Meetings

Comparative Medicine

Medical research has always depended heavily on animals as subjects for testing and evaluating new therapies. These usually have been normal, healthy animals in which the disease or abnormality to be studied was introduced experimentally. Although many human illnesses cannot be induced in animals, diseases are known to occur in animals which closely duplicate human illnesses. Some animal diseases have been used as models for research on these conditions.

More such model disease systems are essential to study mechanisms underlying the broad spectrum of human health problems. This need has prompted the National Institute of General Medical Sciences to initiate a comparative medicine program. The goal of this program is to identify, study, and use selected animal diseases which resemble human disease processes. Discovery of appropriate models will enable study of the multiple causes of disease and strengthen research on clinical disease conditions by avoiding many of the severe restraints imposed on human clinical investigation. This program would also identify the best animal systems for pharmacology-toxicology and drug research.

As a first step in developing this program, the National Institute of General Medical Sciences assembled a Workshop Conference of experts in the use of animal disease models for advancing information on human health. The importance and potential of comparative medicine had been suggested by earlier meetings held at Pennsylvania (*1*), New York (*2*), and Michigan (*3*). This meeting was to provide specific recommendations for the director and staff of NIGMS to consider in planning their program.

The meeting was chaired by Rene Dubos of the Rockefeller University. Other participants were two physiologists, two behavioral scientists, five physicians, two veterinarians, and one investigator trained in both veterinary and human medicine, variously representing medical schools, veterinary schools, departments of biology, and the NIH intramural program.

The conference emphasized that although many diseases of animals closely resembled conditions seen in man, they were not exactly the same conditions scaled down in size or time. However, the study of these diseases will be fruitful because they will reveal the underlying mechanisms and provide a clearer understanding about the related process in the human. To make comparative medicine effective, an interdisciplinary, interprofessional effort must be made with particular attention paid to the influence of environment on health, including behavior and social interaction. "A study of phenomena basic to the diseases of all species" was adopted by the conference as a broad definition of comparative medicine.

The principal disciplines involved are pathology, physiology, psychology, anatomy, and pharmacology. Interaction of these basic disciplines and all of the medical professions is necessary for two reasons: first, to study the normal and the diseased states in various species in order to identify similarities and differences between them and the similar condition in the human; second, to investigate the multiple causes of disease. The conference members pointed out that very few diseases have a single cause even when the cause is a microorganism. It has already been shown that infectious, degenerative, and neoplastic diseases can be influenced by such factors as temperature, environment, and social pressure.

There is a hazard in the study and use of animal disease model systems. Many of these models, which have been the basis of research problems in the past, have eventually become projects devoted entirely to studying the model. The thrust of the comparative medicine program must be to study the mechanisms of diseases and not the models themselves. Basic to this concept is the fact that comparative medicine is an interdisciplinary science; medical research problems in animals must be approached from a comparative point of view, including comparison to the human. Comparative medicine would also rekindle an interest in the natural science approach to biological problems in areas of research not yet clearly enough defined for the "reduction analysis" approach.

In training as well as research there is a need for greater exchange between medicine and veterinary medicine in order to bring the disease problems of the former and the research material of the latter into perspective. Both of these medical fields need to develop closer interchange between the clinical and the basic medical disciplines, especially physiology, psychology, biochemistry, and pathology. Through this exchange a comparative medicine program can begin immediately by building on the many animal colonies and animal programs which are already in existence, such as the regional primate research centers, zoological parks, veterinary clinics, and the animal colonies of medical schools.

Potential for Comparative Medicine

Comparative medicine will be most useful in areas of medical research where duplication of human disease in the laboratory is not possible either by transmitting it to laboratory animals or by altering the animals' physiology to create the same disease. The usefulness of comparative medicine can be demonstrated by utilizing it in areas of medical research most urgently in need of development. Several such areas currently of program interest to NIGMS are pharmacology, toxicology, anesthesiology, genetics, behavioral science, and trauma.

In the field of pharmacology, the use of certain laboratory animals for specific tests has been popular for many years; however, it has recently been demonstrated that chemicals which are teratogenic in one species may be safe for another species. The effect of psychopharmacological drugs on one species may vary considerably from the reaction on another. The metabolism

of drugs varies from species to species. It has been clearly demonstrated, for example, that the baboon is superior to other primates except possibly the chimpanzee in the study of reproductive problems. However, it may not be superior to the dog for cardiovascular research. The baboon is an animal in which epilepsy-like seizures may be readily created. It may also prove to be a most valuable animal for dental research. A study of this animal in depth by scientists of many disciplines has revealed valuable information in comparative medicine which will aid scientists in many fields.

The study of anesthetic products on a comparative basis has just begun. There is a considerable variation of susceptibility among different species of animals to anesthetic products and methods of anesthetizing. These differences can be useful in detecting dangerous side effects of anesthetic agents earlier, as in pharmacology research,

As in man, degenerative diseases occur in all species of animals as they grow older. Large numbers of aging animals are available in the population of companion animals—dogs, cats, and horses—which are kept by modern society until they are aged. Those in the clinics of veterinary colleges or other animal centers associated with large medical research programs will provide naturally occurring disease research models that could not be duplicated in a research laboratory. Many of these clinics will be able to accomplish the detailed clinical diagnosis and study necessary to make this valuable research material available.

Zoo animals offer an important opportunity to study environmental health problems. Over a period of years, these animals develop physiological adaptations to their captive urban environment, and may develop health problems which are specifically initiated by the environment.

The effect of social or behavioral stress on health can be evaluated in companion animals. Although psychotherapy will not be possible for these animals, correction of the animals' problem by the administration of drugs, by hormonal changes, or by changes in the environment may be possible and in a comparative way demonstrate valuable new approaches to psychological problems.

Research on animal genetics is a well-established research field with an experimental basis. As more information becomes available on human ge-

netics, study of the large colonies of inbred laboratory animals and closely related animals such as dairy cattle produced by artificial insemination programs may provide valuable comparative leads as an important basis for human health research. Many of the inherited defects in the human such as cleft palate are already known to occur in animals. The coordinated approach to comparative medicine as suggested by the conference may reveal and make available many new models of genetic defects.

Trauma and injury are common among animals. Animals could contribute valuable information in the study of devices calculated to restore weight bearing and mobility in a very short time. The animals can be used to evaluate materials proposed for prosthetic replacement of tissue. They are valuable also in studies of tissue transplantation and other reparative efforts.

Plans for the Development of Comparative Medicine

The Workshop Conference concentrated on consideration of institutions or disciplines having the greatest potential to contribute to comparative medicine, and discussed the way in which they could more effectively advance medical research through comparative medicine.

Comparative Medicine in the Medical Center

A program in comparative medicine is needed at university medical centers and could contribute greatly to their immediate and long-range research goals. Medical centers have certain advantages as the major focus for attempts to develop such programs. First of all, they are already centers for ongoing research projects in human-oriented studies and at the same time employ animals of a wide variety in order to solve these problems. These medical centers contain groups of scientists with highly specialized abilities and knowledge, who could contribute to and profit by a comparative approach. Finally, their training programs would be of value to potential members of a comparative medicine group.

For the most part, the medical center can contribute to a comparative med-

icine program by providing training opportunities, by stimulating active research in disease, and by encouraging experienced scientists to participate in this work. Opportunities already are present for training in depth in various disciplines. What especially is lacking is the knowledge and the specific intent to see disease problems from a broad biological viewpoint. The goal of a comparative medicine program at a medical center thus would be to create an atmosphere that would stimulate interest in the study of a wide range of animals and plants. It would be a center of information in the field and would have the mission of extending knowledge both in breadth and depth.

There is a strong tendency for research scientists at most medical centers to penetrate more and more deeply toward molecular levels, with the result that they tend increasingly to neglect study of the entire organism and the overall disease process itself. On the other hand, a broad-based program in comparative medicine in such an environment could be a valuable complement to this trend, and could provide important new biological tools for the highly specialized scientists to use. Current in-depth studies by many medical scientists employ a wider range of comparative zoological material, but utilization of such material is often fortuitous rather than planned.

Such a loss of perspective results in overlooking opportunities that could come from full exploitation of the diverse possibilities provided in nature. Valuable insights can come from the entire biological spectrum. This does not exclude the molecular aspects of comparative medicine. The study of enzyme systems and fine structure should go hand in hand with the study of the whole animal. Specific recommendations include:

1) Bringing knowledge of disease processes to the zoologist. Medical specialists (pathologists, physiologists, microbiologists, biochemists) could participate in the presentation of courses in disease problems at the undergraduate level. Areas in the scope of a pathologist would be of great interest to a zoologist in dealing with basic processes such as inflammation, cell degeneration and necrosis, wound healing and regeneration, neoplasia and nutritional deficiency conditions.

2) Bringing zoologists and veterinarians into established training programs at university medical centers.

Fellowships could be made available for zoologists or veterinarians who would desire to enroll in the Ph.D. programs in pathology, biochemistry, physiology, and other fields. Support might be provided for those with Ph.D. degrees in zoology who desire to obtain specialty research training in medical center programs.

3) Providing long-term support for comparative medicine programs to be developed within medical centers. Programs of this sort would of necessity be structured as appropriate to a particular university or medical center. For the most part, this support would probably require long-term commitment of salary support for a chair or professorship in comparative medicine, for the salaries of several additional faculty persons, and for the initial construction of laboratory and animal facilities.

One possibility is that such a program in comparative medicine could be placed administratively as a division within a department of pathology, and could be physically placed in the vivarium of the medical center. It is clear that the academic and research activities of the scientists in such a program would have to be distinguished from the service functions of the vivarium.

A conjoined title between disciplines such as pathology and zoology could be supported and might contribute to interaction between such groups.

Comparative Medicine in the Veterinary College

The vast wealth of clinical materials constantly presented to veterinary medical clinics may well represent one of the greatest sources of available comparative medical research material. These animal models would provide new avenues for sophisticated research not permitted on human beings. Animal diseases of comparative interest are frequently conditions which occur sporadically and are not the subject of great economic loss. Therefore, they have not been the subject of interest or research support by the agriculture or animal production community.

At the present time, little use is made of this rich source of information due to the lack of program support and physical facilities. There is obvious need to establish, at colleges of veterinary medicine, research hospitals staffed by disciplinary trained scientists

who are sufficiently well supported that acquired and inherited animal diseases similar to those of man can be collected and studied. The nature of many of these studies will require long-term handling, observation, and treatment of subject animals. Special holding facilities will be necessary at certain centers to allow for the long-term maintenance of genetic lines and specific mutant stocks.

A potentially useful source of animals seen at veterinary colleges and certain animal research facilities are the animals that age as companion animals. They are especially valuable in chronic disease studies, in studies of the effect of environment, long-term medication, and social pressures. Specific examples of aged animals are the dog, the cat, and, more recently, the horse, which are ordinarily kept until they live out their days rather than until they live out their principal usefulness.

Artificial insemination rings which keep valuable bulls until they are in their advanced years provide another source of aged animals. If these animals can be studied in depth by research programs associated with large clinical programs, much significant and useful comparative medicine material will have been developed.

The preservation of such experimental models is of utmost importance so that veterinary medicine may make its maximum contribution to human health. It is expected that certain comparative studies would be conducted in-depth at colleges of veterinary medicine; however, it is recognized that more scientists with interests in specific diseases can be found in the many medical schools. An important role of the comparative medicine center at the veterinary college would be to make available to scientists throughout the country animals with specific model diseases.

It is of utmost importance that a coordinated effort be made within the National Institutes of Health to develop a system for disseminating information concerning the availability of existing animal models. In addition to the establishment of centers at certain veterinary colleges in close cooperation with medical institutions, a number of other programs should be initiated:

1) Symposia in comparative medicine to include investigators from medical and veterinary medical schools in order to exchange information on the potential material available in veteri-

nary clinics and on the needs for comparative medicine material in medical schools.

2) Fellowships (multidisciplinary) in comparative medicine designed to integrate veterinary and human medical research programs and to apply comparative methods to biomedical research programs.

3) Publication of a compendium (by organ system) of existing animal models as to their nature, location, and present level of information pertaining to each topic.

Role of Zoological Parks in Comparative Medicine

Zoological parks traditionally have been devoted primarily to exhibiting animals to the public; scientific and educational efforts have been built around this core objective. Research for the most part has been restricted to activities that would least disturb this fundamental direction. Taxonomy, anatomy, and to some extent physiology and pathology are amenable to these restrictions. Little effort, however, has been made to learn of the diseases which affect zoo animals and to extrapolate from this knowledge information this is of value to the science of medicine.

Notable exceptions can be found in the United States at the Penrose Laboratory in Philadelphia, the San Diego Zoological Gardens, and the Oregon Zoology Center in Portland. The Welcome Institute for Comparative Physiology and the Nuffield Institute for Comparative Medicine at the London Zoological Garden have begun not only to make use of this source of comparative material but also to use it for research on an experimental basis.

The potential cannot be truly judged until much greater effort has been made to exploit the comparative medical aspects of zoo animals both in captivity and their natural habitat. The history of all biological research has taught us that the results of greatest significance are nearly always those which come as unexpected dividends. However, justification for funding agencies must be based on less ephemeral predictions. Fortunately, even limited efforts have yielded a considerable harvest from which we can point toward future possibilities. A few specific examples are:

1) Much valuable knowledge about the relationships of nutrition to ar-

teriosclerosis has been gained by studying specimens at Philadelphia and London zoos. Extension of these and related studies are contributing to our basic knowledge of arterial disease.

2) There has been a significant increase in the incidence of cancer in the animals of the Philadelphia Zoo during the past 30 years. This may have significance in relation to the pressure and pollution of urban environment. Indeed, zoo animals are usually located in urban areas and share with man the hazards of air pollution and crowding. Behavioral and pathological studies may help clarify the effects of urbanization upon the human population.

3) Metabolic bone diseases, especially of primates, have presented exciting and puzzling analogies with such human disease as osteitis fibrosa cystica.

4) Endothelial changes in parasitic infestation particularly by trypanosomes closely resemble those seen in man.

Those zoos which have a university affiliation are especially worthy of support because they are familiar with medical research methods and problems and can be expected to work profitably with medical research institutions.

In order to encourage the development of research programs in zoos, the conference suggested the following activities:

1) Organization and support of a series of seminars in comparative medicine based upon studies of zoo animals. These should be held in outstanding zoos. They should utilize participants from such disciplines as physiology, biochemistry, and ethology but should emphasize pertinence of the work to human health and disease.

2) Establishment of a directory of zoo animals based upon identification of individual animals, up-to-date records of the environment, health, and age of each specimen. Careful postmortem study of each animal is essential.

3) Establishment of full-time research directors in zoos in close academic affiliation with universities, medical schools, or schools of veterinary medicine. Individuals of accomplishment in comparative medicine should be sought for such positions. These research directors should be encouraged to continue their own research programs, to develop training programs for young investigators and ancillary personnel, and to encourage visiting scientist programs.

Role of Physiological Sciences in Comparative Medicine

Animals show physiological and behavioral adaptations or adjustments that make them uniquely suited to live in their particular environments. The comparative study of adaptations found within different species of animals with a continuum of varying degrees of stress makes it possible to define the physiological limits for such adaptations.

The goals of the suggested program are to measure and define such adaptation in both character and degree in a variety of environments such as cold, the desert, high altitude, tropics, salt water, and fresh water. To study animals in their natural environment is entirely different from a study of the animals under laboratory conditions. No understanding of the true adaptation of the animals can be gained unless one has observed first hand the extremes of the environment and the behavior and way of life of the animal. There is a peculiar lack of understanding of the value of field studies among most people in the health sciences. It is generally assumed that the same knowledge can be gained by bringing the animals to the laboratory. This is far from the truth. It is true that after the animals have been studied in the field, many problems can then be studied under more controlled conditions in the laboratory. In order to carry out these investigations the following are needed:

1) Well-established laboratories situated in extremes of environments, that is, an arctic laboratory, or desert laboratory, or tropical laboratory, or high-altitude laboratory, preferably associated with a university. These laboratories should have a permanent staff and should be well equipped. In addition, there should be facilities for collecting animals and maintaining them under almost natural conditions.

2) The second need is support of field stations and expeditionary efforts to conduct studies of animals found in particular environments where no well-established laboratory is present.

3) In order to make it possible to choose the right locations for field studies, it is recommended that a survey be made of available field stations throughout the world and a reliable list of the animals and services available at these field stations be prepared.

An integrated training program that permits circulation of the trainees be-

tween established environmental centers or participation in field expeditions should be initiated. The expeditions and study at well-established field laboratories offer unique opportunities for training of younger participants. Trainees will be exposed to people who are used to working in the field and with first-hand knowledge of wild animals. It is assumed that the groups investigating animals in the field will include scientists representing various disciplines such as (comparative) physiology and biochemistry, pathology, veterinary medicine, and human medicine. This will offer opportunities for training of participants as well as for the trainees.

Behavioral Sciences in Comparative Medicine

The behavior of an organism as it adjusts to its environment plays an important role in any study of health and disease. Often this role goes unremarked because the omnipresence of behavior tends to make it all but invisible; often, too, its role is ignored because the study of behavior appears not to have yielded a sufficient number of useful laws.

Although much is known about behavior, in only a few species has the behavior of animals been studied in any detail. On the one hand, psychologists have tended to concentrate their efforts on working out principles of learning in such laboratory animals as the rat and the pigeon (although more recently their efforts have been extended to the primates). On the other hand, the zoologists (including ethologists) have tended to concentrate their efforts on the naturally occurring behavior of a variety of animals in normal environments. Another difference may be seen in the psychologist's predominant interest in the behavior of human beings—mostly in natural settings where controls are impossible or difficult to institute—while zoologists have limited their studies to infrahuman organisms.

It is no longer necessary to keep these two avenues of approach apart. A science of behavior should be developed that does not restrict itself to any method or any organism but which would include both laboratory and naturalistic studies of a variety of animals, man not excepted.

In addition to the development of research projects between zoologists

and behavioral scientists, a research training program should also be developed. Study and training in behavior should be undertaken at centers where large numbers of animals are kept such as zoos, biological stations, veterinary colleges, and the vivariums of medical schools.

A number of research studies might profit by a comparative approach. Among them would be the study of social groups and the effects of crowding, the amount and kinds of stimulation required for normal or optimal development, and conversely the effects of deprivation. The role of parent-infant and peer-peer relationships upon social structure would relate closely to these more basic studies. In cooperation with the sciences basic to medicine, comparative studies of the biochemistry of memory and learning, and comparative studies of behavioral genetics are needed.

The knowledge gained by these comparative studies may have a direct application to man by revealing the basic mechanisms underlying antisocial behavior, crime, delinquency, and development of the individual's potential.

Summary

Many scientists are conducting research on human diseases which cannot be transmitted readily to laboratory animals or duplicated in the laboratory. Information offered by animal disease models should be compiled and made available to these scientists through the publication of extensive lists of animal disease models and annotated bibliographies for specific conditions.

Reports should be obtainable for answering certain specific needs in fields such as the potential of animal disease models available in zoos, the potential of animal disease models available in veterinary clinics, the use of animal disease models in the evaluation of drugs and other new therapies, and animal disease models as they may be studied in the natural habitat.

Symposia should be held on the comparative material available in zoological parks, and how it might best be made accessible. Meetings should be held between medical researchers and the clinical staffs of veterinary schools to explore the potential of veterinary clinics for contributing more material to comparative medicine.

Most urgently needed are scientists

trained to study specific animal disease problems using the comparative method and emphasizing comparison to the human.

Another need is training through fellowships to provide interim postdoctoral training at medical research institutions for veterinarians, psychologists, and zoologists, and to induce thorough study methods and laboratory procedures used in human medicine and duplicated in animal disease research. Such training would provide a better appreciation of animal diseases that are potentially important to human health research, and how they might be adapted to human health research methods.

Special fellowships should be made available for physicians to work in veterinary schools, zoological parks, or animal colonies to learn the clinical and pathological aspects of animal disease. Behavioral scientists working in medical research programs would then become familiar with the impact of various behavioral problems on diseased conditions developing in animals.

Integrated programs in which the joint research efforts between those trained in animal disease and those trained in human medicine must be developed. The appointment of full-time investigators using the comparative method to study animal disease models is strongly recommended. Such joint research could take place between medical schools and zoological parks, between veterinary schools and medical schools, or between any institutions conducting research in human health and having access to a large animal population, properly trained veterinary pathologists, and other animal health specialists. Many existing resources of animal disease material are not utilized to full capacity for contributing to comparative medicine.

Support for specific studies of the physiology of adaptation, the effects of environment on animal health, the interrelationship between diseases and the interrelationship between behavior and disease are also recommended.

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