Meetings

Chemical Mutagenesis

The question of whether nontoxic chemicals and drugs present a hazard to the population by causing mutations or other disturbances in genetic function was taken up at a meeting held at the National Institute of General Medical Sciences, Bethesda, Maryland, on 28 May 1968; the meeting was attended by 11 scientists (*1*), including geneticists, molecular biochemists, pharmacologists, and clinicians. The following specific questions were considered. (i) Does a serious clinical problem exist due to mutations resulting from human exposure to chemicals (drugs, pesticides, and others)? (ii) Is there any way, at present, to relate to man the mutagenicity due to chemical agents observed in any organism (such as microbes and insects)? (iii) Is it feasible, with the present state of knowledge, to develop rapid, inexpensive, and accurate tests to predict the hazard of any specific chemical in producing mutations in man?

Chairman James Crow (University of Wisconsin) pointed out the parallelism between the discussion of this problem and those that took place 10 to 15 years ago regarding radiation protection and possible radiation hazards. Out of the discussions on radiation hazards came the public policy for control, the ratio of benefit to hazard being the decisive factor. However, as Crow pointed out, with chemical mutagenesis, the problem is totally different. In the case of radiation, the mechanisms of possible control were relatively simple, and one could extrapolate from one organism to another with reasonable confidence. This does not appear to be true with respect to the variety of chemicals to which the population is exposed. Two possible approaches were suggested: first, to attempt to identify compounds as being mutagenic by means of laboratory tests, and second, to detect in some way the existence of something affecting the human mutation rate and to determine what is causing that change.

With respect to the question of whether a real clinical problem exists, it was clear that there is no example of harmful effects in man which can be attributed to mutation resulting from exposure to a specific drug or chemical. In this sense, no overt clinical problem exists. However, knowing that some common substances can cause mutations in microorganisms and insects suggests that there may be a problem too subtle to be identified. Nor can the possibility be dismissed that a problem might emerge suddenly, as in the case of the teratogen thalidomide. Indeed, in view of the prospective increased use of drugs that affect fundamental cell processes, such as antimetabolites in nonmalignant disease and the likelihood of use of immunosuppressive agents in autoimmune diseases, continual alertness for such a possibility is mandatory.

It was the consensus of the group that, instead of waiting for some obvious, and perhaps catastrophic, demonstration of chemical mutagenesis in humans to occur, some limited exploration might be feasible now. Epidemiological studies might be carried out with some reasonable expectation of detecting increased genetic disease and perhaps associating it with some particular drug.

One suggestion was to accumulate data on the offspring of persons known to have been exposed to certain specific compounds. One such compound is atabrine, which interacts with nucleic acids and is subsequently found in tissues in concentrations a thousandfold higher than in plasma. A vast number of persons in malarious areas were given this drug during World War II. Dominant effects should show up in offspring, and a properly conducted survey might bring this out. Negative data might aid in the identification of actions of a compound in vitro which are not likely to be useful in predicting effects in the human.

Although the influence of chemical agents on genetic processes in lower organisms has been studied, too little is known about species phylogenetically higher than insects so that tests with even approximate predictive value could be designed. To all the manifestations of genetic change, such as gene mutations, gene deletions, exchanges, chromosome breaks, and others, must be added pharmacological variations which become increasingly complex and difficult to evaluate. The distribution of the drug, its metabolic products, the cellular concentration in various organs, and the like, add to the complexity of the problem. Indeed, the very interpretation of many obvious, easily recognized genetic alterations is still uncertain. The significance, or importance, of chromosome breaks which have been observed in human cells is still unknown. The problem is compounded by the possibility that some substances which are not mutagenic in themselves might be converted into mutagens metabolically or prove to be so in combination with other factors such as other drugs, agricultural chemicals, radiation, and so forth. For example, caffeine by itself is not a strong mutagen in bacteria, but in the presence of ultraviolet light mutations are observed, presumably due to an inhibitory effect of caffeine on the genetic repair mechanism.

The conclusion of the discussions was that no laboratory or clinical tests are now available for predicting a mutagenic hazard in man with any degree of certainty. It was agreed that to condemn a useful, or potentially useful drug, on the basis of any single available test would be a disservice.

However, there is reason to believe that in time such tests can and will be developed. Studies of chemical mutagenesis in the mouse are being conducted, and these bear watching. M. Legator (Food and Drug Administration) described his host-mediated test which represents an attempt to utilize an in vitro system in an in vivo situation. In this test, the drug is administered to the mouse, and then a bacterial suspension is introduced into the peritoneal cavity. Later, the bacteria can be examined for mutagenic changes. The mouse-dominant lethal test appears capable of picking up selected types of compounds. However, no one test is likely to be satisfactory for the purpose. Rather, it will be necessary to utilize a battery of screens in order to obtain satisfactory answers.

Technological advances can be expected to increase the speed and accuracy of scanning cell populations, but

a great deal needs to be known about the significance of genetic alterations before interpretations can be made. What does a chromosome break mean? Are all breaks initiated the same way? Are some mutations due to failure of repair? Are mutations due to direct damage of the nucleic acid or to breakage of protein backbones, or to secondary factors? Are all breaks harmful?

It was agreed that much more basic work on mechanisms and interpretation of genetic alterations is needed, but that this, in itself, is not likely to solve the problem. More trained pharmacologists are needed in the field of genetics in order to extend the basic findings to the practical level of human utilization.

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Notes

1. Participants in the conference included: Bruce Ames, Berkeley, Calif.; John Burns, Nutley, N.J.; Paul Calabresi, New Haven, Conn.; James Crow, Madison, Wis.; Kurt Hirschhorn, New York; Herschel Jick, Boston, Mass.; Robert Krooth, Ann Arbor, Mich.; Leonard Lerman, Nashville, Tenn.; Frederick Philips, New York; William Russell, Oak Ridge, Tenn.; and Margery Shaw, Houston, Texas.

Biological Oceanography: Models

The Committee on Oceanography, National Academy of Sciences–National Research Council, invited an ad hoc group of scientists to meet at the University of Washington at Seattle, 6–7 April 1968, to review the current status of the work on ecological models in biological oceanography and to advise on recent developments in quantitative modeling techniques that might be useful for studying marine ecosystems.

The review and initial discussion included the following points. Many of the ecological models in use today are too vague and ill defined to provide a solid basis for study of the structure and behavior of ecosystems. Food web diagrams, with their array of directional arrows even for a moderately diverse fauna, illustrate the difficulty of using a descriptive approach to determine biological productivity or policies of resource management.

Discussion of ecological models becomes more profitable when restricted to models susceptible to quantitative formulation and testing. The quantitative model provides an essential guide to the design of entire research programs so that submodels can be developed and validated by field observations and fitted into a larger model. Quantification of biological processes is essential if biologists hope to make effective use of chemical and physical information. Quantification and the use of standard mathematical terminology is also essential if biologists hope to communicate effectively with specialists in other disciplines.

The past accomplishment of ecological models in biological oceanography is to have provided insight into the organization and function of marine ecosystems, particularly of the plankton. It is doubtful that some of the present concepts could have been developed in the absence of these models. The models have served as a fertile source of ideas for laboratory experiments and the design of field-sampling programs. They have also helped to assess man's effects on the environment or populations. The models have further served the usual purpose of mathematical models in synthesizing fragmentary studies. Finally, they have been useful in teaching.

The group concurred that there are many opportunities for the application of mathematical models in biological oceanography as well as growing computer capabilities to aid the development of models, and noted that simulation models are not yet widely used in biological oceanography. The following most critical constraints to rapid expansion in the development and use of models were identified. They apply in part to ecology in general, and in part they are specific to the field of biological oceanography.

1) There is insufficient quantitative knowledge about functional relations such as the manner in which the demographic characteristics of a given species change with population density, or how the efficiency of food assimilation depends upon environmental factors.

2) Useful data for building detailed, comprehensive models, and for validating them, are scarce. The obvious way of directing the proper collection of data is through the stimulation and encouragement of model building, which will point to the data most needed.

3) There is no agreement upon the resolution required for a realistic ecosystem model. At one extreme are models of gross energy or mass transfer between trophic levels and, at the other, models that rival the complexity of nature itself by including numbers of individual animals of each species.

4) Biological oceanographers, with only a few notable exceptions, have made little advance in synthesis of the available knowledge. Marine ecosystems are so complex, and available information is so incomplete, that many people may regard prospects for meaningful synthesis to be poor. There is also a lack of examples demonstrating significant achievements with complex ecological models in biological oceanography. One outstanding exception is provided by the field of fishery population dynamics, where models important in resource management have been built for seals, whales, tuna, halibut, and salmon, among others.

5) Development and improvement of simulation models are usually multidisciplinary efforts, but there seem to be few people who can serve as leaders for such efforts.

6) It is doubtful that experience in ecological modeling is sufficient to support development of an ecological computer language, although a general language may be useful in the future. However, computer subroutines to assist biologists in modeling some general ecological processes would probably increase the use of simulation modeling techniques.

The following suggestions were considered to accelerate the development of quantitative modeling in biological oceanography. (i) Encourage specialists knowledgeable about the use of models in other fields to enter biological oceanography. (ii) Use models in teaching introductory courses in biological oceanography to reach students from other disciplines early in their careers. (iii) Publicize the potential of ecological models to those concerned with socially beneficial goals such as the conservation of renewable resources. (iv) Encourage agencies to establish or support interdisciplinary teams for developing computerized models that could be used to plan research and management for studying and eventually regulating total ecosystems. These teams should include theoreticians and experimentalists so that there is an interchange of suggestions derived from the model and from observations in the field or laboratory. (v) In the absence of groups