A factor in the slow-down of innovation is the cost and complexity of the process of discovering and evaluating a new drug. Much of this cost is unavoidable but some of it appears to be wasteful because the tests are done more to satisfy regulatory requirements than from any substantial evidence that they are necessary in a scientific sense. Another source of waste is needless repetition of standard tests to satisfy the slightly differing requirements of national licensing bodies.

Deliberate, systematic research to discover new drugs has a relatively short history. Most drugs now in use have been discovered within the last forty years. During this time there has been a continuous evolution of the methods used both in the laboratory and in man. At the outset the methods of study could best be described as intelligently opportunistic. Short cuts were used and the development cycle from synthesis of a new structure to its marketing as a therapeutic agent could take as little as two or three years. Intervention by government agencies came about because of concern about safety and quality of medicines and was accelerated by drug disasters such as that with thalidomide. At the outset most regulatory bodies set up by governments concerned themselves mainly with safety and particularly with the requirements for animal toxicity testing. Inevitably this intervention took the form of guidelines and recommendations for the number and type of tests that should be done and the complexity of these requirements has increased progressively with the expansion of knowledge. Toxicologists have been successful in developing animal models for many known types of toxic effect by appropriate choice of species and dose, although often they were devised retrospectively e.g. hepatic necrosis with paracetamol, teratogenicity with thalidomide. Despite these successes the interpretation of many of the findings in toxicity tests carried out at high doses in animals remains empirical and is a great source of argument and confusion.

Meanwhile considerable developments have taken place in the study

of drugs in man. New techniques of physiological, biochemical and psychological measurement have made assessment of pharmacological action much more precise. Methods used to detect organ damage in disease have been applied to detect minor degrees of organ toxicity caused by drugs e.g. measurements of enzymes released from damaged cells, in blood or urine. The standard of the best clinical research, in terms of design and execution of experiments and the expertise and training of those carrying them out, has improved greatly from the rather haphazard approach of the early days.

These developments argue for a shift in emphasis with fewer and more relevant tests in animals, early entry into man and subsequently free movement back and forth between animal and human studies as the project develops. This approach has the added advantage that the studies are made in the appropriate species and in the right disease. Species differences in response and the very unsatisfactory nature of many animal models of human disease are important limitations in transferring animal data to man.

Although these arguments are scientifically convincing their application faces several important constraints. The most important of these is the attitude of regulatory authorities. If regulatory bodies maintain extremely stringent and time-consuming requirements before a drug can be given to man the number of new compounds brought forward for human study will decline. However, simplification of the regulatory requirements must not be at the price of creating avoidable hazards in man. Regulators and scientists are ultimately responsible to the community in which they work and that community must be reassured about the propriety of a course of action that could be open to uninformed criticism.

In previous years the World Health Organization has issued a number of valuable technical reports on various aspects of drug safety testing and early studies in man. However, many countries have developed their own national technical requirements for drug regulatory purposes. Any revision of international guidelines must consequently be based on effective consultation. Because it is broadly representative of scientific interests in medicine, CIOMS is well placed to arrange these consultations. Indeed at its Ninth Round Table Conference in 1977 on Trends and Prospects in Drug Research and Development, it was recommended that CIOMS should seize the initiative to sponsor an international analysis of legal standards and decision-making processes within national drug regulatory agencies,

and to effect an objective analysis of existing toxicological requirements. WHO has supported CIOMS in this endeavour and has co-sponsored a programme directed to these aims entitled "Drug Development and Use: medical, social and economic implications". It is interesting to note that the Organisation for Economic Co-operation and Development (OECD) is making a similar effort to coordinate international requirements for toxicity testing of pesticides, agricultural and industrial chemicals.

Following a series of consultations with eminent experts having an involvement in these issues, it was decided that the first report emanating from the CIOMS programme should be addressed to "Safety requirements for the first use of new drugs and diagnostic agents in man". The following terms of reference were agreed.

"The procedures necessary to take compounds as efficiently as possible, consistent with safety, through the preclinical stages of their testing and subsequent evaluation in man to the point where potential therapeutic activity is demonstrated".

These terms of reference defined those studies which are sometimes termed Phase I and II A in the United States of America. Thus the recommendations made do not include large scale therapeutic trials or post-marketing surveillance but are confined to studies of human tolerance, dose ranging and early measurements of drug action. Such studies are often initiated in normal volunteers and progress to patients.

The report is addressed to all those who must assume responsibilities connected with early studies of new drugs in man, the pharmaceutical industry, governmental agencies concerned with drug regulation, physicians who undertake early human studies of drugs, members of research-ethics review bodies, etc. However, we hope that it may appeal to a wider audience because the issues are of importance to the whole medical profession and the general public. Drug toxicity often features in news media and in the concerns of individual patients. It is most important that discussions of these issues should be well informed and we hope that this document will be of value to those who help form opinions in the community.

FROM ANIMALS TO MAN

The great majority of research designed to produce new therapeutic agents has its starting point in animal experiments. There are a number of very important examples where a knowledge of disease mechanisms or a hypothesis about the causation of disease led directly to studies in man, e.g. thyroid extract to treat myxoedema, or 1-dopa in the treatment of Parkinson's disease. Most drug studies start from a known biological mechanism (a receptor, enzyme, metabolic intermediate) and involve a collaboration between medicinal chemists and pharmacologists. If the action of a new chemical entity appears to have a potential application in therapy further studies of structure activity relationship, physicochemical characteristics and metabolic disposition will be undertaken to try and optimize these properties. The feedback loop from pharmacologist to chemist is a very important factor in modern drug development. If these findings maintain the initial promise the drug will be submitted to tests for toxicity using both *in vitro* systems and laboratory animals. The tests in animals will include acute and subacute observations at different dose levels. The highest dose levels are intended to cause a toxic effect so that the adverse effects of the drug can be identified. Once these studies have been completed and analysed the sponsor of the drug, usually a pharmaceutical company, will have to take the decision whether or not to take the drug into the human phase of research. To do so normally involves obtaining the approval of the company's own experts, the involved clinical research scientists and their ethics committees and, in some countries, review by a government agency.

The transition from a largely self-contained animal research programme within a pharmaceutical company to human studies in a hospital is complex and raises many issues. The group of experts who wrote this report are all personally concerned with research at this interface between animals and man, industry and medicine. The report and its recommendations reflect their concerns in the early 1980s and the prospects for making drug research, as well as its products, more effective.

The report is arranged in sections dealing with the main topics that must be considered beginning with pharmacology and toxicology and ending with studies in man. The appendices I and II give more details of possible strategies for investigating the pharmacology and toxicology of a new compound and are intended as examples for those who are less familiar with the field.

THE PURPOSE OF TOXICITY TESTING PRIOR TO EARLY ADMINISTRATION OF DRUGS TO MAN

The aim of toxicity testing carried out prior to the early administration of drugs to man is to reject compounds of unacceptable toxicity and to identify potential target organs and tissues for adverse effects of the drug so that in early human studies particular attention can be paid to monitoring these organs and tissues for structural and functional changes (Appendix I). Ideally the circumstances of dose and the duration of administration under which these adverse effects are likely to appear should also be identified. It is important to establish whether toxic effects are reversible or irreversible and whether or not they can be prevented. If the mechanism of a toxic effect can be established predictions to man are likely to be much more accurate.

There are four principal classes of adverse effect to be considered before administration of a new substance to man:

Class I: excess of the principal pharmacodynamic action, due to overdosage or unusual sensitivity.

Class II: effects due to pharmacological actions unrelated to the action involved in the therapeutic use of the drug.

Class III: toxic effects due to the substance or a metabolite resulting in tissue damage which was unpredictable from the known pharmacological actions of the drugs.

Class IV: immunologically mediated and other hypersensitivity reactions (including other rare responses to small doses of unknown cause).

In studying responses in Classes I - III it is essential to determine the nature and shape of the dose-response curve. It is particularly important to establish whether an effect is seen only after exposure to very high doses. Exposure to extremely high doses and/or excessively long periods of administration may result in misleading adverse effects. If a threshold in the dose-response relationship is exceeded or homeostasis is disturbed toxicity may appear that has little relevance to doses in the pharmacological range.

Predictive Value of Current Animal Tests

The position based on current preclinical toxicity testing practice is that relatively few Class III or IV adverse effects first come to light in clinical trials. When such adverse effects in humans occur they nearly

always do so when the drug comes into more widespread and prolonged use.

In the cases of responses in Classes I - III above it is reasonable to expect that animal tests will be useful for making predictions concerning effects that may occur in man. One obvious limitation is that humans can describe subjective sensations that may not produce an easily detected change in the behaviour of animals. Fortunately toxic effects of this kind do not usually cause irreversible changes in man although the symptoms may be very unpleasant. Class IV responses are unlikely to be detected even if specifically sought. Even if an animal model can be found such effects are often not reproducible in other than (possibly rare) susceptible individuals in the target species due to the idiosyncratic nature of the effect.

Many animal studies are based on the use of relatively inbred strains. The experimental results obtained in such animals are more likely to be consistent but the restricted genetic background contrasts with the heterogeneous genetic make-up of humans exposed to the drug. Interspecies differences in pharmacokinetics, metabolism or response, which may be intrinsic or dependent on such functions as diet, also restrict the extrapolations that can be made between species.

The possibility of teratogenic, embryo-toxic or adverse postnatal effects gives rise to considerable concern in studies of new drugs. These can be avoided in early studies by precluding women of child-bearing potential from them. In the case of fertility, reversible, minor effects are of no great concern unless there is an accompanying risk of genetic damage. In our opinion negative results in general toxicity tests and in mutagenicity studies provide an adequate safeguard at this stage.

Virtually the only safeguard against Class IV effects is to look for structural analogies to known sensitisers. An important aspect of safety in early clinical trials is to be on the alert for idiosyncratic reactions.

The importance of interrelating drug response to blood levels in humans and blood and tissue levels in various animal species cannot be overemphasized. Clearly establishing such relationships may not be possible until the drug has been administred to humans and reinvestigated in animals using a “ping-pong” approach to the investigations. However, data on this subject should be obtained as early as possible to enable the toxicity studies to be re-evaluated and complementary animal studies to be performed. An important

parameter in these interspecies comparisons becomes the plasma concentration of free (unbound) drug which is achieved. Often, marked differences in pharmacokinetics occur between man and experimental animals; these must be taken into account both in interpretation of toxicity data already to hand and in planning future work.

For those situations in which formation of significant amounts of *active* metabolite(s) are thought to be likely in man (on the basis of structural and other considerations), the levels of these metabolites must be considered in assessing the relevance of the animal species used for the early and subsequent toxicology and pharmacology studies. It is unreasonable to attempt experiments in more than about a thousand rodents or a hundred other species whereas a drug may be taken by up to 10 million human beings which shows the relative statistical insensitivity of the animal studies. One of our main concerns relating to the predictive value of current animal tests is that potentially useful agents are being rejected because of adverse effects in animal studies that would have no human counterpart under clinical conditions of usage.

Improving the Predictive Efficiency of Animal Testing

Ethical and legal reasons (e.g. risks of liability, the caution of pharmaceutical companies and the inertia of regulatory bodies) seem likely to maintain the same general strategy of toxicity testing as now, but improvement must be possible in its tactics and timing. Every toxicity test will contain a common core of techniques and observations, but additional clinical and laboratory investigations should be employed, focused on the known or predicted properties of the compound under examination. Thus, there should be flexibility in the preclinical test requirements for drugs according to their intended use and nature (e.g. less stringent requirements may be justified for drugs intended for the treatment of cancer than for drugs intended for the treatment of relatively trivial disorders). More important is the need for highly skilled interpretation of toxicity data with flexibility in its application. It is necessary to consider what weight should be attached to a positive or negative result in any particular test in the context of all the available toxicological information, including pharmacokinetic, metabolic and pharmacodynamic results. There is a need for a systematic comparison of data from animal tests and human studies. This might show that some animal tests are more predictive than others, or that alternative methods or tests of shorter

duration and on fewer animals are adequately predictive. There may also be scope for the application of improved statistical analytical techniques. Old methods shown to be of little value should be discarded. The present, largely empirical, methodology of toxicology should not be frozen by regulations but should be allowed to develop and to be modified in the light of advancing scientific knowledge. It is just as necessary that novel methods are not added to requirements until there is adequate proof of their validity and sufficient experience of their use.

Because of the importance of comparative pharmacokinetic information, it is important to obtain information from humans as early as possible, otherwise the conventional series of animal tests will proceed although the observations made may be largely irrelevant to man.

There are examples where requirements peculiar to one regulatory body lead to unnecessary testing with only marginally modified protocols and with waste of resources, time, money and animals (as shown by comparison of the national requirements listed by Adler, Janton and Zbinden, 1981). We believe that there should be full international acceptance of the results of properly conducted experiments.

Toxicological Information Required for Substances to be Given by Special Routes of Administration

In principle, the toxicological information required for the evaluation of human hazard should be relevant to proposed clinical use in terms of the route of administration. The local effect of an agent at the site of its administration must always be examined. Theoretically there may seem to be no need for the systemic toxicological evaluation of topically applied agents which are not absorbed. However, in practice it is rare for none of the dose to be absorbed into the body. Moreover, data relevant to this may not have covered all the circumstances that may occur in clinical practice. Thus abrasion of the skin may result in absorption not seen where the skin is intact, or agents that are not absorbed through the skin may be ingested by accident or because a child licks its skin etc. Hence, some information relevant to systemic toxicity is usually necessary even for locally-acting and non-absorbable agents.

Where substances are given by an enteral route, they are subject to the activity of enzymes (e.g. in the lumen, the gut wall and the

bacterial flora of the gut) which they are not subjected to when administered by a systemic route. Both this and species differences in gut flora need to be borne in mind in the interpretation of toxicological studies in animals.

A fundamental difference between the enteral route and other routes is that the latter may avoid presystemic metabolism in the liver or gut and lead to the exposure of tissues that escape exposure after oral administration. Presystemic metabolism and excretion in the bile is a special problem in rodents where these mechanisms are particularly effective. Despite the use of high doses by mouth or by gavage the tissues of the animal's body, other than the liver, may have not been exposed to appreciable amounts of the drug. Exposure of small laboratory rodents by the inhalation route can also pose methodological difficulties. Moreover the efficiency of the nasal and pharyngeal filtering system may effectively prevent exposure of the lower respiratory tract so that the results in nose-exposed animals may not adequately exclude inhalation hazard for man. In such cases the intravenous route of administration, which ensures that the drug reaches the tissues, may offer advantages.

Intravenous administration, particularly by continuous infusion, is often useful in the investigation of systemic toxicity of drugs intended for parenteral administration. The intrinsic difficulties of the technique are surmountable, with experience. This method avoids the wide swings of concentration that occur with once daily oral dosing.

Compounds with Special Types of Biological Activity

No standard set of tests has gained universal acceptance for drugs of all types, nor would it make good biological sense to try to develop such a standard battery of methods. For agents with particular types of biological activity special kinds of toxicological tests may be needed but these should not be seen necessarily as additions to a basic group of tests. Scientific appraisal, based on knowledge of use, dosage, mode of action etc., should demonstrate the nature of the tests required. Four examples serve to justify this flexibility in approach:

Compounds with very high pharmacological activity. These are highly potent compounds, often with human doses in the microgram range, but there appears to be little justification for treating them in

a special manner. The usual criteria adopted in toxicity tests should apply, the doses used should be multiples of the pharmacologically effective dose or the anticipated human dose although, especially in the case of these compounds, there should be a ceiling set at, perhaps, 100 times this dose for the top dose in toxicity tests. As with many other safety tests, interpretation of the results of tests with such compounds may be complicated by the fact that exaggerated pharmacological actions resulting from doses in excess of the effective dose may produce adverse effects. This points to the crucial importance of having pharmacodynamic profiles over a range of doses for these compounds before embarking on toxicity studies.

Practical difficulties may arise with highly potent compounds in that, since doses will be low, blood concentrations will also be low and so sufficiently sensitive analytical methods for metabolic and pharmacokinetic studies in animals, in toxicity tests and in early human studies may be extremely difficult to develop.

Compounds with high and specific pharmacological activity that are difficult to make and very expensive. It is difficult to synthesize adequate quantities of, for example, peptides to carry out the usual range of toxicity studies. However, economic considerations cannot be allowed to prejudice safety. If there is indeed proven pharmacological specificity, and if carefully designed acute and subacute toxicity studies in animals carried out over a fairly wide dosage range confirm that no effects other than those related to the specific pharmacology are seen, then it would be reasonable to allow cautious short term administration to man without recourse to longer term toxicity studies. If the early human studies were promising, more extensive animal studies would be justified. With compounds of this kind it is important to examine their effects on the appropriate special systems of the body e.g. immune and endocrine systems.

Substances of this type may become more common in therapeutics because of advances in biotechnology. The toxicity and other safety testing of a biotechnological product should be planned on the basis of its chemical and biological composition and resemblance to synthetic or natural substances already in therapeutic use, its pharmacodynamic action and intended use in man. Such compounds should undergo toxicity testing appropriate to a novel molecular entity unless they are shown in all ways to be identical to a substance occuring naturally in the human body.

Compounds that are naturally occurring substances of known biological action. The key point with these compounds is that their biological action must indeed be known. It is quite possible that at higher doses biological actions other than the primary one seen endogenously may be unmasked. These actions should be detected in acute and subacute studies in animals over a range of doses. The other point is that these compounds may well be given by unusual routes of administration as far as the body is concerned, so that the normal feedback mechanisms may not operate and again careful tests for hormonal disfunction and effects on the immune system should be carried out. A distinction should be made between giving physiological doses of such compounds, for example in replacement therapy, and pharmacological doses where unexpected actions may be unmasked. If a specific antagonist exists, it is very useful to know that the toxic effects can be reversed by it. Thus, the fact that a compound is naturally occurring is not sufficient reason for carrying out only minimal animal studies before administration to man. As far as possible, all the actions of the compound should be identified. Here again the most important requirement is for thorough pharmacodynamic studies over a range of doses in appropriate physiological systems backed up by acute and subacute toxicity studies.

Materials of biological origin, e.g. vaccines, pose particularly difficult problems of toxicity testing. The feasibility of detecting adverse effects is likely to be greatly constrained by considerable differences in the response of various species e.g. antigenicity.

Compounds with high but well understood toxicity, e.g. antimetabolites and cytotoxic agents. Each such compound will constitute a special case, as it will only be used in patients (not healthy volunteers) with a serious, possibly terminal condition. The balance of acceptable risk versus possible benefit is different and a higher risk may be justified if there is sufficient potential benefit. However, within the constraints imposed by the properties of the compound toxicity testing should still be done, despite the limited range of doses that can be employed, say with a cytotoxic substance. As an example, in the case of procarbazine it would have been important to have detected inhibition of monoamine oxidase, as well as its antimitotic activity.

In summary, the minimum requirement before a drug should be given to man is a good knowledge of its pharmacodynamic profile supported by some acute and subacute toxicity studies. The precise protocol for these studies will vary according to the nature of the compound.

The above discussion is based on general considerations. An example of the type of tests that might be carried out is given in Appendix II. We emphasize that these serve only as an example and should not be taken as specific recommendations for automatic application in all circumstances.

MUTAGENICITY AND CARCINOGENICITY

Production of malignant tumours by a drug is one of the most feared forms of toxicity. Two types of safety test are used to try to detect it: (i) short term mutagenicity tests and (ii) prolonged *in vivo* exposure to the drug in laboratory animals. The short term tests are relatively inexpensive and quick to carry out but their relevance to the prediction of human cancer risk is limited. Long term animal carcinogenicity tests which cover a large fraction of the lifespan of mice or rats are costly and cause a delay of two years or more in the development of a compound. They overcome some of the difficulties in interpretation associated with *in vitro* tests, but they cannot be extrapolated directly to man under the conditions in which drugs are used in the clinic. Lifespan studies also create problems owing to the high incidence of tumours in controls.

Prediction from Chemical Structure

The ability of experts to predict potential carcinogenic or mutagenic activity from a knowledge of the chemical structure of a compound and its probable pathways of metabolism (e.g. formation of epoxides, N-oxides, etc.) has improved during recent years, although not yet to the point that it can replace the need for laboratory tests.

Chemically reactive, electrophilic, molecules are the main source of carcinogenic risk, but electrophilic activity is only associated with mutagenicity if a covalent bond is formed to DNA. The likelihood of the conversion of an agent to an electrophilic metabolite can often be predicted as can the potential reactivity of metabolites with DNA. Less predictable is whether under *in vivo* conditions an active metabolite will reach the DNA of stem cells and the extent to which the DNA damage can and will be repaired.

Mutagenicity Tests

Short term mutagenicity tests are relevant to (a) mutagenic hazard, (b) carcinogenic hazard and possibly (c) non-specific ‘ageing’ effects. The principles for testing a drug for mutagenicity are the same as those for any ether chemical except that some types of pharmacological activity are necessarily associated with electrophilic activity. For example, the alkylating agents used in cancer chemotherapy are directly mutagenic and metronidazole is able to kill obligate anaerobic microorganisms because they possess nitroreductase activity which converts the drug to an electrophilic

metabolite which is mutagenic. Occasionally anticancer drugs with high carcinogenic potential will have to be examined very carefully when their use in clinical trials for the treatment of cancers in patients with a long prognosis for life is proposed. The risk-benefit ratio is of ethical concern in this case.

The strategy for testing drugs and other agents for mutagenicity is to start with highly sensitive and artificial screening tests. If these give negative results, no further tests may be needed. But if they give positive results, it may be necessary to undertake further tests which are easier to interpret in terms of likely hazard to man.

The following is an example of a group of tests that might be useful.

(1) A test designed to demonstrate the induction of point mutations (base pair substitution and frame shift mutations) in established bacterial tests systems such as *Salmonella typhimuiium, Escherichia coli* or *Bacillus subtilis.* The tests are conducted with and without appropriate metabolic activation systems.

(2) A test designed to demonstrate the production of chromosomal damage in appropriate mammalian cells grown *in vitro* with and without the use of appropriate metabolic activation systems.

(3) The induction of mutations in mammalian cells grown *in vitro.*

or

Tests designed to induce recessive lethals in *Drosophila melanogaster*

(4) A test designed to demonstrate the induction of chromosomal damage in the intact animal using either the micronucleus test or, preferably, the metaphase analysis of bone marrow or other proliferative cells.

or

The induction of germ cell damage as demonstrated by the dominant-lethal test in the rat or mouse.

Unfortunately there is still considerable disagreement amongst experts from different countries concerning the optimal testing strategy.

Reliability of *in vitro* Tests

In vitro mutagenicity test systems may give falsely negative results because enzymes necessary for the conversion of a drug to an elec-

trophilic active metabolite are not present. In the case of both the bacterial and mammalian cell *in vitro* studies it is normal practice to include tests in the presence of enzymes derived from mammalian liver (e.g. S-9 fraction derived from rat liver microsomes). However, in a particular instance the appropriate drug-metabolizing enzyme may be absent or physiological factors that control the activity of these enzymes may not operate under *in vitro* conditions. Of particular importance is the absence from *in vitro* test systems of enzymes produced by the intestinal wall or by gut microflora which are not present in the liver. Under *in vivo* conditions these may act either directly oh orally-administered drugs or on a drug or conjugate that is excreted in the bile. Theoretically either false positive or false negative results may be obtained in *in vitro* tests for these reasons. A very significant source of false positive results may be the absence from *in vitro* tests of systems that normally inactivate electrophilic molecules (e.g. glutathione).

It is clear from the above discussion that the results of *in vivo* mutagenicity tests must generally be regarded as taking precedence over those of *in vitro* tests. However there is still considerable disagreement amongst experts concerning the validation of the existing range of *in vivo* tests.

Value of Mutagenicity Tests for the Prediction of Carcinogenicity and the Reliability of *in vivo* Tests for Carcinogenicity

Mutagenicity tests are considered to be relevant to the prediction of carcinogenicity on theoretical genetic grounds and the empirical association between the two properties. However, non-genetic mechanisms are also important in the genesis of tumours, and current mutagenicity tests have been developed because of their response to known potent carcinogens, rather than from the results obtained with a range of substances with weak or no oncogenic potential.

Their inadequate theoretical basis and limited practical validation means that there is need for considerable caution in interpreting the results of mutagenicity testing, particularly if only a single *in vitro* method has been used.

There is a growing view that non-genetic mechanisms may be more important than genetic ones in the causation of cancer. In the mammalian body there may be numerous cells that have already been ‘initiated’ by sunlight and other ionizing radiation and whether or not cancer develops may depend on exposure to promoters which

facilitate tumour development from initiated cells. This burden appears to be greater than that from drugs (Doll and Peto, 1981). It is therefore arguable that some potential for DNA damage need not be a bar to development of a drug for a serious disease.

Reliability of Long-term Tests for Carcinogenicity in Animals

It is often assumed that doubts about possible carcinogenicity can be resolved by long-term studies in laboratory animals. Unfortunately this is untrue, because of the many factors capable of giving false positive and false negative results in the prediction of cancer risk for man. False positive results may be obtained because of the administration of excessively high doses of the test substance that bring entirely unphysiological mechanisms into play, and the abnormal states of overfeeding, celibacy and induced endocrine disorders found in laboratory animals (Roe, 1981). False negative results may ensue from species differences in pharmacokinetics, drug metabolism and responsiveness, and the statistical insensitivity even of an experiment involving a thousand rodents.

Several drugs that have come under suspicion of carcinogenicity in recent years have done so because very high doses have increased the incidence of one or more neoplasms of endocrine glands or other hormone dependent tissues. An illustrative example concerns certain neuroleptic drugs which predispose to islet cell tumours of the pancreas in rats. In the same studies, control females were prone to an increased incidence of pituitary and mammary tumours, possibly because their serum levels of prolactin were raised by prolonged overfeeding. It is not known whether high doses of neuroleptics would affect the pancreatic islets of rats in a more normal endocrine state.

These findings emphasize the need for carcinogenicity tests to be interpreted cautiously in the light of all the information available about the properties of the test compound and the characteristics of the test system.

Relative Roles of Short-term Mutagenicity Tests and Long-term *in vivo* Animal Tests

Mutagenicity tests are coming to be regarded as screens to decide whether *in vivo* carcinogenicity tests are necessary. This view must be

tempered by the risk that both techniques may give false positive and false negative results. A more reasonable approach is to regard the tests as complementary, the former being hypersensitive for carcinogens acting by alkylation of DNA, while long-term *in vivo* studies are geared to the detection of carcinogenicity by both genetic and non-genetic mechanisms. A policy of relying upon screening tests prior to early human studies is reasonable in the present state of knowledge. Further work will be needed to determine the best choice between bacterial test systems and *in vitro* and *in vivo* methods using mammalian cells. In the long run the *in vivo* systems seem preferable as they leave intact the defence and repair systems of the cell.

The risks of either type of carcinogenic action are probably minute in short-term human studies.

Problems with Compounds that have a Well-established Endocrine Action

Natural hormones determine which genetically coded information shall be expressed but they do not alter DNA. However, hormones may also act as embryonic organizers and thereby give rise to structural abnormalities (e.g. vaginal and cervical abnormalities in female progeny of women and in animals given massive doses of oestrogens, natural or synthetic, during pregnancy). The presence of these abnormalities may predispose to development of cancer. Also exposure to hormones, especially to prolonged or high exposure, may upset homeostasis with consequential overgrowth and eventual neoplasia of endocrine glands or hormone-dependent tissues. Very high doses of hormones may saturate the ability of the liver to metabolize and detoxify them so that liver changes, which may proceed to neoplasia, ensue. These three mechanisms must be borne in mind when evaluating the potential carcinogenicity of hormones. In addition a synthetic hormone may theoretically not only exhibit hormonal effects but also may be capable of conversion to electrophilic metabolites that carry a risk of mutagenicity. For this reason it is appropriate to screen synthetic hormones for mutagenicity.

In the case of hormones, it is especially likely that thresholds exist with respect to certain of their effects. For this reason the concept that they should be tested for carcinogenicity by giving them in maximum tolerated doses is wrong. Tests for carcinogenicity in animals

should aim to simulate the hormonal status of humans given the drug not to produce a near fatal alteration of hormonal status. The problem is compounded by the abnormal endocrine status of laboratory animals used in very prolonged tests. For example, laboratory rats have a high incidence of prolactinomas of the pituitary with circulating prolactin levels 10-20 times normal (Roe, 1981). This is a very unsatisfactory background against which to evaluate carcinogenic effects whose expression may be modified by hormonal factors. There is an urgent need for research on methods of maintaining laboratory animals in normal hormonal status for a large fraction of their life span.

Requirements for Phase I and Early Phase II Clinical Trials

As an example of the possible place of mutagenicity testing in the early development of a drug, as distinct from the methods that may be appropriate before full marketing, we believe that bacterial mutagenicity tests should be carried out before a Phase I clinical trial. An unequivocal positive result would prevent work in man until the mechanism of the action or its consequences had been shown to be irrelevant to him e.g. by demonstrating that the effect was due to a metabolic process that was absent from man. We are concerned that a potentially valuable new compound should not be lost solely on the results of the bacterial tests, either because of a regulatory judgement or a management decision in industry. If a compound is confirmed to be a mutagen in the now standard bacterial strains selected for their sensitivity and disablement of normal repair systems, it is important to try to establish the mechanism. The activity of the compound in other types of mutagenicity test should be examined, namely those demonstrating point mutations in mammalian cells and those for detecting cytogenetic lesions, especially *in vivo.* Only if the overall pattern of these data were to suggest a risk to man, should there be a bar to Phase I trials. Even then these tests should not rule out human studies of a new drug which offered hope in the management of a serious condition without effective alternative therapy. Guidelines on mutagenicity testing should be formulated and interpreted cautiously so that all the information available about the biological properties of the compound, the intended use and the behaviour of the test systems can be taken into account.

ETHICAL ISSUES ASSOCIATED WITH ANIMAL EXPERIMENTATION DURING DRUG DEVELOPMENT

Unnecessary animal experimentation is properly regarded as unethical. However, in relation to the development of drugs, the distinction between "necessary" and "unnecessary" may be difficult. In future the prediction of activity on the basis of a knowledge of molecular biology may play an important role but this point is still far off. Tests using animals to assess both pharmacology and toxicology will continue to be essential, for the foreseeable future, if new drugs are to be developed.

There is some scope for reducing the level of animal experimentation in relation to safety evaluation. In this connexion the following possibilities were identified:-

i) It is important to establish the acute toxicity of a new agent and the principal targets for its toxic action. However, it may not be necessary to know its LD_{50} with great precision.

ii) Differences in requirements of different regulatory bodies can lead to unnecessary repetition of animal experiments.

iii) In some instances, animal safety tests, whose necessity is arguable, are required by regulatory bodies in relation to new formulations of established drugs synthesized by a standard process.

iv) There may be a point at which animal experimentation in relation to the development of a drug which closely resembles an existing one could be deemed unethical. However, a supposed 'me too' drug may be found to offer more substantial advantages than expected and it may also have a different profile of toxicity.

It was not within the remit of the Group to give detailed consideration to possible solutions to these problems, but they recognized that public concern exists about them. On the other hand the need for new medicines to relieve human suffering is great and it would be wrong not to recognize that extensive animal experimentation is an unavoidable component of such research for the foreseeable future. The Council for International Organizations of Medical Sciences (CIOMS) is undertaking an international study on these problems with the aim of preparing "Guiding principles for biomedical research involving animals".

PHARMACOKINETICS AND DRUG METABOLISM

Information on drug pharmacokinetics and metabolism (biotransformation) potentially provides a more useful basis than administered dose for characterizing the relationship between the concentration of drug reaching the target organ(s) and the intensity and duration of the drug's pharmacological and toxicological effects.

Pharmacokinetics and Drug Metabolism Data in Animals which is of Particular Relevance to Early Studies of a Drug in Man.

Under the conditions used (species, sex, strain and age of animal, dose level, route of administration, drug formulation and purity, etc.) for pharmacology and toxicology studies, the following characteristics of the drug's 'fate' should be established:-

a) The rate and extent of drug absorption.

b) The level of drug achieved in the systemic circulation, its rate of attainment and persistence and its relationship to dose, pharmacological and toxicological effects.

c) The routes and rates of excretion of the parent (i.e. unmetabolized) and total drug.

d) The possible accumulation and persistence of drug related material in particular organs. (Evidence of this type may indicate the need for more detailed toxicological investigation of the organs concerned).

Examination of the effects of single and multiple doses of the drug are usually required. Detailed information on the drug's biotransformation products although of interest is seldom essential.

Situations in which some animal drug metabolism and pharmacokinetic data may be important. Animal drug metabolism and pharmacokinetic data are especially important when there is greater than usual uncertainty about how to extrapolate animal pharmacology and/or toxicology data to man. This is most likely to be necessary in the following situations:-

a) The dose is not reproducibly related to pharmacological and/or toxicological effects in one or more animal species.

b) Marked species, sex or other differences in the pharmacological and/or toxicological properties of the drug are observed.

c) The therapeutic index is low. The dose response relationship in animals is very steep and/or non-linear changes significantly between single and multiple dosing. Data of this kind may indicate saturation of protein binding, a particular drug metabolizing enzyme and/or an active transport process.

d) The therapeutic effect of the drug is likely to be difficult to quantify in short-term human studies or its onset is slow.

e) Pharmacological and/or toxicological properties of the drug and/or structural considerations indicate that it may mediate much or all of its effects through an active metabolite(s).

f) Structural or other considerations indicate that the drug may be metabolized via a metabolic reaction in which marked genetic variations are known to occur in man e.g. N-acetylation.

g) A new combined formulation of drugs which individually have well-established pharmacological and toxicological properties is being considered. In this case it should be established that one drug does not interfere significantly with the pharmacokinetics and drug metabolism of the other(s). Negative evidence of this kind would minimize the need for additional toxicological studies on the combined formulation.

h) For deuterated analogues of drugs with well-established pharmacological and toxicological properties, identification of the changes resulting from deuteration on the drug's pharmacokinetics and metabolism may provide the basis for decision on whether additional animal toxicological studies are needed on the new drug.

These situations are most likely to occur with highly lipophilic compounds, particularly when they are given in large doses at which saturation of one or more routes of metabolism, transport or binding may occur.

Detailed studies on the nature of drug metabolites are generally unnecessary except in situation (e) above.

Type of drug for which relatively limited animal drug metabolism and pharmacokinetic data are likely to be needed.

a) A major reformulation of a drug is involved for which there is extensive experience in man with other formulations.

b) The drug is very polar (i.e. one which is unlikely to be persistent or extensively metabolized) and has well-established counterparts for which there is human experience.

c) The drug under consideration has similar pharmacological and acute and subchronic toxicological properties which are linearly related to dose over a relevant, wide dose range in several animal species.

d) A single dose of drug (non-radiolabelled tracer dose) is given at levels well below those producing a biological effect in animals. (NB: The relevance of such a study to the situation at higher doses may be questionable).

e) Drugs likely to be given to man in single doses.

Radiolabelled drugs: situations in which some animal drug metabolism and pharmacokinetic data are essential. In the case of a radiolabelled drug consideration must be given to possible radiation hazard as well as the intrinsic toxicity of the drug itself. Fortunately there is a large body of knowledge regarding radiation hazards. It is well established that the extent of tissue damage is dependent on the nature and energy of the emitted particle, the concentration of isotope achieved, the duration of tissue exposure, the distance between the radioisotopic drug molecules and cell target(s) and the nature of the cells exposed. Rapidly dividing cells, sensory cells and slowly repairing cells are especially vulnerable.
Before embarking on studies with radiolabelled drugs the clinical pharmacologist requires assurance that:

a) the site of labelling is a chemically and metabolically stable one, i.e. the label is unlikely to be incorporated significantly into intermediary metabolism pathway;

b) the label is effectively cleared from the body; and

c) the label does not concentrate and persist at specific tissue sites and in particular that it does not concentrate and persist in particularly vulnerable tissues e.g. retina, bone marrow, central nervous system (CNS), ovary or testis.

In many cases sequential studies of tissue distribution (e.g. autoradiography) in small animals are an adequate means of obtaining this information. Ideally pigmented animals should be used for

such a study in order to allow for the possibility that drug related material may be localized on melanin. If significant accumulation and persistence of the radio-isotope in an organ is observed a parallel study should be embarked on in which the organ is isolated and the radioisotope concentration determined quantitatively. Information on routes and rate of excretion may also be needed in additional species, if there is reason to believe that major differences in excretion routes are likely between the species used in toxicity testing and man.

Additional Uses of Drug Pharmacokinetics and Metabolism Data in Animals

Although seldom necessary before early investigations of a drug in man are carried out, more detailed drug pharmacokinetics and drug metabolism studies in animals may also provide important information on the following:-

a) The rate limiting factors for termination of drug action over an appropriate dose range.

b) Any active metabolites which may be formed and the assessment of their contribution to the overall biological properties of the drug, relevant both to drug safety and the development of further therapeutic agents.

c) Rationalization of species, strain, age, sex, etc. differences in the biological effects of the drug or unexpected dose response relationships.

d) The induction, activation, inhibition, non-specific protein binding etc. properties of the drug after single and multiple doses.

e) Development of treatment for overdosage and development of antidotes.

f) Identification of situations in which particular individuals (for genetic, disease or other reasons) may be especially vulnerable or non-responsive to the biological effects of the drug.

g) Means of sparing precious drug material.

Use of Drug Pharmacokinetic and Metabolism Studies in Man

In the early stages of drug investigation in man the following features of its pharmacokinetics and metabolism should be established:-

a) The relationship between administered dose and systemic blood levels with time (this provides information on the amount and rate of absorption and/or first pass metabolism, the drug's half-life(s) and volume of distribution and the possible dose dependency of this).

b) The extent of interindividual variation in a). (It has to be accepted that this will almost certainly miss variations due to a low frequency allele in a genetic polymorphism in the population).

c) The steady state kinetics of the drug (to detect possible drug accumulation and altered drug biotransformation with time).

d) The rate and route of clearance of drug from the body.

e) The relationship of the concentration of drug (and where possible metabolites) in biological fluids to the pharmacological actions and other biological effects. (This information is important in order to establish the relevance of the animal pharmacology and toxicology data to man, and to enable the continued clinical investigation of the drug).

PHARMACOLOGICAL ACTION: THE LINK BETWEEN ANIMALS AND MAN

A drug is a molecule which produces effects on living tissue which are termed pharmacological effects. In medical practice if these effects have a favourable effect upon a disease process, they are regarded as being therapeutic, while if it is adverse, they are termed toxic. Observation of an adverse or toxic effect when a drug is used for one purpose sometimes leads to a new therapeutic application in another. The antidiabetic and diuretic properties of the sulfonamides are one of the best known examples.

One of the main problems of preclinical drug assessment is to understand the pharmacology of the compound to the point at which a judgement can be made about the likely uses of that type of action in a specified disease process. As pharmacological actions can usually be reproduced in different species including man they are particularly important in making predictions for early human studies.

General Pharmacology

Good quality general pharmacology in animals is essential to the assessment of the safety and prediction of the likely outcome of early clinical trials. The majority of the adverse effects likely to arise during early human studies are directly related to the pharmacological action upon which the therapeutic use is based.

The pharmacological profile of a drug determines, to a large extent, the preclinical pharmacological and toxicological investigations necessary prior to early clinical studies. In addition to detailed studies of the specific pharmacodynamic activity of a candidate drug, the nature of which will be determined by the particular effect for which it has been developed, it is important to investigate the general pharmacological properties of the substance prior to its administration to man. Knowledge of general effects will help to demonstrate the probable safety in use. The nature and extent of the general studies is determined by the scope of the specific investigations which they complement.

General pharmacological screening for safety mainly relies on classical methods, which permit detection of broad classes of activity, rather than precise delineation of actions and mechanisms. Examples of the types of activity sought are outlined in Appendix 2. The methods employed will depend upon the experience and preferences of the individual experimenter, as use of specific techni-

ques is less important than ensuring that broad classes of activity which affect vital functions have been investigated.

It is important to examine the actions of a wide range of doses, and to relate them to the dose producing the desired effect. It is also necessary to show whether effects change on repeated dosing (to exclude cumulation, potentiation or tachyphylaxis) and for compounds producing certain types of action, particularly in the central nervous and cardiovascular system, to exclude withdrawal or rebound phenomena (e.g. opiate addiction, excessive sympathetic responses after withdrawal of drugs such as clonidine or beta-adrenergic blockers).

Also of concern are those safety hazards specifically related to pharmacology of the central nervous system (CNS). During the course of preclinical pharmacological and toxicological studies careful attention should be paid to gross behavioural changes. Further scientific work is needed to investigate the relationship between animal behavioural changes seen in these studies and CNS symptoms during early clinical studies. In our present state of knowledge preclinical testing will miss many problems caused by CNS symptoms in man, e.g. lightheadedness, paraesthaesiae, depression, tiredness, depersonalization, bad dreams, etc. In rodents symptoms, such as nausea and vomiting cannot be detected. Indeed it is with symptoms of this type that preclinical toxicology has been shown not to match adverse effects observed in clinical trials (Fletcher, 1978).

Pharmacological studies should include some measurements made after prolonged periods of drug administration and not just single doses. Subacute pharmacological studies may have greater predictive value than high dose toxicity studies.

Preclinical and clinical toxic hazards related to pharmacological actions can be considered in similar categories.

CLASS I Toxic effects which are directly related to the main pharmacological action. These are dose related effects. If a greater than expected amount of the drug reaches its site of action, or the tissues are unusually sensitive to a normal amount, toxicity may result. Examples include:

a) Warfarin producing haemorrhage.
b) An anxiolytic benzodiazepine producing coma.
c) A positive inotropic agent producing myocardial microhaemorrhages.

Testing for Class I toxic effects is relatively simple and if properly and thoughtfully done, the standard procedures are adequate. Difficulties arise from differences between animals and man in respect of the pharmacokinetics of the drug and sensitivity to its effects. These problems can be partly overcome by intelligent interpretation of the general preclinical pharmacology of the compound backed up by measurements of the concentrations at which these effects occur.

CLASS II: Effects not related to the pharmacological action through which the therapeutic effect is mediated. In this category, (which is not always easy to distinguish from Class I), the pharmacological effect producing toxicity is different from that responsible for the therapeutic effect. It is useful to know how the position of the dose response curve for the Class I effect relates to that of Class II as this gives some idea of the likelihood of their occurence at therapeutic doses.
Examples (some with the aid of hindsight) of Class II effects where the clinician might wish for specific toxicological tests are:

a) The extent of penetration of the blood/brain barrier by a new penicillin and its epileptogenic potential.

b) The degree of alpha-adrenergic blockade produced by a phenothiazine which is relevant to the risk of orthostatic hypotension during clinical use.

c) The anticholinergic effects of a tricyclic antidepressant drug which causes predictable side-effects.

There are certain toxic effects which are very difficult to predict by preclinical toxicological testing and, inevitably, these cause much concern to clinical investigators.

Long-term effects. Some pharmacological effects which may cause toxicity only become manifest clinically during prolonged dosing. An example is the cochlea damage caused by an aminoglycoside (although very high doses can cause a more rapid onset). Another is retinal damage caused by chloroquine. Detection of damage to special sense organs produced by drugs is a difficult problem in its own right and one in which the currently used tests such as the "behavioural startle" response to loud noise are not sufficiently sensitive.

Pharmacogenic problems

Inherited pharmacokinetic differences in man and their safety implications in early clinical trials can be of importance and will depend upon knowledge of likely metabolic routes. This is one reason for caution when increasing the dose during early clinical studies. One method of minimizing the problem is to use the same volunteers through each dose level, but this only postpones the problem to a later stage of the study. An example of this type of reactions is hypotension caused by debrisoquine in a normal volunteer who was unable to hydroxylate it.

Hypersensitivity reactions ("Allergy"). These are amongst the most common of adverse effects in therapeutic use of drugs in man. They cannot be predicted from a knowledge of the pharmacological action of the drug nor are toxicity tests in animals of much value in this regard. Fortunately they are very rare in early human studies, probably because the number of doses given is insufficient to produce sensitization. Sensitization might be a problem if a group of volunteers were being exposed to a number of related compounds which caused crossed sensitization e.g. different semisynthetic penicillins.

How Far do Present Procedures Safeguard Subjects against these Problems during Early Trials?

It is necessary to match up the requirements in preclinical toxicology with the adverse effects that may occur in man. Generally speaking Classes I and II actions (see toxicity tests page 9) should be covered by:

i) a rough quantitative assessment of acute toxicity;

ii) good quality general pharmacology;

iii) animal pharmacokinetic data to make the general pharmacology and toxicology relevant to proposed clinical trial; and

iv) general toxicology of a dose and duration related to the proposed therapeutic dose, suspected therapeutic/toxic ratio, and duration of the proposed clinical trial.

While these generalizations would probably command broad agreement, important details such as the number and type of species, man ner of carrying out the tests and their interpretation are often highly controversial.

Drug induced impairment of fertility should not be a problem in early clinical trials, if gonadal histology is normal in toxicological testing over 28 days in animals. Proof that this is not so is difficult to come by. If women of child-bearing potential are excluded from Phase 1 trials, there would seem to be no need for teratology testing. If it was essential to administer the drug to women of child-bearing potential teratology tests would be necessary.

Although the risk of carcinogenicity must be very small for short term administration of drugs during early clinical trials, the possibility cannot be completely dismissed. Some potent carcinogens such as nitrosamines can cause tumours in animals after a single dose. Although full-scale animal carcinogenicity testing for short-term clinical trials is generally not indicated, there is a widely held opinion that mutagenicity testing in bacteria provides some safeguard. The number and types of mutagenicity tests to be applied and their interpretation are controversial (see page 23). The proposed use and the nature of the drug must be taken into account. If the drug was intended only for short-term administration, e.g. a parenteral antibiotic or an intravenous antiarrhythmic, there would not be much concern about a weakly positive mutagenicity test. A non-steroidal anti-inflammatory agent or a hypotensive/3-adrenoceptor blocking agent with positive mutagenicity tests would be another matter, because a patient might take it daily for many years. An alkylating agent for use in the chemotherapy of neoplastic disease would be expected to be mutagenic as part of its pharmacological action. However, as the survival of patients with certain types of cancer, e.g. lymphomas, improves the mutagenic potential of alternative forms of treatment may become an issue.

Quality of the drug material. Chemical purity and the nature and amount of any residues of the synthetic process are important. The clinical investigator needs to know that the substance that will be administered to man is essentially identical to the one used to study its pharmacology and toxicology. The exact formulation used in early trials is less important and very early administrations are often done with solutions in water to avoid problems of bioavailability. The number of products of biological origin seems destined to increase with the rise of biotechnology. These substances create special problems in analysis and standardization but improvements in analytical methods should be adequate to cope with them.

EARLY HUMAN STUDIES

Objectives

The approach to human studies must be on a high scientific level, comparable to that of the preclinical studies. Studies that are not well designed and carefully carried out are unethical. The following are the major objectives of early human studies.

a) To demonstrate a pharmacological action in man which is likely to be useful in the treatment of specific diseases.

b) To characterize the dose (concentration) response curve with special emphasis on interindividual variability and margin of safety.

c) To devise dosage schedules to be used in the continued clinical evaluation of the drug.

d) To devise and validate methods for monitoring subjective and objective drug response in these later phases of drug evaluation.

Two stages of early clinical trials can be defined.

Stage 1: early, searching, heavily monitored clinical-pharmacological studies in limited numbers of subjects, often normal volunteers. These will cover observations of human tolerance, short-term safety and early dose ranging.

Stage 2: studies to develop further the clinical data generated in Stage 1; including early clinical studies and further studies of the mechanism of action and safety. These studies should provide the basis for the large scale clinical trials which must precede marketing.

Choice of Subjects

During the past decade there has been increasing emphasis on the use of healthy young male volunteers for initial drug studies in man. Individuals who are young and healthy are unlikely to suffer a sudden deterioration of health for reasons unrelated to the administration of the drug under study. This reduces the number of adverse effects requiring investigation and makes it easier to define the cause. Because the risk of serious illness or death in healthy people can be calculated, it is possible to obtain commercial insurance for normal volunteers but it is very difficult to do so for patients. Although females of child-bearing potential are not usually included in the early stages of

a study, once satisfactory teratology results are available they can be. It is standard practice to exclude from clinical trials women who may be pregnant.

There are some disadvantages in using normal subjects. Although many types of pharmacological action can be measured in them, generally speaking, therapeutic effects cannot. Thus it might be possible to demonstrate a hypnotic effect of a minor tranquiliser in normal subjects but the anxiolytic effect could only be demonstrated in anxious patients. It is common practice to progress from studies in normal subjects to patients with mild to moderate forms of the disease that the drug is intended to treat. Here again the aim is to minimize the number of events which are unrelated to the administration of the drug by excluding seriously ill patients.

There are instances, notably in cancer chemotherapy, in which it is inappropriate to use normal subjects or patients with less severe forms of the disease. Thus, the decision about the choice of the most appropriate subjects for an early study should be based on the nature of the expected action, rather than any general rule of procedure.

Duration of Early Human Studies

There are all sorts of drugs for all sorts of conditions. In therapeutic usage they range from single dose administration (e.g. intravenously administered antiarrhythmics) to drugs used only chronically (e.g. a drug which modifies immune mechanisms in rheumatoid arthritis). It is difficult, therefore, to be dogmatic about how long a drug may have to be given to demonstrate an action relevant to its therapeutic effect. The more discriminating our methods of evaluating drug action in man, the earlier we may be able to pick up relevant actions in drugs used in the treatment of chronic conditions. Because of these differences in the way that drugs must be given in the early stages of clinical development, according to the pharmacological nature of the drug and its therapeutic actions, there is need to define the length of exposure required to reach a stage at which a judgement can be reached that a drug has potential therapeutic usefulness and may be reasonably safe.

Early tolerance and dose ranging observations are always made with single doses and these are normally extended to 8- or 15-day observations for drugs that are intended for chronic use. These studies can give a considerable amount of information about potential

therapeutic applications. Drugs in this category include those whose pharmacological action can be translated fairly directly into a therapeutic effect, eg: antiarrhythmics, positive inotropic agents, hypotensive agents, analgesics and antibiotics for acute infections.

Other drugs do *not* fall into this category. In this case studies in normal volunteers will provide information about how well human subjects tolerate doses of the drug and about its pharmacokinetic properties, but will not cast much light upon its potential in therapeutics. Examples include many anti-inflammatory agents, antidepressants, neuroleptics, hypolipidaemic agents, prophlyactics for manic-depressive disease, some anticonvulsants and cytotoxics. This limitation applies to any proposed drug treatment for which the pharmacological action is either not easily detectable in a normal man *or* for which the link between the pharmacological action and therapeutic effect is indirect. Early clinical studies to show whether a drug is likely to be useful and safe in therapeutics may last for longer periods, perhaps up to several weeks. The preclinical toxicity tests will have to be adjusted to take into account this longer period of human exposure in the early phase.

Protection of Subjects

The fundamental ethical principles that guide the conduct of biomedical research involving human subjects are embodied in the Declaration of Helsinki of the World Medical Association (1975) and the Proposed International Guidelines for Biomedical Research Involving Human Subjects of the Council for International Organizations of Medical Sciences (1982).

The first concern of clinical pharmacologists and other physicians, who carry out early drug studies in man, must be with the health and safety of normal people and patients who agree to participate in the research as subjects. The following points should be covered in the procedure used:-

a) Review of the protocol of the project by an independent Ethical Committee.

b) A clinical history and physical examination of the subject prior to the study.

c) Safety tests which normally include an electrocardiogram, blood count, urine analysis and biochemical tests of liver and kidney function. These should be repeated at an appropriate interval after drug administration, often 48 hours after the study.

d) In the case of normal volunteers, who may take part in studies on many occasions, a record should be kept of drug exposure and total volumes of blood taken. It is good practice to place a limit on the number of times a volunteer may take part in studies and the total volume of blood that may be taken over a defined time.

e) Provision of insurance to compensate the subject if he or she suffers harm caused by the drug.

Insurance cover is still a problem and usage varies widely in different countries. Commercial insurance cover is available for normal volunteers in some countries. Large pharmaceutical companies usually provide cover for early studies in man, but the terms of this cover are often not well defined. The situation with patients who have a disease that might well prove fatal during the course of a study is particularly difficult (Ciba Foundation, 1980). It is clearly impractical and inequitable to pay compensation to every patient who dies of his disease during a research project designed to improve its treatment. On the other hand, proof of a causal connexion between drug administration and a particular complication is often difficult and sometimes impossible (e.g. a stroke in a woman on the contraceptive pill).

Facilities and Methodology

Every clinical research project should have a proper written protocol which defines the objectives, study design, methods of measurement and safety procedures. There will normally be specially prepared forms for recording the results as they are obtained.

The studies should take place in a fully equipped laboratory which has all the necessary measuring equipment, resuscitation facilities and staff trained to use them. If these studies take place in a well equipped general hospital, it is an added safeguard, because trained staff such as anaesthetists and intensive care facilities will be available.

Methods of Measuring Drug Action

One of the most hopeful trends in clinical pharmacology has been the improvement in the ability to measure drug effects reasonably accurately in both normal volunteers and patients with disease. The types of measurements made can be divided into three broad categories:

Physiological measurement. Examples of measurements of this type include blood pressure, heart rate, cardiac contractility, airflow into the lungs, skeletal muscle power, etc. In the early days of the development of human physiology many of these measurements were made using invasive techniques that involved cannulization of blood vessels, intubation of airways and so on. Pressure against invasive research techniques in the middle 1960s gave a temporary setback to work of this type but this has largely been compensated for by recent improvements in non-invasive methods. Examples include the use of ultrasonic techniques to measure the velocity of circumferential-fibre shortening in the left ventricle and the velocity of flow in the aortic arch, long-term monitoring of the electrocardiogram using portable tape recorders and radioisotope techniques for measuring blood flow through the brain and other tissues. The availability of non-invasive methods has also made it possible to undertake long-term studies of conditions such as heart failure and cardiac arrhythmia which are essential for judging the therapeutic response to cardiovascular drugs.

Although drugs with a potent cardiovascular action must be considered som of the most hazardous agents in early drug studies in man, it has been possible to measure effects of hypotensive agents and membrane-active agents in normal volunteers. It would be fair to say that some animal measurements of physiological effects are only just beginning to catch up with the accuracy of human measurement.

Biochemical measurements of drug action. Drugs exert their effects by interfering with the physiological control of the human body by inhibiting or stimulating receptors, inhibiting enzymes, decreasing excitability of membranes and so on. The measurement of drug action in man by studying the biochemical rather than the physiological effects is a rapidly growing and important area. There are many examples, such as: assessment of the effect of a sympathetic inhibitory agent by changes in concentration of noradrenaline in plasma or its metabolites in urine; assessment of the effects of non-steroidal anti-inflammatory drugs by measurement of changes in prostaglandin synthesis; measurement of the effects of angiotensin-converting enzyme inhibitors by assay of angiotensin I and II in plasma. Biochemical measurements of drug action in man suffer from only one important limitation, the difficulty of localizing the effect to a particular organ or system. This problem is most acute with the

human brain. The inaccessibility of cerebrospinal fluid, except occasionally in the lumbas theca makes it difficult to obtain a fluid to analyse which will give a reasonable measure of drug effects upon the brain. Thus physiological measurements give a superior localization of drug action, but biochemical measurements are essential in evaluating general effects such as inhibition of enzymes. Biochemical measurements, usually of enzyme concentrations in plasma are also most useful in studying drugs designed to prevent tissue necrosis (e.g. after myocardial infarction) and to evaluate drug-induced injury to organs such as the liver.

Psychological measurements. Evidently psychopharmacological measurements are essential for those drugs used in conditions such as anxiety, depression and schizophrenia where a psychodynamic effect is the main objective of treatment. They are also most important in the assessment of drug side-effects many of which have subjective rather than objective manifestations. One of the most important differences between human and animal pharmacology is the difficulty of detecting minor behavioural disturbances in animals, which might yet pose a very severe limitation to the use of a drug in man. The use of questionnaires, visual analogue scales and rating scales has made it possible to measure almost every kind of subjective sensation experienced by man. Both the precision and accuracy of such measurements are less than in the case of physiological and biochemical measurement and there are problems of standardization of measurements but they are nonetheless very useful. Rating scales and questionnaires need to be carefully validated and there may be linguistic problems in transferring them between different countries.

Implications of improvements in measurement techniques. The greater sensitivity and specificity of measurements of drug action in man makes it credible to evaluate the pharmacological action of a new drug in relatively small groups of patients or volunteers. This greatly simplifies the cost and time that has to be expended in demonstrating that a new drug has a pharmacodynamic effect in man and, since the number of individuals exposed is small and they are very closely observed, the preceding safety tests in animals can be somewhat abbreviated. Unfortunately the translation between pharmacodynamic action and therapeutic effect still requires extensive clinical trials in diseased patients. For example a human volunteer

study might demonstrate that a new drug inhibited the neuronal uptake of noradrenaline or inhibited the enzyme monoamine oxidase, but to prove an antidepressant activity would still require a controlled trial in depressed patients. However the compound with the most favourable profile of pharmacodynamics and pharmacokinetics could be selected on the basis of comparative studies in healthy volunteers.

Nature of Serious Reaction in Clinical Trials and their Frequency

Serious adverse drug reactions in normal volunteer studies are very rare indeed. In evidence to a Congressional Committee in the United States, Dr Frances Kelsey (1981) stated that only two deaths were known to the Food & Drug Administration in over 150 000 indicidual studies. In one case the subject had concealed relevant medical information from the investigator, and a causal connexion had not been proved in the other. She concluded that early drug studies were very safe. Over the past five years the clinical pharmacology unit of a large pharmaceutical company has undertaken studies involving around 1000 male volunteers. These were split roughly equally between studies on established products and new chemical entities. During this time there have been only four subjects manifesting minor reactions - syncope, dizziness, mild hypotension and diarrhoea. These findings are similar to those recorded by Zarafonetis and coworkers (1978).

The common effects are syncope, often related more to the procedure than to the drug, and central nervous system side-effects such as sedation. Syncope is frightening for the subject and the investigators, but rarely causes harm unless the subject falls or is taking a drug that may modify the normal baroreflex response to hypotension.

In Phase I studies in patients there have been some serious side-effects of drugs due to known aspects of their pharmacology, e.g. cardiac failure and bronchospasm with beta-blockers, excessive hypotension with vasodilators, extreme diuresis with loop diuretics, abnormal movements with central dopamine antagonists, etc. These reactions are not common and, in general, are readily dealt with clinically as their basic nature is understood. Drugs which produce a dose-related untoward effect in animals, e.g. gastrointestinal bleeding with non-steroidal anti-inflammatories, may also cause similar effects in man.

The oculomucocutaneous reaction to practolol, hepatitis occurring in association with halothane anaesthesia and chloramphenicol-induced aplastic anaemia are examples of severe idiosyncratic reactions which are so rare, and which usually require prolonged drug exposure, that similar reactions are must unlikely to occur during the early stages of human study.

Numerical Aspects of Detection of Adverse Reaction in Early Clinical Trials

Serious adverse reactions of medium to low frequency are most unlikely to be detected in early tests for statistical reasons. Preregistration trials can be categorized under four heading and approximate numbers of normal subjects or patients entered into each of the phases are given below:

Phase I — Volunteer studies 25 - 50 subjects

Phase IIA — Clinical pharmacology in patients 50 - 100 patients

Phase IIB — Definitive dose finding studies 100 - 250 patients

Phase III — Full development preregistration studies 250 - 1000+ patients

These relatively small numbers limit the incidence of adverse reactions at which one has a good chance (95%) of detection. For reactions with no background incidence the number of patients required to detect adverse reactions is given in Table 1. Assuming that three events are required before any action should be taken, it shows the large number of patients needed even for relatively high incidence adverse effects.

Table 1

Expected incidence of adverse reaction		Required number of patients		
		Event 1	2	3
1 in	100	300	480	650
1 in	200	600	960	1 300
1 in	1 000	3 000	4 800	6 500
1 in	2 000	6 000	9 600	13 000
1 in	10 000	30 000	48 000	65 000

(These numbers are based on the statistical assumption that the number of adverse reactions observed follows a Poisson distribution, which in turn depends upon assumptions of randomness and independence).
The problem can be many orders of magnitude worse, if the adverse reactions closely resemble a spontaneous disease with a background incidence in the population under observation. Exactly the same numerical considerations limit the sensitivity of animal toxicity tests.

Quality of Early Clinical Trials

If we are correct in believing that compounds should be brought to study in man somewhat earlier than is the case at present, this places an increased responsibility upon the investigators undertaking early trials. Performance in these trials has improved over the years, but in some cases, it still falls short of standards acceptable to the scientific community. Among the problems that occur are the following:

i) collaboration between sponsor and investigator may be less interactive than is desirable;

ii) potentially serious adverse drug reactions may be poorly documented and the relevant forms are not properly completed;

iii) patients may be admitted to trials who do not fulfil the selection criteria which makes interpretation of potential adverse effects difficult;

iv) pre-treatment assessment is inadequate or incomplete and therefore it is difficult to interpret post-treatment findings;

v) appropriate actions that are needed to evaluate the potential adverse drug reactions properly are often not instituted e.g. skin reactions are not photographed, blood is not taken or, if taken, is not stored under appropriate conditions, etc.;

vi) treatment may be instituted before appropriate safety assessment samples have been taken or the results received;

vii) rechallenges after an adverse event may be undertaken without appropriate monitoring;

viii) parochial attitudes may be adopted and the sponsoring organization and experts in the evaluation of adverse drug reactions may not be involved until very late in the day;

ix) occasionally adverse drug reactions are published without adequate investigation and may lead to problems in determining the true situation; and/or

x) often there appears to be a lack of appreciation of the regulatory and legal implications of handling adverse drug reactions sensibly.

These problems are even more severe in the later stages of clinical trials when contact between the investigators and the sponsoring organization is usually less close.

We believe that a study done to a poor standard is not only wasteful, but is also unethical, because it exposes the subject to some risk without any corresponding benefits. Ethical Committees might be encouraged to take an interest in this problem by examining details of some completed study, selected at random from among those that they have approved.

There is evidently a need for a substantial improvement in the discipline and training of the individuals who undertake the very responsible task of carrying out clinical trials. These investigators must appreciate that many millions of patients throughout the world may be treated on the basis of their findings. If the original studies are not of a high quality, patients may be exposed to hazards that could have been avoided.

DRUGS FOR RARE DISEASES

The process of drug development is now an extremely costly business. The total process of the development of a new drug may cost over US $ 100 million. To obtain an adequate return on their investment pharmaceutical companies have been obliged to concentrate their research largely on common diseases. This results in a paucity of drugs for serious but uncommon diseases - so-called ‘orphan diseases’. Examples include Wilson’s disease, haemophilia, etc. If research into these less common diseases is to take place in a meaningful way, the research and development costs for these disease areas must be reduced to the minimum allowable consistent with the seriousness of the disease and the need for a new treatment. For instance, expensive carcinogenicity and fertility tests might be waived. A further inducement might be to extend the duration of patent rights in order that a reasonable return on investment by a pharmaceutical company could be obtained.

The problem is likely to be particularly important in relationship to the use of the techniques of molecular biology to produce human proteins to treat deficiency diseases such as coagulation disorders and immune deficiencies of different types. The number of patients who might benefit is almost certainly too small for a new product to be able to bear the present level of development costs.

CONCLUSIONS

Development and testing of a new drug represents one of the most complex projects in the applied sciences. Unlike projects of similar complexity in the physical sciences and engineering, the element of the truly unknown is much greater. The balance between the desire to develop new forms of treatment to relieve human suffering and the equally strong or stronger desire to avoid doing harm is a difficult one. Partly because of the uncertainties and partly because of past disasters, governmental organizations have assumed the main responsibility for deciding what is reasonable in studies conducted in man. This responsibility has been discharged with care and caution. A considerable degree of caution is entirely proper when it comes to decisions about marketing drugs which may be administered to millions of people. Unfortunately caution almost inevitably means tedious bureaucratic procedures and a degree of rigidity in requirements. Our discussions have been concerned with the much narrower question of what is necessary before carefully monitored studies are undertaken in small numbers of humans for relatively short periods of time.

Early studies in man are important for two main reasons. If they are carried out to a high standard, the studies later in development can be much better designed in terms of dose range and frequency and the monitoring of side-effects and toxicity. A more important reason in the long term concerns the possibility of selecting between different members of a chemical series so that the one with the most favourable balance of properties is chosen for development. The possibility of discovering useful properties during human studies, which were not observed during the pharmacological work-up in animals, is more difficult to quantify, but many existing types of therapeutic drug action were first discovered in this way.

In the belief that taking more drugs into man will increase the number of useful therapeutic agents available, we have re-examined the studies in toxicology, mutagenicity, pharmacology and clinical pharmacology which cover this stage of the development process. One of the most striking features lies in the complexity of the studies that might be done in any particular project. Obviously it is impossible to do them all on grounds of time, cost and relevance, but the exact choice is a matter of fine scientific judgement. This complexity alone is a strong argument against the intervention of regulatory

bodies which may adopt a check list of approach. Yet a core of tests is necessary and the choice will alter, sometimes very rapidly, as knowledge advances.

We believe that the role of official bodies should be confined to monitoring the performance of early studies and we welcome signs that the attitude of some of the major organizations concerned, such as the drug control authorities in Sweden, the United Kingdom and the United States of America are becoming more attuned to this idea. However, if governmental agencies take less reponsibility for early studies in man, then pharmaceutical companies and clinical investigation will have to take more. We took note of opinions that the standard of some clinical studies falls far short of what is desireable and that these failings are not confined to small centres with poor laboratory facilities. If the standard of performance is low, it is inevitable that public opinion will force regulatory bodies into a more active role and science, and ultimately patients will be the losers. Our recommendations include one concerning the need for more training for those who undertake studies in man.

RECOMMENDATIONS

1. There is an urgent need for more effective and safer medicines for many diseases. We believe that the chance of discovering such medicines will be increased if more compounds are brought forward for study in man.

2. The process of developing drugs has become very complex and costly. If resources are used on low priority matters, there will be less available for more important ones. Thus the efficiency with which such studies are carried out is a matter of general concern. We believe that the procedures could be made more efficient without jeopardizing the safety of experimental subjects.

3. Toxicity tests in animals must always be carried out before the first administration of a new drug to man. The design of these studies must take into account the chemistry of the compound, its pharmacological action, pharmacokinetics and the proposed use in man. The type, extent and duration of these tests must be adapted to the circumstances and any guidelines relating to them should be flexible. Closely supervized and monitored early studies in man should be permissible with less extensive animal tests.

4. As toxicity tests in animals are costly and time consuming, the methods used must be appraised for their predictive value by comparison with results obtained in man. Based on these findings, unnecessary investigations can be discarded and validated alternative techniques can be substituted.

5. Concern about the risk of carcinogenesis has led to frequent use of screening tests in artificially sensitive bacteria at an early stages of drug development. It should be widely recognized that such tests may give misleading results and we are concerned that development of potentially valuable medicines may be abandoned because of them. Judgements should be based on the results of several appropriate and proven tests. New short-term methods require thorough validation before they are generally adopted. Guidelines on mutagenicity testing should be formulated and interpreted so as to minimize these problems.

   Carcinogenicity tests in animals are carried out in highly artificial conditions affecting diet, environment, endocrine status, etc. In consequence it may be difficult to interpret them and impossible

to reproduce the results in another laboratory. There is an urgent need for reappraisal of the methodology and value of these tests.

6. Transfer of data between animal species and from animals to man is more accurate, if based upon a knowledge of drug kinetics and metabolism, rather than reliance solely upon the dose. Because pharmacologists, toxicologists, clinical investigators and specialists in drug metabolism and kinetics tend to work in isolation from one another, there is a need to integrate these skills to a common purpose when comparing data between species.

7. We place particular emphasis upon accurate measurement of drug action in man. This includes measurement of physiological, biochemical and psychological parameters to characterize the main and subsidiary actions. Carefully monitored, sensitive measurements in man are the best guide to eventual therapeutic activity. When carried out by skilled investigators in a well-equipped clinical laboratory the incidence of serious adverse effects is very low.

8. Because of its central position in drug development, we are particularly concerned that the standard of human studies with drugs should be uniformly high. The present position is not always satisfactory. Methods of improving the training and self-discipline of investigators are needed.

9. We see no scientific justification for repetition of very similar animal toxicity tests in different countries. There may be good reason to include a range of human genetic stock, environment and diet in clinical trials, but even here there is a need to avoid wasteful repetition for administrative rather than scientific reasons.

10. Early studies in man will often disclose problems that require further investigation in animals. Close collaboration between clinical investigators and laboratory scientists is essential to facilitate this movement from animals to man, back to animals when necessary, then to continue in man. Such contacts should also ensure that toxicity tests are more relevant to the circumstances of the clinical studies. More should be done to bring the toxicologists and pharmacologists into contact with the investigators who are responsible for the early human studies.

Appendix I

TOXICITY TESTS

The design of animal toxicity tests should be approached with flexibility and pragmatism. The following outline indicates the framework for such an approach in the state of knowledge prevailing in 1981/2.

1. *Acute Toxicity Tests*

   Appropriate acute toxicity tests (observations of lethality, clinical effects and autopsy findings) should normally be done in one or two rodent species, by the intended route of administration and by a parenteral route.

2. *General Pharmacology*

   The general pharmacology of the compound should be investigated, in addition to the detailed study of its main pharmacological actions which provides the pharmacological rationale for the development of the drug.

3. *Animal Pharmacokinetics*

   Preliminary animal pharmacokinetic studies should be carried out, using either a chemical method specific for the drug or an appropriately radiolabelled molecule. The studies should be applied to the species treated in the toxicity tests, so that results can be viewed in proper perspective. They may also aid interpretation of data from pharmacological experiments.

4. *Subacute Toxicity Tests*

   At present, the duration of animal testing can only be related arbitrarily to the intended period of treatment of man.

   When the intended clinical usage involves up to three doses during one day, or three doses spread over several days (dependent upon the half life of the drug), toxicity testing should be done for 14 days. For repeated dosing of man up to 10 days, animal tests of 28 days duration should be done.

   The toxicity tests would normally consist of once daily dosing of a rodent and a non-rodent species, employing a sufficient number of animals of each sex to give a valid result.

The investigations made would be adapted to the nature of the compound, but in general they should comprise extensive clinical observations, a general screen of haematological and clinical chemistry tests to reveal organ damage, and autopsy and histopathological examination of a wide range of organs and tissues. Variations of this scheme may be required dependent upon the intended route of administration (oral, topical or parenteral), the frequency of dosing and the importance of demonstrating the evolution and reversibility of lesions by intermediate and post-treatment sampling.

5. *Reproductive Toxicity Testing*

A detailed review of fertility studies, fetal, and peri- and postnatal toxicity testing is beyond the scope of the present paper. Drug-induced changes in fertility should not be a problem if gonadal histology is normal in animal toxicity tests of 28 days duration.

Appendix II

GENERAL PHARMACOLOGICAL SCREENING

Some examples of tests in use to assess pharmacological effects upon the major organs and systems of the body

SYSTEMS AND ACTIONS

Examination	*Possible Method*
1. *Central Nervous System*	
General behaviour	in acute toxicity test: general observation.
Effect on induced sleep; sedation	after short-acting barbiturate anaesthetic.
Anti- or pro-convulsant activity	in acute toxicity test; in electro-shock test.
Analgesia	tail pressure.
Coordination	rotarod.
2. *Cardiovascular System*	
Cardiac activity	anaesthetized dog or cat.
Blood pressure control	direct BP measurement; heart rate, rhythm and contractile force. Response to pressor and depressor agents, e.g. noradrenaline and acetyl choline, and to carotid artery occlusion. If effects are found reexamine in conscious animals.

3. *Autonomic Nervous System*	
	BP and heart rate response to stimulation of vagus nerve and sympathetic trunk; response of nictitating membrane.
4 *Respiratory System*	
Respiratory rate, rhythm and volume	anaesthetised dog or cat; effect of vagal stimulation and anoxia; possibly response of isolated trachea.
Bronchial tone	preparation to constricting.
5. *Gastrointestinal System*	
General motility	charcoal meal transit time; response of isolated segments of intestine to standard spasmogens and antispasmodics in the presence of the test compound.
Stomach ulceration	for specific classes of compounds.
6. *Genitourinary System*	
Diuresis	conscious rat.
Uterine muscle	reponse to standard spasmogens.

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