# SECOND INTERNATIONAL PHARMACOLOGICAL MEETING

VOLUME 8

# Evaluation of New Drugs in Man

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# INTRODUCTORY REMARKS

C. HEYMANS

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THE PROBLEM of the pharmacological and clinical evaluation of new drugs is a very real and pressing one for pharmacology and clinical medicine. Many meetings and symposia have already been devoted to this fundamental problem. In several books and monographs, views on the ethical, pharmacological and clinical aspects of the evaluation of new drugs have been put forward, but opinions and suggested requirements differ strikingly. In several countries regulations have been laid down, but these have so far failed to grasp the magnitude of the distance which separates the laboratory investigator from those who have to assess clinically the therapeutic value and eventual toxic effects of new drugs.

In a motion addressed to WHO (the World Health Organization) the Section of Pharmacology (SEPHAR) of the International Union of Physiological Sciences has suggested that WHO should undertake a worldwide approach towards classification of the fundamental problems and techniques involved in the therapeutic evaluation of newly developed drugs. In making this suggestion in the interests of promotion and improvement of rational therapeutic measures, SEPHAR is prepared to support such a programme, by giving technical advice wherever it is needed.

This present symposium is, we are convinced, going to be very useful and effective in clearing up and promoting the main fundamental aspects of the very significant problem of pharmacological and clinical evaluation of new drugs. We hope that some general recommendations will result.

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# SCREENING FOR SAFETY

# CHAIRMAN'S OPENING REMARKS SAFETY ASSESSMENT OF NEW DRUGS

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HISTORICALLY, the most evident trend in the safety assessment of new drugs has been to employ more and more laboratory animals for longer and longer periods of time. Thus, 20 years ago much the same hematology, clinical chemistry, gross and microscopic pathology were reported in the toxicity studies as are called for today. We customarily used rats and dogs for chronic toxicity studies, occasionally including monkeys where they seemed to be indicated. We employed several different dosages of a drug administered by the route indicated for the proposed clinical trial and the chronic studies conventionally ran for about 3 months if the agent was going to be administered to man for any substantial period of time. Acute toxicity studies sufficed for known agents being administered as a single injection, etc.

Over the course of time we have seen the absolute numbers of animals increased and the duration of these studies prolonged for an ever-increasing period of time. Thus, today such chronic toxicity studies are conducted commonly for a period of 1 or 2 years. Longer chronic toxicities may be anticipated if this trend continues. Setting aside the current enthusiasm for the assessment of teratogenesis and toxicity in new-born animals, which remain to be evaluated as important contributions to safety assessment, there seems to have been no real assurance that the protracted extension of toxicity studies has really contributed a substantially greater element of safety to modern drug evaluation.

In practice, one finds that if he could plot the amount of information regarding the potential toxicity of a drug against the duration of the chronic toxicity study, there would be at best something resembling perhaps a semi-log relationship of information obtained to the duration of the toxicity study. In other words, a great deal of information can be obtained with regard to the acute toxicity of a drug by conducting such studies in laboratory animals. A great deal of information can be gained over the first, say, 3 days of a subacute toxicity study wherein extensive dosages

of the agent are employed. The first 3 weeks of a subacute or chronic toxicity study are most revealing and within the first 3 months of either a subacute or a chronic toxicity study conducted at up to lethal doses one will almost invariably have taken the full measure of relevant information that he will have gained from a toxicity study that might last as long as a year or 2 years, or more. On such a semi-log plot it would seem to be of little difference whether one extrapolates the time span from 1 year to 3 years except as this exceeds the normal life span of the rat and does not constitute more than one-third of the life span of the dog.

Probably the reason so little information is obtained with regard to the toxicity of a drug after the first 3 to 6 months is that the process of adaptation on the part of the animal to the agent takes place at the maximal rate at which any particular functional system can adapt under the specific circumstances imposed by the stress agent. In other words, after a period of adaptation there is much less likelihood that one will see manifestations of toxicity that previously had not been recognized. Alterations of function of such organs or systems as hemopoiesis, cataract formation, electrolyte, cardiovascular, pulmonary, gastrointestinal, renal and even perivascular changes, such as might be seen in certain hypersensitive states, become manifest within a period of 6 months or less if the dosage of the agent is adjusted to constitute a maximal stress. Thus, it seems generally wasteful and unproductive to extend such toxicity studies indefinitely if still greater insight into the actions of or reaction to the agent can be gained by employing time, personnel and facilities in another manner.

The full potential of the safety assessment of new drugs in depth, rather than by protracted duration, has not been realized fully. Long-term studies ordinarily are not designed to give insight into the effect of a compound on specific functional capacities at an enzyme level or at a subcellular structural level. Older conventional approaches can give very little insight into the effect of the body on the compound as it alters the agent within the capacity of the many biochemical reactions at its command or the adaptation of these capacities to the stress of a compound administered at maximal doses.

Thus, it has seemed sensible to couple fundamental studies dealing with drug metabolism and pharmacodynamic effects at an organ or subcellular level with high intensity toxicity studies conducted for relatively short periods of time (months). Where this has been done we have gained a greater total insight into the distribution of the drug, into the balance of its intake and elimination as by excretion or degradation, into the handling of its metabolic products and into the variation from species to species in this total assessment than could possibly have been done by simply drawing out the duration of a conventional toxicity study.

In practice, we have compared the information obtained by short-term,

high intensity toxicity studies coupled with careful balance and metabolic studies against currently conventional toxicity studies carried out for a period of 2 years. There is no question but that a more comprehensive insight into the drug–host interaction is gained by the more sophisticated study. Actually, the Pharmacology Division of the Food and Drug Administration is believed to subscribe in principle to this concept.

The question may be raised as to whether this same concept of toxicity studies in depth, rather than of protracted duration, is adaptable to the assessment of potential carcinogenesis of new products. It is true that by concept and by experimental design the heritage of studies of carcinogenesis has run counter to this proposal of studies in depth instead of protracted duration. However, it should be pointed out that this attitude is no different from the concept of safety assessment of drugs, historically. Actually, the documentation of the philosophy that potential carcinogenesis or co-carcinogenesis can be unmasked by studies in depth rather than by protracted duration is inadequate to counter the bias of past precedence. Work is urgently needed to assess the extrapolation of this concept to such an important segment of safety assessment. It seems reasonable that this can be documented as one utilizes appropriate carcinogenic studies in mice, or other short-lived animals, coupled with the effects of specific agents on nucleic acid metabolism, in tissue culture studies, in isolated systems, and in the total animal.

It is clear that the advancement of safety assessment by studies in depth requires knowledge, ability and point of view more familiar to the biochemist than to the conventional pathologist or toxicologist. The technics involved make liberal use of enzymology, radioisotopic procedures for studying drugs and the most sophisticated systems for the isolation and identification of metabolic products. On the other hand, the final assessment of safety requires an ability to relate these many observations, one to another, and to project their transposition to man. This transposition can be sharpened appreciably by conducting similar metabolic studies in man prior to the final assessment of utility under clinical conditions.