Bull Pan Am Health Organ 15(1), 1981.

ANIMALS FOR MEDICAL RESEARCH AND TESTING[1]

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Today a wide variety of laboratory animal "models" makes an invaluable contribution to research on human disease. This article describes the general nature of that contribution, giving particular attention to the need for additional models and to the current role of nonhuman primates in biomedical research.

Historical Perspective

Throughout history animals have played an important role in man's quest for knowledge about himself and his environment. According to early Vedic records, veterinary medicine in ancient India during the period 1500-500 B.C. was quite advanced. During this time man acquired the art of medical practice by observing animals and birds. The Greeks studied and taught both human and veterinary medicine and appreciated the interrelationship between the two. Greek anatomists also practiced dissections on pigs and other animals.

During the Roman and Byzantine periods, medicine reached a high level of sophistication. Virgil, Aristotle, Hippocrates, and their followers all studied animal life, since religious and legal sanctions existed against dissecting human cadavers. Galen, physician to Marcus Aurelius, extensively studied the anatomy and physiology of the Barbary ape because of its similarity to man. From their observations of animal life, these men arrived at many conclusions relative to human medicine that are as valid today as when they were formed more than 2,000 years ago. Both human and veterinary medicine deteriorated during the Dark Ages, at which time man viewed animals as totally different from himself and was unable to see any common elements in the two branches of medicine.

Medicine reappeared with the Renaissance. Mondino at Bologna revived pig and dog dissections in the 14th century. In the 16th century Leonardo da Vinci made his important contributions as a comparative anatomist. In the 17th and 18th centuries, the entire field of medicine was revitalized by the work of men like John Hunter, Marcello Malpighi, Stephen Hales, Robert Hooke, Edward Jenner, and others, and their work laid the foundation for men like Louis Pasteur and Robert Koch. Then, as now, work with human beings was limited and much of the study was done on animals, with significant advances frequently a direct result of animal observations.

From that time on there has been steady progress in developing links between man's study of himself and his study of animals. The potential importance of the mouse as a model system for experimental research was recognized as early as 1889 when it was established that malignant tumors could be transplanted successfully in the species. The optimism resulting from this discovery faded as results varied so greatly that investigators often could not verify their own observations, much less expect another researcher in a different laboratory to do so.

Selecting and Breeding Research Animals

Once the taboos against meddling with nature's order were relaxed, the science of genetics furnished the means of standardizing ani-

[1]From *Animal Health in the Americas, 1980,* PAHO Scientific Publication 404, Pan American Health Organization, Washington, D.C., 1981, pp. 64-74.

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mals through intensive inbreeding. Today gnotobiotic technology allows us to develop and maintain models with profound immunologic defects. As biomedical research becomes increasingly more sophisticated, the challenge of assuring a good supply of healthy, well-defined, and characterized laboratory animals also becomes more complex. Techniques of the future include the combination of blastocysts to produce a mosaic animal with four parents and the isolation of pronuclei in fertilized eggs before they merge to obtain isogenic animals that are identical for every pair of genes. In addition, by the turn of the 21st century, most primates used in research probably will be laboratory reared. The use of these animals will greatly expand the potential for better research and testing.

Feeding Problems

In the future particular attention should be paid to other factors which can influence the results of our sophisticated tests. Nutrition is a factor that must be recognized. Concern for contaminants in animal feed has reached major proportions. In an extremely short time, we have gone from conducting major toxicology studies with no consideration of contamination levels in feed to wanting to know maximum acceptable levels of contaminants. Unfortunately, there are an infinite number of potential contaminants, and it would be impossible to look for all of them. In addition, there is little knowledge of what levels are dangerous or what levels can be practically attained in feed. It is important that researchers test for and document a reasonable number of contaminants that could affect a project so that in the future results can be compared and a contaminant's significance evaluated.

A recent literature survey showed that, when reporting research results, a very small percentage of investigators indicate the diets used. Since the analytical technology in the nutrition field is so far ahead of the biological information available, it is critical that scientists document nutritional information in an effort to make their experiments as reproducible as possible. As more is learned about different nutritional levels, results from many experiments may be greatly altered.

Microbial Problems

The microbiological status of animals also can determine the outcome of an experiment. Agents that do not normally produce disease may create problems in experimental situations when the animals are subjected to stress. Other agents may not produce disease under experimental conditions, but can cause misinterpretation of results. Because of these intricate relationships, it is desirable to use laboratory animals that are as "clean" as possible and to define the microbial agents present.

Many assumptions about disease have been changed as a result of the new and exciting work in slow and latent viruses. Some syndromes which were considered metabolic diseases, genetic diseases, or aging processes have been found to be infectious diseases with long incubation periods. As in the study of transmissible mink encephalopathy and scrapie in sheep and their relationship to human encephalopathies like Kuru and Creutzfeldt-Jakob disease, models for human disease are often found accidentally during the study and delineation of the mechanisms of animal diseases. Today a change is being observed in the scientific community: individual research is giving way to the team approach. A positive step in this direction has been the establishment of comparative medicine departments, which have led to collaboration between physicians, veterinarians, and other biological scientists in the selection and care of animal models as well as in the design of experimental protocols.

Breeding and Selection of Mutants

The World Health Organization has designated the National Institutes of Health (NIH) as a Collaborating Center for Defined

Laboratory Animals. We have an active genetics program responsible for breeding and properly maintaining over 100 inbred strains of mice and rats, a large proportion of which have been obtained by exchange with other institutions throughout the world. However, our breeding efforts are not limited to rodents. Cats, dogs, poultry, swine, goats, sheep, and nonhuman primates all are being bred for use as laboratory models.

Many of the models used today are the result of incidental observation. For example, researchers in Japan recognized a male rat with naturally occurring hypertension. Through a series of matings, they developed a colony of hypertensive rats with one subgroup having extremely elevated blood pressure levels, making these animals good models for the study of this condition and its treatment. Another example of a spontaneous mutation that has been recognized and developed into an animal model is the athymic or nude mouse which originally came from Scotland. Since the majority of models we are using are the result of fortuitous happenstance, the need for careful observation of animal colonies and recognition of unusual specimens cannot be overemphasized. Technicians should be trained to discern seemingly minor aberrations or unusual characteristics and to preserve rather than destroy such animals.

The genetic background of laboratory animals also can be a critical factor in the success of an experiment. Any institution which provides research animals to other organizations must be particularly concerned about the genetic integrity of these animals. At NIH a program has been instituted to prevent genetic contamination of a strain either through human error or accidental mating and to detect mutations as they occur. During the past several years our geneticists have developed individual genetic profiles for many inbred mouse and rat strains produced at NIH. Every strain has unique characteristics that can be detected through chromosomal analysis using biochemical, immunologic, and morphological markers. By comparing a specific animal's profile to the genetic profile for the strain, we can determine if the animal itself has become an experimental variable.

These genetic profiles are not limited to rodents and inbred animals. Our geneticists are also developing profiles for a breeding colony of dogs. In this case, they are characterizing the types and frequencies of genetic factors for the breeding group rather than a specific profile for a strain. These group profiles should be of value in selecting characteristics for breeding that are not readily evident. For example, dogs with higher frequencies of lipoproteins may be artificially selected for developing a model for atherosclerosis. The chances for success in this type of project are increased greatly if profiles are available for the animals involved.

Animal Disease Models

Spontaneous Diseases

In addition to models obtained through selective breeding, naturally occurring animal models of spontaneous disease are invaluable to biomedical research. Occasionally veterinary practitioners will recognize an unusual problem and request help in identifying a condition from a veterinary school or research institution. It is important that breeders as well as veterinarians recognize the value of congenital defects and aberrant conditions and promote the study and evaluation of these animals at appropriate institutions rather than accepting euthanasia as the only course of action. Institutions are encouraging owners and practitioners to make these animals available for research by establishing special referral clinics to deal with unusual conditions. The study of these animals will add vital information to our fund of knowledge and in time may help breeders to alleviate newly defined genetic problems. In addition, these animals may serve as the basis for new areas of biomedical research.

Several examples of important advances re-

sulting from this communication between private practitioners and veterinary institutions come to mind. Dwarfism in the malamute dog has become a recognized model for chondrodisplasia. In addition to providing breeders with more information about a genetic defect, recognition of this model has created new research possibilities in the areas of anatomical development, bone growth, and cellular abnormalities. Gray collie syndrome has resulted in the identification of cyclic neutropenia. A colony of ragweed sensitive dogs has been developed through the identification of animals with atopic dermatitis at clinics. Old dog encephalitis may provide a model for the study of severe demyelinating diseases in man. Important similarities have been found in the pathologic findings in mature dogs with old dog encephalitis and in those in humans with multiple sclerosis, subacute sclerosing panencephalitis, and neuromyelitis optica. In addition, some patients with multiple sclerosis have high titers to measles virus, which is antigenically similar to canine distemper virus, the cause of some cases of old dog encephalitis.

Recent solutions to veterinary problems now are being recognized as potential sources for treatment of human conditions. Marek's disease, a lymphoma of chickens affecting the nervous system, has been shown to be caused by a herpesvirus. Chickens now can be protected from Marek's disease with a vaccine developed using turkeys. Although this vaccine was developed to solve an agricultural problem, it may indicate new possibilities for cancer research. Identification of viral enteritis in children has been based on veterinary research and literature detailing the development of a vaccine to protect calves from this disease. Diagnostic tests for antibodies induced in cats by a leukemia-causing virus may lead to a better understanding of human leukemia. Development of new diagnostic and surveillance tests, as well as a vaccine for feline leukemia, may spur development of human diagnostic procedures.

Wild Animal Models

Wildlife populations also are excellent sources of naturally occurring animal models of spontaneous disease. Some of our most widely used laboratory animals were considered exotic wildlife only a few decades ago. The golden hamster was first introduced into the laboratory in 1930 as a new animal model for the study of kala-azar. Today the most valuable and commonly used wild animal is the nonhuman primate, ranging from the most primitive species to the most highly developed.

The use of experimental animals as surrogates for the bacterial diseases of man began in the mid-19th century with the discovery of microorganisms as the etiologic agents of infectious diseases. Current bacterial research depends on both spontaneously occurring animal disease models and laboratory induced infections in suitable animal species. The animal model system can help solve problems of infectious disease including virulence, mechanisms of host resistance, pathogenicity, and chemotherapeutic or antimicrobial drug action on the agent.

Studies of human infectious disease utilize nonhuman primates when these species appear to be uniquely susceptible to selected organisms pathogenic to humans for which no other suitable experimental animal can be found. In addition, nonhuman primates respond to certain bacterial organisms more like humans than any other susceptible animals. For example, pneumococci will cause pneumonia, septicemia, and meningitis in baboons and chimpanzees similar to the same conditions seen in humans. In other instances mycoplasma will cause pneumonia, shigella will produce enteritis, and mycobacteria will cause tuberculosis in various species of nonhuman primates as they do in man. Macaques, African greens, chimpanzees, baboons, and selected New World species are highly useful animal models for research in bacterial disease.

Tuberculosis is a major disease in both humans and animals, and an estimated 50-100 million people contract it each year. As a result of work by Schmidt and others, the rhesus monkey has been recognized as a valuable model for evaluating new chemotherapeutic agents. This model has also been used widely for appraising the benefits of immunizing agents. Studies in tuberculosis immunology have been conducted in delayed hypersensitivity, protection with BCG and various other vaccines, and the effect of isoniazid on the delayed hypersensitivity response. Recently, rhesus monkeys have been used in the development of the soluble fluorescent antibody and lymphocyte stimulation diagnostic tests.

Rhesus monkeys have been the primary model in the extensive study of enteric infections, and today dysentery is one of the most common diseases affecting them in captivity. Rhesus are susceptible to natural and experimental shigellosis, a disease which mimics that seen in man. Since rhesus seem to be the only animals that develop the disease spontaneously, they have been studied extensively from an epidemiologic, pathogenic, immunologic, and therapeutic basis. Recent studies have investigated the immune response to antitoxin in the prevention of the experimental disease. In addition, Saslaw and coworkers have shown that folic-acid insufficiency greatly increases the susceptibility of monkeys to infections, primarily dysentery.

Pneumonia is one of the most common diseases of the respiratory tract and as frequent a cause of death of wild animals in captivity as are diseases of the digestive tract. Lobar pneumonia in monkeys is more similar to croupous pneumonia in man as regards pathogenesis and the nature of etiologic factors than is croupous pneumonia in swine and cattle.

Recently, the rhesus, marmoset, and grivet have been utilized for the experimental induction of *Mycoplasma pneumoniae* and *M. hominis*. These animals have been used primarily to obtain information about host-parasite interaction. The disease in humans usually presents low mortality with little opportunity for adequate assessment of the pathological process. In the rare fatal cases, most pathologic changes seen result from secondary factors, thus complicating the picture. The use of nonhuman primates in these infections has been extremely valuable in the assessment of pathogenic change, study of immune response and, ultimately, treatment and control.

Gonorrhea is one of the most frequently reported diseases in the United States of America. The chimpanzee has been one of the primary animal models in the study of this disease. Since use of the chimpanzee undoubtedly will be limited in biomedical research, gonorrhea may be studied in geriatric or reproductively unsuitable animals in breeding colonies, since the disease can be inducted, observed, and then treated with minimal effect.

In addition to these diseases, nonhuman primates now are being utilized in experiments and investigations in the areas of febrile diseases, anthrax, bacterial endophthalmitis, *Yersinia* infection, streptococcal infection, leprosy, malaria, and vaginal mycoplasmosis. As we become more sophisticated in our studies of the host-agent relationship, these animals undoubtedly will be used for the study of newly recognized bacterial diseases such as Legionnaire's disease. In addition, with the increasing studies on chemotherapeutic agents, nonhuman primates may become increasingly important as models for definitive studies of drugs used in infectious diseases prior to ultimate application in man.

Although nonhuman primates have been important surrogates for man in the study of bacterial infections, they have been used more widely for research in viral diseases, since the host spectrum for viral infections is much more limited. There is some evidence that we all carry potentially oncogenic viruses in some, if not all, of our body cells. Although there is no positive proof that any human cancer results from infectious agents, evidence from experiments using New World primates overwhelmingly suggests that many cancers are caused by viruses.

Since 1968 more than 30 different herpes-

viruses have been isolated from various primate species in which they are responsible for a wide variety of clinical and subclinical infections and oncogenesis. Neotropical nonhuman primates are used for experimental studies with many of these viruses. Primate cells transformed *in vitro* by herpesviruses provide the tools for basic virologic and immunologic studies, and provide target cells for studying immune responses of innoculated animals. Further, these induced tumors are well-characterized and provide potential models for studies of basic tumor cell biology, therapy, and prevention.

The search for a viral etiology of human cancers continues principally because of the clearly defined relationship of a number of animal viruses to cancer induction in a variety of animal species. Recent studies on virus-associated cancers in neotropical nonhuman primates has enhanced the possibility of discovering the relationship between viral agents and human cancer. The use of New World species is an important contribution toward the solution of the virus-cancer problem where risks limit the studies that can be carried out in man.

Neotropical primates also have played an important part in our understanding of hepatitis. In the United States, 50,000 to 60,000 cases of hepatitis are reported each year, and WHO reports one million cases annually. These numbers undoubtedly represent only a fraction of actual infections and minimally a two-to-three-fold gap exists between reported and actual cases. Hepatitis has been called the single most common, notifiable, and serious infectious disease for which no specific treatment exists.

During a period when the causative agents of most common viral diseases were isolated and characterized in great detail, all efforts to isolate hepatitis viruses in cell systems or to transmit viruses to laboratory animals failed. Finally, in the late 1960s and early 1970s there were major breakthroughs in human hepatitis research. Transmission of hepatitis A from man to chimpanzees and some species of marmosets and from animal to animal provided systems for studying this disease other than in human volunteers. Today the mystax marmoset is considered the most favorable species in which to study this virus. It is now possible to study hepatitis A in the laboratory and to perform serum-neutralization tests in that species. In addition, infected marmoset livers remain the major source of hepatitis A virus antigen for development of diagnostic tests.

Marmosets will continue to play an important role in the elimination of viral hepatitis. Although the chimpanzee remains the only nonhuman primate known to be susceptible to hepatitis B, the marmoset probably will be useful in safety control tests of the hepatitis B vaccine. Also, marmosets may play a role in the study of non-A-non-B hepatitis, the third major form of the disease. Finally, marmoset tissues probably will be essential for the cell culture adaptation necessary for the development of a vaccine against hepatitis A. And use of this neotropical species also will be critical for safety and efficacy tests of any hepatitis A vaccine prior to use in man.

Research on Reproduction and Contraception

For almost any study of reproduction and contraception, the use of animal models is a necessity not only in testing hypotheses but also in developing and testing particular therapies before human clinical trials are begun. Much of the progress in contraceptive research during the past 20 years has resulted from animal investigations. From a qualitative point of view, nonhuman primates have been most important in gynecologic research.

Screening of New Products

Rhesus monkeys are used for large-scale screenings of new drugs and devices. These primates are particularly valuable for several reasons. Female monkeys have menstrual cycles of approximately 28 days. These cycles are not estrus cycles, but true menstrual cycles

with overt menstrual flow. Like women, these monkeys have two ovaries, but generate only a single ovulation per menstrual cycle. Accordingly, these models are valuable for studies of follicular growth. Despite the apparent availability of 400,000 follicles in the ovaries, only one ovulates per cycle; the selection of the dominant follicle and communications processes between ovaries appear to be identical to those in women. Basic research into the factors regulating folliculogenesis probably depends on these primate models and is a major research objective of the National Institute of Child Health and Human Development. The problem of producing single ovulations in women who must be induced to ovulate is yet to be solved. Like women, these monkeys have high frequencies of multiple ovulations when ovulation is induced with either human menopausal gonadotrophin or clomiphene citrate.

To a significant degree the cynomolgus monkey, a closely related macaque, may be an adequate surrogate for the rhesus. It is a particularly good surrogate in studies of the hypothalamic-pituitary ovarian axis which regulates the menstrual cycle. We have found, however, that the cynomolgus is not adequate in studies of the fetal placental-maternal interaction during gestation.

Contraception

The intermediate primates, particularly rhesus monkeys, have been used extensively in studies of contraceptive agents. When extensive anatomical similarity is required, these animals often are irreplaceable models. The uteri of other commonly used laboratory animals, such as the rat, rabbit, dog or pig, are bicornuate, suitable to litter bearing species, whereas the rhesus monkey's uterus and the association with the fallopian tubes and ovaries are a miniturization of that of the human female. Of course, there are points of dissimilarity that must be taken into account; people are not just big monkeys. However, when compared to other laboratory animal choices, intermediate nonhuman primates present overwhelming reasons to be chosen for gynecological studies.

In addition, these animals are particularly valuable for studies of contraceptive agents, since they have an equivalent follicular and luteal phase of the menstrual cycle. In many respects, the endocrine hormone profiles of the rhesus and cynomolgus are very similar to that of women. Furthermore, the time-course of events associated with fertilization and implantation are almost identical. The fertilized egg becomes implanted eight to nine days after fertilization. As in women, the developing syncytiotrophoblast immediately begins to secrete chorionic gonadotrophin. This unique hormone is produced during pregnancy only in humans and higher nonhuman primates. It is an unequivocable marker of pregnancy and extremely important for estimating efficacy in contraceptive studies.

Fertility and Pregnancy

Nonhuman primates also have been valuable in other studies involving the menstrual cycle. Recent research has shown that infertile rhesus monkeys experience luteal phase defects, including inadequate and short luteal phase infertility, as often experienced by infertile women. In addition, research concentrating on estrogen hormone replacement in the menopause utilizes these primates, since the menopausal changes experienced by intermediate primates are virtually analogous to those experienced by women.

There are other similarities between the human being and the nonhuman primate that make these animals valuable for pregnancy studies. The long process of organogenesis is closer between monkeys and man than between man and any other animal. Nonhuman primates usually have an intrauterine climate with only one fetus and the mechanism of parturition is very similar in women and monkeys. In addition, the size of the nonhuman primate fetus is sufficient to permit acute and chronic studies. The relatively small volume

of the rat feto-placental compartment makes it impossible to take repeated blood samples from that model.

In Vitro *Fertilization*

Finally, the nonhuman primate can be an important research tool in evaluating certain aspects of *in vitro* fertilization. For example, they will probably be very useful in projected studies to determine if oocytes should be collected directly from the ovary as generated spontaneously, or if they should be collected after induction of multiple ovulations. Since this question is difficult to resolve using human subjects, the nonhuman primate offers the best model for this research. These animals also will be valuable in studies of the process of embryo transfer. Studies of endometrial receptors for estrogen and progesterone will help determine the potential success of implantation. Studies of the characteristics of the primate endometrium will help determine the range of conditions conducive to embryo transfer that will provide the highest potential for a successful pregnancy.

Other Research

The use of wildlife in biomedical research certainly is not limited to the nonhuman primate. The possibilities for using wildlife in biomedical research are limited only by man's imagination. Analogs of more than 200 diseases in a great variety of animals, many rarely seen in laboratories, have been identified in a survey of spontaneous and experimental disease processes in lower animals and invertebrates. These remain as unexplained curiosities, while the possibility exists that many of these fundamental processes are identical to human diseases.

Unusual Research Animals

Many wildlife species are currently under investigation, and it is noteworthy to mention a few as an indication of the range of both animal and disease processes being explored. Marine animals are being used in a variety of experiments; neurophysiologists are studying the giant axon of the squid, large neurons in the aplysia or sea hare, and the brain in the octopus; horseshoe crabs produce a compound which may be used for *in vitro* pyrogen testing that could replace the test requiring rabbits; barnacles are being studied both for their giant muscles and their tenacious secretions; and marine mammals are being used in some exciting respiratory, cardiovascular and neurophysiology research. The woodchuck may prove to be useful in the study of hepatitis B. The woodchuck virus is similar in many respects to hepatitis B, and animals with this disease develop hepatic cell carcinoma. Fortunately for our research efforts, the woodchuck develops hepatic cell carcinoma in four to six years, compared with the 20 to 40 years it takes man. Several species of deer are used to study sickle cell anemia and thalassemia. Naturally occurring leprosy has been found in armadillos captured in southern Louisiana. Data obtained from studying these animals indicate that the leprosy organism might exist outside of humans, and that soil and insects represent possible reservoirs of infection in areas where the disease has occurred. Wild rodents have been used in a variety of cancer studies, and an Argentine rodent called the tuco-tuco may serve as a useful model for human maturity onset diabetes.

From these examples it is obvious that we have not exhausted the possibilities for learning from naturally occurring entities in wild populations. Those of us charged with providing laboratory animals have a responsibility to remain aware of the potential offered by wild animals as models and sources of genetic material. In a manner somewhat analogous to domestic plants, through selection of our laboratory experimental animals, we have ended up with a relatively small gene pool. While this is beneficial for most biomedical research, we must recognize that it may be to our advantage to maintain access to that wider pool of genetic composition as well as to microbial

flora available in wild animals. Moreover, for some studies, wild animals provide models for human disease in studying environmental factors and endemic infections that cannot be mimicked in the laboratory.

The Need for New Models

Reliable animal models have been crucial to the control and eradication of infectious disease during the last half century. However, we still do not have animal models for many disorders that are plaguing society today. The diseases that challenge biomedical scientists today are subtler in their onset, slower in their development, and more protracted in their course than the conditions of a century ago. A few examples of those disorders still in search of models include: cystic fibrosis, infectious mononucleosis, Huntington's disease, chronic recurrent bronchial asthma, multiple sclerosis, Parkinson's disease, endometriosis, otosclerosis, gallstones, pernicious anemia, appendicitis, psoriasis, and acne. These disorders represent the challenge to laboratory animal science—to identify a living organism with inherited, naturally acquired, or induced pathological processes that in one or more respects closely resembles the same phenomenon occurring in man.

Humane Care Issues

Before closing, I would like for you to consider with me the ethical and legal responsibilities shared by all of us who provide and use research animals. Humane care issues, while not new, have become amplified in recent years, and there are those who are attempting to deny the use of animals for any purpose. Those of us who provide animals, and those who use them, be it for the laboratory or for food, fiber, sources of energy, or as companions, must be prepared to deal with this issue which is surrounded by so much emotion. We must let it be known what the impact will be if further restrictions are placed on the use of experimental animals; that the biomedical community is searching for alternatives to animal experimentation not only for humane, but also for economic reasons. We must explain that alternatives to testing in the combined complex physiological systems found in the intact animal are currently quite limited, and to meet present needs can only be considered complementary or supplementary. We must make it understood that it is an extremely small proportion of our subjects which suffer pain; that we do have a concern for humane care; that it is to our scientific advantage to have animals which are properly cared for; and that most of us in biomedical research are in this field because of a respect for life. Coupled with this is a need to do all we can to secure those resources necessary for the proper treatment of those animals entrusted to our care.

We need to recognize that issues of humane care and conservation must be continually addressed, not only among ourselves, but also through dialogue with those responsible organizations whose primary function is to deal with such issues. Those which recognize the need for utilizing animals for human health and welfare can be helpful in improving our activities.

Future Developments

We must also face the potential advent of new legislation and international conventions. What we do in our own countries may well have an impact on others, especially in these times of extensive international commerce. This has been well demonstrated in the case of the U. S. Food and Drug Administration's Good Laboratory Practices Regulations, which have had an impact on the pharmaceutical industry beyond the United States. It can be anticipated that a convention on the use of live animals for experimental purposes may emerge from the Council of Europe, which also will have an impact on those of us from countries not a part of that union. The Convention on International Trade in Endangered Species is having its effect on the avail-

ability of certain primate species used in biomedical programs.

Thus, there are many challenges ahead of us. In meeting these challenges, it should be remembered that teamwork is essential. There is a wide variety of complex, interrelated factors involved in the provision and characterization of animal models for today's biomedical programs. In this era of specialization, it is virtually impossible for any one individual or any one discipline to have all the knowledge needed for this purpose. Moreover, there is a great need for international collaboration to do that which must be done for the benefit of all nations, the developed as well as the developing. The Primate Breeding and Conservation Center in Iquitos, Peru, is an example of this cooperation.

All of us share a responsibility to ensure that we are conscientious in providing for the best possible utilization and the appropriate treatment of those animals entrusted to our care. If we properly discharge this responsibility, we should be able to maintain our credibility with the public, and with legislators and regulators. This, in turn, will enable continuation of work essential for improving the quality of life throughout the world.

SUMMARY

The genetic backgrounds of laboratory animals can be a critical factor in the success or failure of medical research. This is why any institution providing research animals to other organizations must be highly concerned about laboratory animal strains' genetic integrity. It also explains why the U.S. National Institutes of Health have instituted a program to prevent genetic contamination of animal strains by developing specific genetic profiles—so that by comparing a specific animal's features to the genetic profile for the strain it can be determined whether the animal itself has become an experimental variable.

It is also true, however, that many animal disease models employed today have resulted from incidental observation of animals with unusual features. That being the case, the continuing need for careful observation of animal colonies and recognition of unusual specimens can hardly be overemphasized. Among other things, technicians should be trained to notice animals with seemingly minor aberrations and to see that such animals are preserved.

Today a wide variety of laboratory animal models obtained through selective breeding or occurring naturally makes an invaluable contribution to biomedical research. These models provide essential tools for studying spontaneous human disorders; human reproduction, contraception, and fertility; and a broad spectrum of bacterial, viral, and other diseases.

Consider spontaneous disorders, for example. Dwarfism in the malamute dog has become a recognized model for chondrodisplasia. Work with gray collie syndrome has led to identification of cyclic neutropenia. A colony of ragweed-sensitive dogs has been developed. And animals with so-called old dog encephalitis may provide a model for the study of severe demyelinating diseases in man.

Moreover, chickens can now be protected against Marek's disease (a lymphoma) with a vaccine developed using turkeys; this work could indicate new possibilities for cancer research. Similarly, diagnostic tests for antibodies induced in cats by a leukemia-causing virus may lead to a better understanding of human leukemia.

Wild animals, especially nonhuman primates, also provide excellent surrogates for studying human illness. Some nonhuman primate species are highly susceptible to disease organisms pathogenic for man, and they respond to certain bacterial organisms more like people than do any other susceptible animals. Baboons, chimpanzees, macaques, African green monkeys, and other species provide good models for studying human pneumonia, shigellosis, gonorrhea, tuberculosis, anthrax, plague, streptococcal infections, malaria, and other nonviral diseases.

In addition, nonhuman primates have been used extensively for research on viral diseases. To take only two examples, evidence from experiments using New World primates overwhelmingly suggests that many cancers are caused by viruses; and neotropical primates have played an important part in our understanding of hepatitis.

Nonhuman primates have also made major contributions to research on human fertility and contraception. In this vein, rhesus monkeys are now used for large-scale screening of new drugs and devices. The intermediate primates, particularly

rhesus monkeys, have been used extensively in studies of contraceptive agents. Nonhuman primates have also been valuable in other studies involving the menstrual cycle. And nonhuman primates may become important research tools for evaluating certain aspects of *in vitro* fertilization.

Of course, many wild animals other than the nonhuman primates contribute to biomedical research. Indeed, the possibilities for using such wildlife are limited only by man's imagination. Several deer species are used to study sickle cell anemia and thalassemia. The woodchuck may prove helpful in studying hepatitis B. And the brain of the octopus, large neurons in the sea hare, and the giant axon of the squid are all contributing to neurophysiological research. Obviously, we have not exhausted the possibilities for learning from naturally occurring wild animal populations; and so those charged with providing laboratory animals have a responsibility to remain aware of the potential offered by wild animals, both as models and as sources of genetic material.

Issues relating to humane animal treatment also deserve consideration. We must let it be known what the impact will be if further restrictions are placed on the use of experimental animals. We must make it understood that only an extremely small proportion of our animals suffer pain. And we must do all we can to secure the resources needed for proper treatment of those animals entrusted to our care.

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CHOLERA IN THE UNITED STATES

A case of cholera has been reported from Florida. The patient, a woman 46 years old, experienced sudden onset of explosive diarrhea, abdominal cramps, and vomiting on 29 November 1980. There was only minimal fever. The illness was assumed to be food poisoning and was treated symptomatically. The symptoms continued unabated, however. On the third day of illness the woman's physician ordered a stool culture and started her on oral tetracycline. Within two days the diarrhea had ceased and the patient was markedly improved. Treatment with tetracycline was continued. A stool culture grew toxigenic *Vibrio cholerae,* serotype Inaba, biotype El Tor.

Over the period 21-25 November the patient had eaten approximately six dozen raw oysters. These had been harvested from an approved area of Apalachicola Bay in Florida on 17 or 19 November. No other consumption of seafood was reported, and the patient had not traveled recently outside of western Florida. An epidemiologic investigation is underway to determine if the oysters were the vehicle of transmission and if there were other cases. Thus far no other cases have been detected. During the past two months, routine monitoring of the portions of Apalachicola Bay that are approved and open for oyster harvesting has shown fecal coliform levels to be within the limits required by the National Shellfish Sanitation Program.

The last cases of cholera reported in the United States in persons who had not recently traveled out of the country occurred in Louisiana in 1978. In those cases, ingestion of steamed crabs was epidemiologically associated with infection. The Louisiana isolates were also serotype Inaba and biotype El Tor. The Florida and Louisiana strains will be compared by phage typing and other methods to determine if they are identical.

Source: Morbidity and Mortality, Vol. 29, No. 50, 1980.