pouring into the Bureau of Medicine is of the magnitude of several thousand reports per month. This data currently represents the largest collection of safety, efficacy, and manufacturing about pharmaceuticals that exist in the world today. Together with the system necessary to evaluate and analyze this information, we have created a scientific tool for the measurement of drug effects, which is only the first of a series of giant strides the Food and Drug Administration is contemplating in the near future.

Information Needed for Clinical Trials of New Drugs*

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Received August 17, 1965

The kinds of information a physician needs before he prescribes a drug for the first time and the importance of proper animal and clinical testing are discussed.

Although I am a member of the Advisory Committee on Investigational Drugs to the Food and Drug Administration, this paper does not necessarily reflect the views and opinions of the Committee nor of the FDA.

This paper discusses in general terms the kind of information a physician should have before he introduces a drug into a human for the first time. Other papers in this symposium indicate some methods that have been used or proposed to handle this information so as to derive the maximum benefit for the investigator and the minimum risk to the patients he studies. There is obviously a great need to supplement and improve the methods and systems now available. Dr. Kelsey has spent the major part of his time during the past two years in seeking a forward looking far-reaching solution to this problem. It is by the ready availability and interchange of information available about drugs that we can best carry forward the progress made in developing new and potent agents for use in the conquest of disease. Time, properly trained people, and facilities are too short in supply for us to squander them in nonproductive endeavors and in repeating useless experiments. We must look to the entire globe as the boundaries from which and to which this information must flow. The thalidomide incident demonstrates the importance of easy access and interchange of information on drugs across national boundaries and language barriers.

One of the factors that calls forth strong emotional reaction to a discussion of the information that should be in hand before a drug is administered to a human comes from man's innate hostility towards the formal regulations established in any area which limit his freedom of action. The fact that they come from the government produces a synergistic effect. This reaction is not peculiar to the field of drugs and by its very nature and scope does not lend itself to any productive discussion in the setting and time available here. However, the pragmatist realizes, I think, that more and not less regulation must be expected in a society increasing in complexity as rapidly as ours. Certainly, any reasonable extrapolation of the immediate past into the future gives credence to this prediction. It is then for us, especially those with special knowledge and training, to try and make whatever regulations are imposed work to the maximum benefit and minimum hindrance of progress and to make strenuous efforts to modify these regulations when cold, hard facts can be marshalled to support such changes. I am increasingly convinced that the FDA is committed and dedicated to such a course of action in the field of drugs.

Before deciding to study a drug in humans, the proper answers to the following questions should be at hand. (1) What is the need and importance of a new drug for treatment of a given disease? (2) Is there evidence from preclinical studies that the drug might be expected to be effective in the disease? (3) Has sufficient data been obtained to permit estimation of the human dose that would be effective? (4) Is there enough information about the possible hazards and discomfort of the drug to the patient?

* Presented before the Divisions of Chemical Literature and Medicinal Chemistry, Symposium on Drug Information, 148th National Meeting of the American Chemical Society, Chicago, Ill., Sept. 1, 1964.

It is from clinical medicine and therapeutics that the answer to the need for a new drug comes. The evaluation of the effectiveness of a compound and the determination of a probable therapeutic dose range are in the province of pharmacology, and in particular the area of pharmacodynamics. The assessment of the safety factor and possible hazards is in the domain of toxicology. The points I have given are self-evident. I make no claim to their originality. Too often we focus on the safety factor and give less attention to the other three equally important areas.

There can be little argument about the futility of developing drugs for diseases which do not exist. As I have said, there are differences of opinion about the importance of developing and testing new drugs for the treatment of diseases for which adequate therapy exists. There is a lack of qualified clinical investigators and the patients and facilities for their studies on new drugs. It is logical that the clinical investigators give top priority to the evaluation of new drugs for diseases where our therapeutic armament is deficient. I think they are already doing this. Although one hears many complaints about the lack of interest of clinical investigators in doing studies on new drugs, in many cases this is really lack of interest in using new drugs for conditions in which adequate therapy exists and the new drug has little promise of being more effective than those already available. One might anticipate that there would be little difficulty in finding cooperation for the study of a new and promising drug for the treatment of lung cancer.

Before a physician enters on clinical investigation of a new drug he should have some evidence from preclinical studies that the drug can be expected to be effective. With our expanding understanding of the fundamental and basic levels of cell organization and function, it is more and more possible to make predictions about the relationship between structure of compounds and their biological activity. But, as yet, most of the preclinical evidence comes from *in vitro* and animal studies. Unfortunately the predictability of the preclinical screens varies widely with the screen employed. Some success has been achieved in using *in vitro* tests as screens for drugs. They have the advantage of simplicity, speed, and ease of quantitating results; but with our present state of knowledge they may often be misleading. There are a number of examples that can be cited to illustrate the point. The diuretic potency of the organomercurials is not always related to the magnitude of the inhibition of an *in vitro* sulfydryl catalyzed system such as succinic dehydrogenase. The efficacy of the chlorothiazide type of diuretics is not quantitatively related to their *in vitro* carbonic anhydrase inhibitory action. It seems obvious that another parameter, the ability of the compound to reach the site of action, influences the effectiveness in the animal or man. It might be anticipated that in such *in vitro* tests negative results have more import than positive results, since they indicate that even if the compounds can reach the site of action they would not be effective. The contributions that can be made by *in vitro* tests are also limited by our knowledge, as yet, about basic mechanisms of drug action. Without this information it is difficult to set up the appropriate *in vitro* screen.

Before use is man, compounds should be studied in animals, even if *in vitro* screens are available. The use of animals in pharmacology and pharmacodynamics is based on the premise that there has been an orderly phylogenetic development of the processes of growth, maintenance, and reproduction in the higher vertebrates. It must be recognized that in this development, species have developed differences as well as maintained over-all similarities. Thus one must anticipate that there are biochemical dissimilarities not only between different species, but as Williams has so clearly shown, even between members of the same species, indeed even in littermates. Many of the differences are fortunately only qualitative and are confined largely to the duration of drug action. Were this not so there would be much less progress in the development of new drugs. It is not likely that we could afford the luxury of trying every compound prepared against all human diseases; we are dependent on the preclinical screening program and to an increasing extent upon theoretical knowledge of the relationship between structure and biological activity.

Brodie has presented a number of examples to illustrate the marked variation in the responses of various species to drugs. Merperidine is metabolized in man at a rate of about 17% an hour and the analgesic effect of a single dose lasts 3 to 4 hours. In dogs, however, the transformation of merperidine is much more rapid, 70 to 90% per hour. If this compound had been tested in only one species, the dog, it might have been discarded as useless because of its short duration of action. The mouse metabolizes hexobarbital 20 times as rapidly as man, and antipyrine 60 times as rapidly. Sex differences may also be large. Hexobarbital induces sleep about four times as long in female as in male rats. This sex difference is not observed for hexobarbital in mice, guinea pigs, rabbits, and dogs. There is evidence of the importance of genetic factors in the rate of metabolism of compounds in the same species. Different inbred strains of rats oxidize antipyrine at widely different rates. As Brodie has found, the half-life of antipyrine is 114 minutes in the M-250 strain of rats as compared to 290 minutes in the Buffalo strain. The differences among individual animals in the same inbred species are much smaller than in members of a strain that has not been inbred. As might be expected, these differences between individuals occur in man, an animal which tends not to be highly inbred. Bishydroxycoumarin and ethyl biscoumacetate show an eightfold variation in rates of metabolism among different individuals. The sensitivity of negroes with sickle cell anemia to antimalarials is well known. Differences in the rate of absorption and excretion can have profound effects on the action of drugs in various species. This fact provides a strong argument for using intravenous administration in the preclinical studies for all drugs even if this is not contemplated as the ultimate route for its use in man.

The use of drugs labeled with radiocarbon, tritium, or other radioactive atoms to follow absorption, distribution, metabolism, and excretion is increasing rapidly. Often methods to estimate the drug chemically, especially in body tissues and fluids, are not sensitive or specific enough to be useful. The presence of a radioactive tag for the molecule greatly simplifies the procedures. The tag also permits the drug molecule to be followed through metabolic pathways. Radioactive labeling should lead to the same de-

tailed information about metabolism of drugs that we have obtained about normal cellular metabolic processes by this technique.

The preclinical evaluation of the dose which might be expected to be effective in man suffers from the same difficulties as the estimation of its efficacy and usefulness. The variations between species and among members of the same species on rates of absorption, excretion, and metabolic conversion complicate the problem very much. Here again, more data obtained on more species will probably permit the most accurate estimate to be made of the first dose that should be tried. A conservative dose used for the initial studies in man can always be increased as information and experience are gained.

The safety of a drug can only be judged in relative terms. Any drug can be shown to have undesirable effects in animals and man under the proper conditions. It is the balance between the efficacy of the drug and its toxicity which decides whether it merits clinical trial. It is obvious that a much smaller difference in the effective and toxic dose can be tolerated for a drug to be used in the treatment of leukemia than for a drug used to treat athlete's foot. Toxicity may arise from several causes. In some individuals unusually susceptible to a drug, a safe therapeutic dose for most patients may produce effects of overdosage. Side effects beyond the primary action of the drug may be minor or of great clinical importance. Examples are the nausea and respiratory depression of narcotic drugs. Hypersensitivity involves the reactions due to sensitization of some individuals to certain drugs. The reactions vary from mild skin rashes to lethal anaphylactic reactions. Unfortunately there are not reliable animal studies that can predict this kind of response to a drug. The synergism between drugs given to a patient simultaneously is not predicted from preclinical studies. It is not possible to test in animals all of the combinations that might be encountered in patients under treatment for a disease. There remains the true toxicity of the drug, when administered in large doses or over long periods. Death may be caused by exaggeration of the therapeutic effects of the drug or to the appearance of new effects not evident or important at lower dosages or short term administration. Safety studies usually involve the evaluation of single-dose acute toxicity, short-term subacute toxicity, and long-term chronic toxicity. The drug is administered at several dosage levels and a number of observations other than lethality are made. These include physical examinations, food intake, weight gain, and hematological, biochemical organ function and extensive postmortem pathological studies. Since the thalidomide incident, increased attention is being given to the effects of the drug on reproduction and offspring. Unfortunately, the assessment of safety in this area is probably on the least firm basis. Teratology needs extensive investigation.

The consideration of the difficulties in extrapolating data from animals to man is not a primary goal of this paper. I only introduce the subject to give weight to the requirement for the study of new drugs in as many *in vitro* screens and as many species as possible before introducing them into man. Better methods are required to handle the information efficiently and to make it easily available to experimenters. Obviously where possible the drug should be tested in conditions simulating in the animal as closely as possible the disease for which it is to be used. Unfortunately this is possible in only a limited number of situations.

As Peck and Beyer have stated, it is through expansion of basic pharmacodynamic, biochemical, and metabolic studies, rather than the extension of toxicity studies, that more meaningful experimental designs to evaluate the safety of drugs will come. Knowledge at the fundamental level of cell and tissue function can ultimately provide us with a much more scientific approach to the development and preclinical evaluation of new drugs.

The responsibility for regulating new drugs has been given by Congress to the Food and Drug Administration. The 1962 Kefauver-Harris amendments of the Federal Food, Drug and Cosmetic Act of 1938, and the Investigational Drug Regulations recently promulgated by the FDA on the basis of the amendments, established more rigorous control over studies of investigational drugs in the human. The requirements for information established under the regulations do not differ from what a physician would want to know about a drug before he administered it to a human. These include what the drug is, who makes it and how, the results of laboratory and animal tests with it, and who did the research. The sponsor of the study in humans must also submit a plan for the investigation and information about the qualifications of investigators. Prior to 1962, a manufacturer could distribute a drug for investigational use to qualified investigators if it was clearly marked as such and records were kept of its distribution. The manufacturers were not required to notify the FDA that a drug was under investigation. It was only when a new drug application was submitted to permit marketing of the drug that the information obtained during the investigational period was submitted. Information was not available on studies terminated without submitting an NDA. This situation made it impossible to maintain a central file of the results of drug studies in the human. Much time was wasted and patients were needlessly exposed to danger because studies were repeated on the same or closely related drugs without knowledge of earlier findings by others. At present although this information is submitted to the FDA by sponsors of studies on investigational new drugs, it is considered confidential. Under this handicap it is not possible for the FDA to inform an investigator of the futility of his study. Information that a drug has previously been found to be dangerous or life threatening can, however, be passed on to other investigators. The development of new drugs would move ahead much greater speed if all previous information submitted on investigational new drugs could be made available to the scientific community. It is a goal to which we should strive. The intent of the new amendments and the revised regulations is to protect the public as far as possible from misuse of investigational drugs and to make sure that information on the quality control of the drug and the preclinical experiments are adequate to justify introduction into humans. The manufacturer or other sponsor of the study must file this information in a claim for exemption to the FDA before distributing the drug for study. Permission is not required to proceed, but if review of the material submitted and the protocol of the clinical study suggests there are shortcomings, the sponsor is contacted and asked to remedy the defects. If it appears that the

deficiencies are so serious that they might be life threatening to the subjects receiving the drug, the sponsor is asked to terminate the study and recall the drug. Out of several thousand claims for exemption submitted up to the beginning of the summer, only two were terminated by the FDA.

The Investigational Drug Regulations divide the clinical studies on drugs into three phases. Phase I is essentially the period of pharmacodynamic studies in man. It is the first step in evaluation of the drug in humans. Small doses of the drug are given, possibly to only one or two patients. Different routes of administration and the subject are followed closely by appropriate pharmacological and biochemical studies. Only a few highly qualified investigators with extensive experience in clinical pharmacology and substantial laboratory facilities are usually involved. In Phase II the studies are extend to include the initial therapeutic trial on a limited number of patients. In this phase the patients remain under close observation and study. The regulations and their interpretation provide considerable leeway in these two steps of the clinical investigation and in the information that must be provided from preclinical investigation and in the information that must be provided from preclinical studies. In addition to the pharmacological data which indicate that the compound might be expected to be effective, only acute and subacute toxicity studies would ordinarily be required. In these stages the drug is usually employed in the form of a pure compound and the information needed to establish its identity, purity, and strength are much simpler than when it is compounded into a tablet or capsule. In Phase III the study is broadened to involve a greater number of patients treated by physicians with more widely varying research experience. It is expected that by this time considerably more animal work would have been done and the formulation of the drug would be more or less standardized. But even at this stage, as in the two earlier ones, a reasonable degree of flexibility is permitted the investigator for variations and alternatives in the proposed protocol. It is realized that this flexibility is needed to develop the full potentialities of a drug.

The official definition of a drug under the Federal Food, Drug and Cosmetic Act included, in addition to articles intended for use in diagnosis, cure, mitigation, treatment, and prevention of disease in man or animals, articles other than food intended to affect the structure or any function Kefauver–Harris amendments have begun to bring about far-reaching changes in the character of the agency and of the body of man or other animals. Under this definition, compounds used in studies to establish metabolic pathways, etc., come under the definition, even though there was no intention to determine if the compounds were of value for the cure, treatment, or prevention of disease. In the interpretation of the regulations, the FDA has recognized the problems posed by the inclusion of these compounds and has assured the scientific community that a reasonable approach will be taken to claims for exemptions submitted by investigators for these uses. Ordinarily the compounds studied are known intermediates in metabolic pathways and are used in small amounts for only single doses. As in the case of other Phase I studies, it is not expected that extensive toxicity data will be presented in the claim for exemption.

At present, radioactive drugs are exempt from the provisions of the new regulations and remain under the control of the Division of Licensing and Regulation of the U. S. Atomic Energy Commission.

The new responsibilities given to the FDA under the Kefauver–Harris amendments have begun to bring about far-reaching changes in the character of the agency and particularly its Bureau of Medicine. It is assuming its proper place in our scientific and medical communities. As Lowell Coggeshall says, its evolution shows how a policeman is becoming a professor. It has been provided with more staff and there is determination that the staff have an opportunity to continue their professional growth through relationships with a university and its medical school. Closer interaction with university scientists is already underway. I have long and persistently argued that the FDA must be given the authority and funds to support research and research training on drugs and to properly handle the information about drugs, not only from the data submitted by those requesting exemptions to study investigational agents but the findings reported in the literature of all countries. The FDA needs this authority to carry out its obligations under the law. Through such a mechanism, the FDA and the universities can join together in finding answers to some of the problems in drug development and evaluation badly in need of answers. When this comes to pass, a discussion on the information needed for clinical trials of new drugs a few years hence will have a better scientific basis.