nents. It has a print-out consisting of acoustic patterns that are capable of similar relational computation by machines of the same constitution using the same program. Linguists, biologists, and psychologists have all discussed certain aspects of the machine.

Linguists, particularly those developing generative grammar, aim at a formal description of the machine's behavior; they search mathematics for a calculus to describe it adequately. Different calculations are matched against the behavior to test their descriptive adequacy. This is an empirical procedure. The raw data are the way a speaker of a language understands collections of words or the relationships he sees. A totally adequate calculus has not yet been discovered. Once available, it will merely describe, in formal terms, the process of relational interpretation in the realm of verbal behavior. It will describe a set of operations; however, it will not make any claims of isomorphism between the formal operations and the biological operations they describe.

Biologists try to understand the nature, growth, and function of the machine (the human brain) itself. They make little inroads here and there, and generally play catch-as-catch-can; everything about the machine interests them (including the descriptions furnished by linguists).

Traditionally, learning theory has been involved neither in a specific description of this particular machine's behavior nor in its physical constitution. Its concern has been with the use of the machine: What makes it go? Can one make it operate more or less often? What purposes does it serve?

Answers provided by each of these inquiries into language are not intrinsically anatagonistic, as has often been claimed. It is only certain overgeneralizations that come into conflict. This is especially so when claims are made that any one of these approaches provides answers to all the questions that matter.

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Drug Safety: Experimental Programs

Problems and solutions of the past 10 years are critically reviewed.

Gerhard Zbinden

On 6 November 1958 J. Lehman, chief of the division of pharmacology of the Food and Drug Administration (FDA), addressed the research and development section meeting of the Pharmaceutical Manufacturers Association at Sea Island, Georgia. Although Lehman's views on the subject were well known, through his work with his colleagues at FDA (*1*), rumor had it that new and far-reaching official rules for testing drug toxicity were about to be proclaimed. For those who had feared the introduction of minimum standards, the spokesman of FDA provided no cause for immediate concern. Although he did pronounce certain rules for the toxicologic evaluation of experimental drugs he made it clear that these were only meant as flexible guidelines (*2*). An abstract of Lehman's 1958 talk was published in a journal with limited distribution. The concept became generally known after Lehman spoke at a joint American Medical Association, Society of Toxicology Symposium on 17 June 1963, when copies of his projected slides were made available and gained wide distribution. To this day, Lehman's unofficial rules have decidedly shaped the industry's and FDA's approach to toxicity testing.

The 1958–1963 guidelines recommended various types of experiments: short-term studies in which the acute toxicity was to be evaluated by single administration of the drugs to four animal species and two sets of long-term tests in which the substances were to be given repeatedly. Two animal species were suggested for the long-term studies and three dosages were to be tested. The duration of the experiments was 2 weeks to 1 month for the subacute and up to 6 months for the chronic toxicity tests, with the option for an extension up to 2 years. Drugs were to be administered by the same routes as anticipated in man. Clinical tests included hemograms, coagulation tests, limited tests on liver and kidney function, and determinations of blood sugar. Gross and microscopic examinations were confined to major organs in short-term studies or were to be done in considerable detail in the longer experiments. No specific recommendations were made for the number of treated animals and controls, the frequency of laboratory tests, and the percentage of animals included in the laboratory studies. Less extensive procedures were suggested for the testing of drugs administered by inhalation and by the dermal, ophthalmic, vaginal, and rectal routes.

Lehman's guidelines became rapidly

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and generally accepted by drug manufacturers. As a consequence, a marked uniformity of the toxicologic testing procedures emerged. The FDA continued to resist the establishment of official recommendations, but it adopted the generally accepted format of toxicity studies as what may be called *de facto* minimum standards. In subsequent years changes were brought about by various circumstances. Some of these deserve to be mentioned as an illustration of how an essentially scientific problem develops under the influence of government regulation, legislative investigation, and widespread criticism by laymen and experts.

Mutual Escalation

Testing procedures were not officially standardized, and each investigator was free to add whatever he thought would improve the content or the looks of his report. As a consequence, the less elaborate studies suffered by comparison which sometimes led to additional requests by FDA. In order to avoid the time loss resulting from such a mishap, pharmaceutical companies began to include a multitude of additional tests into their standard procedures. More animals were treated at more dosages, and for longer periods; new animal species were tried; more laboratory tests were included; and more organs were sectioned for histologic examination. This routine became so elaborate that facilities had to be expanded and work had to be assigned to commercial laboratories.

Spectacular Failures

The general expansion of standard testing procedures was hastened by several highly publicized toxic reactions produced by new drugs in man. Animal toxicology and clinical testing shared most of the blame. The lay press, Congress, and the scientific community joined in demanding tighter controls. The still unofficial standards for safety testing of drugs were raised again. For the first time FDA released official guidelines requiring specific methods for the evaluation of teratogenesis and fetal toxicity (*3*). For the first time also legal requirements were established which made submission of toxicologic data to FDA mandatory before drugs could be administered to humans.

Scientific Criticism

The sudden emergence of interest in toxicology among many biologists was a fortunate consequence of the crisis involving drug safety. Biochemists gathered detailed information on the metabolism of drugs from which they hoped to derive a scientific rationale for future toxicologic studies. Species differences were found to be frequent and often fundamental, and the opinion was voiced that toxicologic studies should preferably be conducted in animals whose drug metabolism resembled that of man. It was also demanded that metabolic studies be made in man before prolonged experiments were initiated on animals.

These ideas, strongly voiced by a group of experts appointed by the World Health Organization (WHO) (*4*), found a willing ear within government agencies. For example England's Dunlop Committee already demands comparative metabolic studies in animals and man before initiation of therapeutic trials. The FDA has recently adopted a similar attitude (see *5*).

Another group of workers concerned with pharmacogenetic aspects of drug toxicity discovered that the metabolism of drugs may be abnormal in certain individuals. Such aberrations are often genetically determined and may elucidate many unexplained toxic reactions. Experiments with animals and limited metabolic studies in a few humans rarely uncover these abnormalities. It is important, therefore, that the toxic effects and the metabolic fate of a new drug be studied in a representative sample of humans. Moreover, the availability of a group of individuals with known genetic variations of metabolic pathways would facilitate early recognition of toxic hazards of new chemicals. Toxicologic experimentation upon humans, however, has not kept pace with the rapid development of the experimental sciences. The many legal, ethical, and organizational problems connected with toxicologic investigations in man have only been tackled by few pioneers and remain a major task for the future.

Toxicity Testing Today

In retrospect, Lehman's lectures of 1958 and 1963 appear like a blueprint according to which animal toxicity testing was to develop. It is unlikely, however, that anybody at that time could have predicted just how extensive and expensive these experiments would become. It is not at all unusual for a complete program on testing toxicity of one drug to involve well over 1000 animals, over 1200 hemograms, about 5000 different laboratory tests, over 700 autopsies, and histologic examinations of over 6000 organs. Such a study may cost close to $100,000 not including the expenses for manufacture of the test substance. Extensive additional studies are required when a second route of administration is desired, if a minor chemical variation (for example, different salt or crystal form) is necessary, if the drug is to be combined with another substance or if the new agent will also be given to farm animals or be used as food or feed additive.

Will this immense effort guarantee that no dangerous chemical will ever be given to a large segment of the human population? It is too early to give an unqualified answer to this question. The record of the past 10 years indicates, however, that, apart from a few notorious exceptions, no harmful drug was given to a substantial number of people. With the lessons learned from those exceptions, thalidomide in particular, the chances that a tragedy of similar proportions would occur again have decreased considerably. The number of new chemicals introduced in therapy on humans, however, has not been large enough to put current toxicity procedures to a definite test. The experience of many more years is needed before its usefulness can be fully appreciated.

Moreover, a fair evaluation of the preclinical testing for safety should not only be based on those drugs released for general use. It should certainly also include all agents submitted for trials on humans but subsequently dropped for one reason or another. The comparison of all positive and negative findings in tests on animals and man would help in the assessment of the significance of drug-induced changes in the experimental animal and would allow a more realistic appraisal of the toxicologic methods.

Such a review is made by the sponsor of each new drug; but for drugs which are not commercially introduced this most valuable information is rarely published. Thus, the experience of any one group of investigators remains fragmentary. The FDA, by contrast, has access to all information, but it is

bound by law to keep it confidential. Thus, much information which would facilitate the evaluation and improvement of toxicologic methods is locked away in the files of FDA and the pharmaceutical companies.

The drug companies' reluctance to make such information generally available is understandable. Not only would they divulge important research leads to others, but publication of toxicologic studies would greatly facilitate registration and sale of the drug by imitators in countries where patent protection is insufficient. A solution of this problem is in the interest of all concerned with development of new drugs. Perhaps a voluntary disclosure of pertinent information after a suitable interval of about 5 years from the time of introduction of a drug into clinical trials would be acceptable and would make an extraordinary amount of data available for scientific research.

Objections to the Present System of Toxicity Testing

The drug industry has accepted the rapidly expanding demands for toxicologic testing with reservations but practically without open opposition. Most firms have acquired new personnel and built large facilities in which thousands of animals are housed under controlled conditions. Clinical and histologic processing facilities, often automated and linked to a computer, are showpieces of efficiency and precision.

There has been no argument about the many hematologic and biochemical examinations of normal animals at the beginning of experiments, although an abnormal finding in untreated subjects showing regular growth and food intake and no obvious signs of disease is rare. Statistically significant numbers of male as well as female animals are included in all experiments, to provide for the rather remote possibility that one sex may be more sensitive to the drug than the other (*6*). Extensive hematologic and histologic examinations are performed in many animals in all treatment groups, although appropriate spacing of sampling might often indicate that abnormal effects are not to be expected in animals treated with the lower dosages. But a few other aspects of the toxicologic testing routine have given rise to arguments between scientists in industry and those who are in government control agencies.

Duration of Tests for Long-Term Toxicity

Several toxicologists, supported by the WHO committee (*4*), are of the opinion that a 6-month study would provide all significant information likely to be derived from this type of experiment, with the exception of carcinogenic actions. Others believe that meaningful cumulative toxicity may sometimes become manifest only after a drug was administered to animals for the greater part of their lifespan. Unfortunately there is little published evidence to support or refute either concept. There are some indications that FDA scientists appear to lean more and more toward a substantial prolongation of experiments on long-term toxicity. This led one to speculate that their staff possesses data which would support this attitude. Again, most of the presumable evidence is confidential and ought to be made available for scientific scrutiny before toxicologic testing procedures are once more expanded. In addition, more systematic research on the significance of late toxicity is needed.

Positive Findings in Animals

When a toxicity study uncovers only nonspecific changes such as depression of growth and mild atrophy of organs, the drug is considered safe enough to be released for clinical trials. When definite structural and functional changes are produced, the decision to undertake or continue clinical trials becomes very difficult. Damage to organs occurs frequently in the course of extensive toxicity programs—so much the more if a biologically highly active substance is used, and if, as required by commonly accepted rules, excessive doses are administered to animals. These points are often emphasized by scientists in industry who refer to the many injuries produced in animals by some of our most valuable drugs. They claim that such drugs as cortisone, digitalis, and perhaps even aspirin would not pass the rigorous safety standards of today, and they are concerned that this attitude might delay the development of important new therapeutic agents.

The scientists at FDA, with congressional investigators looking over their shoulders, are also in a difficult position. They can not be expected to disregard an experimental lesion just because experience with other drugs makes it probable that a cautious attitude may perhaps not be justified. What do they do with completely new findings for which there is no experience with other chemical substances? One has obviously arrived at a scientific impasse. The law demands that a decision be made within a specified period of time. Since the state of the art often does not permit a rational and objective defensible judgment the decision must be arbitrary.

What generally happens is that such drugs are referred back to the toxicologist for additional studies, perhaps in another animal species. After enough time has elapsed and a reasonable record of diligence and scrupulous caution has been established the drug is permitted to go on to the next stage of its development. This is an unsatisfactory process for everybody. The best that can be said is perhaps that it gives the clinician a stern warning to conduct the trial on humans with caution. Toxicity tests on animals can rarely be regarded as the decisive factor in determining the suitability of a new drug for human therapy. Other considerations such as the nature of the disease to be treated, the availability of alternate methods of treatment, the newness and uniqueness of the chemical structure, or the pharmacologic properties of the new agent must be weighed against the potential toxic hazards (*7*).

Menace of Unconventional Experiments

Biologists are often tempted to test the action of drugs in a broad variety of exploratory experimental systems. These may include synthesis, uptake and release of biologic substances, ultrastructural changes of cell organelles, inhibition or stimulation of enzymes, interactions with other drugs, alterations of behavior, and the like. Such studies with clinically well-established agents may be reported without fear of further repercussions (*8*). Findings on new drugs undergoing clinical trials must be brought to FDA's attention within a specified period. Alterations of biologic functions and structures with apparent toxicological implications must be reported without delay. These findings, however, are often less well understood than experimental findings obtained by conventional methods. Extensive further studies are often necessary to understand the mechanism and

relevance of the experimental results.

The reaction of governmental control agencies to such reports is hence often arbitrary. It may range from mere acknowledgment of receipt to extensive demands for further studies, warning letters to all clinical investigators, and the request for retesting of old drugs with the new experimental model system. Unexpected findings with toxicologic implications create the most difficult problem for the toxicologist, the clinician, and the government scientist.

It is reasonable to argue that it is unwise to test a new chemical in an unconventional and insufficiently investigated experimental system. But since scientific curiosity is hard to control, such problems continue to arise. The safety of the patients taking part in clinical trials must be the major concern of those involved in the development of a new drug. However, preoccupation with an unexplained experimental finding in animals must not take preference over the systematic evaluation of the compound's therapeutic and toxic potential in man.

Limited Scope of Toxicologic Tests

Probably the most serious criticism of the toxicologic testing procedure is the claim that it represents a narrow-minded attempt to deal with a very complex situation. At the root of the problem is the original concept that a toxicologic experiment should, as far as possible, imitate the anticipated use of the drug in man. Thus, an omnibus procedure was adopted which provided for long-term intake of a drug by the animals, periodic chemical and hematologic examinations with the use of routine tests of a hospital laboratory, and a complete autopsy with detailed histologic analysis of all organs. The only deviation from a straight duplication of the clinical situation was the requirement that higher than therapeutic dosages should be included. Although such procedures were advocated by Lehman and his colleagues (*1*, *2*) as well as other FDA toxicologists (*9*), it is clear from their writings that they did not consider them adequate to deal with all the problems of experimental toxicology. They certainly felt that the procedures could only represent a basic framework, to be amended by special studies depending on the pharmacologic and chemical properties of any given compound. The irony is that most of the additional effort in drug toxicology in the past 10 years was invested in an expansion and mechanization of the omnibus procedure. This is surprising because pharmacologists are most successful when they design their tests for specific purposes to make experimental conditions favorable for the demonstration of the desired effect.

It is easy to enumerate the toxicologic mechanisms which cannot, or can only exceptionally, be demonstrated by the usual toxicologic testing. It is more difficult to suggest satisfactory alternatives. There are, however, many pharmacologic and biochemical methods available which could be adapted for toxicologic investigations (*10*). Furthermore, the use of animals with inherited or acquired diseases or metabolic deficiencies could put toxicity tests on a more realistic basis. Despite these possibilities it must be clearly understood that many toxic drug reactions in man cannot be recognized in any known experimental system. These include, for example, many drug allergies and idiosyncrasies and other injuries which are due to congenital or disease-related peculiarities of response. To deal with those it is necessary to expand toxicologic research on humans.

Future Developments

The major challenge for the future lies in the recognition that drug toxicology is a living science and not an administrative procedure. Thus, its methods must remain flexible enough to incorporate newly discovered biologic concepts. It is encouraging that recent biochemical advances in drug metabolism have contributed much toward a more rational approach to drug toxicology. Pharmacogenetics will perhaps have an even more important influence. It is now up to the scientists in basic research to evaluate recent discoveries of molecular biology and immunology in order to make them useful for the day-to-day problems of drug toxicology.

Despite these exciting developments the usual pharmacologic approach to drug toxicology should not be neglected. Specific experiments should be designed for every type of toxic reaction likely to be encountered with a given drug. For this the advice of the clinicians should be sought, and the feedback mechanism from the clinician to the toxicologist should be rid of menacing undertones. Toxicologic results should be published freely and periodically reviewed in the light of expanding clinical experience.

Fundamental problems of toxicology cannot be solved by a limited effort of a drug manufacturer whose compound happened to be among the first to become involved in a scientific controversy. Such problems have to be identified and efforts for their solution coordinated. For example, a program of the World Health Organization that involves epidemiologists, clinical pharmacologists, immunologists, and experimental toxicologists in the United States and Europe is helping to elucidate the relation between long-term abuse of analgesic mixtures containing phenacetin and the incidence of chronic interstitial nephritis. Among the most pressing problems deserving similar attention is the question of mutagenic effects of chemicals. The trend to use proven or potential mutagens in diseases other than malignant tumors only underlines the urgency of this demand. Other problems which require large-scale collaborative investigations include the effects of oral contraceptives on physical and mental health of women and progeny, the importance of chemicals as cause of autoimmune diseases, the significance of drug-induced chromosomal damage, the long-term effects of enzyme inhibition and stimulation, and many others. It is hoped that participation in joint research programs by the FDA will soon become as important as its regulatory function. It is hoped that the toxicology programs of the National Institutes of Health and the World Health Organization will continue their leadership in the further development of drug toxicology.

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Theodore William Richards and the Atomic Weight Problem

He applied physical chemical principles to critical chemical problems.

Aaron J. Ihde

The birth year of Theodore William Richards, 1868, occurred during a momentous decade in the history of chemistry. At the beginning of the decade there was much skepticism among competent chemists regarding the usefulness to science of the atomic theory, and for very good reason. Although Dalton had introduced his theory 50 years earlier, some of the key questions connected with chemical atomism had never been satisfactorily resolved. At the end of the decade the power of the atomic theory was recognized and the periodic law based upon it was being established.

The decade began auspiciously with the Karlsruhe Congress in September 1860. Younger men in the field, particularly Kekulé and Wurtz, were responsible for calling the congress, which had as its objectives the formulation of an area of agreement among chemists regarding the nature of atoms and molecules and a consensus with respect to a mutually satisfactory atomic weight system. After 3 days of discussion the congress adjourned, with apparent lack of agreement. There had been a notable moment, whose significance was missed by the audience, when the young Italian chemist Stanislao Cannizzaro called attention to the value of Avogadro's hypothesis as an organizing device for the interpretation of chemical phenomena. While Cannizzaro's message was largely misunderstood, the pamphlet which he had prepared and which was passed out before the meeting adjourned was thoughtfully read by one young chemist, Julius Lothar Meyer, who saw that it pointed the way out of a half-century of chemical chaos. His *Die modernen Theorien der Chemie,* published in 1864, utilized as its basis Avogadro's hypothesis. The particular significance of the hypothesis lay in the fact that its application made possible the determination of molecular weights of gases and vapors, and thereby the derivation of molecular formulas of these substances. It further led to acceptance of the concept of diatomic molecules of hydrogen, oxygen, nitrogen, and the halogen gases and to a rational understanding of gaseous reactions. Of particular importance, it led to the stabilization of atomic weights into a consistent system. No longer would chemists use several different sets of atomic weight values (*1*).

A natural outgrowth of reliable molecular formulas was structural theory. Although Archibald Scott Couper had been groping toward structural formulas in his famous paper of 1858, it was not until after the Karlsruhe Congress that structural formulation began to develop fruitfully in the minds of Butlerov, Kekulé, and, to a lesser degree, Crum Brown, Frankland, Wurtz, Erlenmeyer, and Hofmann (see *2*). Before the decade was ended a viable theory of structural chemistry had been established, not only for the simple aliphatic compounds but for aromatics as well. As new and formidable demands were placed upon structural theory during the next decade in connection with the formulas of complex natural products and synthetic dyes, the theory would prove capable of meeting the challenges.

The decade of the 1860's also saw chemical knowledge being utilized by the developing dye industry. By 1868, students of Baeyer had been successful in duplicating the molecule of alizarin, the coloring matter present in an ancient dye, madder. The foundations laid in the 1860's were so sound that it was possible for knowledge of organic chemistry to explode during succeeding decades.

The 1860's were also notable in the

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