The Use of Animal Models Assists Researchers in Today's Scientific Discovery
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The use of animal models in biomedical research is critical for continued progress to combat disease and to discover new and better treatments for existing illness and conditions. The vast majority of scientists and researchers involved in medical exploration agree that without the use of animal models, major medical advances would not have been achieved nor would current research techniques be available.

To solve health problems, researchers must have scientific data that is relevant to the human condition. Data from human experiments is the most scientifically relative. But such experimentation, in many cases, is ethically unacceptable. Few people would offer themselves or a family member as the first subject of research to understand and cure diseases such as AIDS or Alzheimer's. The U.S. Government requires that most safety testing be designed and based on results of animal experimentation and a knowledge of the history of the disease or condition under study. After humans, animals offer the most accurate means to assess human biological reactions and responses.

Nonanimal research models are used in research labs across the country whenever possible. Biological models such as cell and tissue cultures, and nonbiological techniques such as mathematical and computer modeling, are used where appropriate. However, since these methods cannot mimic all the complicated interactions that occur in humans or animals, animal testing is still necessary. Knowledge gained from animal research has helped scientists develop many adjunct techniques that are reducing the numbers of animals required.

Impact Study continued from page 3

Activity Impact: Food production research reduces farmers' losses and increases their output.

Activity: Food Supply Productivity Research

Research Products:
- Prevention and treatment of diseases and disorders impairing the productivity of the food industry
- Biodiversity and ecosystem health

Economic Impact:
- $17.7 billion in losses can be avoided or productivity gained in the United States agriculture industry ($714.5 million in Pennsylvania)

Activity Impact: As a result of the School's teaching activities, its alumni increase their earning power.

Activity: Teaching Product

Teaching Product:
- 3,400 living VMDs able to earn an additional $30,892 per year on average (1356 VMDs in Pennsylvania)

Economic Impact:
- Additional $104 million expended in the national economy per year, on average ($41.6 million in the Commonwealth of Pennsylvania)

Activity Impact: The School's services offered through New Bolton Center treat over 24,700 large animals, reducing economic losses.

Activity: Service Products

Service Products:
- Nearly 8,700 horses, 14,300 cattle and 1,700 other valuable animals treated

Economic Impact:
- Approximately $239.2 million in losses avoided annually (approximately $157.6 million in Pennsylvania)

The Role of Animals in Current Research and Testing

Biomedical research with animals has four major goals:
- To provide biological knowledge upon which disease prevention can be based;
- To provide models for the study of naturally occurring diseases and other conditions in animals;
- To test potential therapies, diagnostic and surgical procedures, and medical devices;
- To study the safety and efficacy of new drugs or to determine the potential toxicity of chemicals to which animals will be exposed.

Researchers must understand the biology and physiology of higher organisms before they can make advances in the treatment and prevention of disease. Animal models provide information on the mechanisms of disease and an organism's own defensive response. Scientists study animal models for clues as to how the disease is transmitted and how genetic susceptibility and other factors may predispose an individual to disease. In the case of infectious diseases, scientists attempt to isolate the disease-causing agent in the affected animals as the first step toward development of a vaccine.

Data from animal studies is essential before new therapeutic techniques and surgical procedures can be tested on patients. Researchers must use animal models to develop and refine techniques to determine if the techniques will achieve their purpose without risking harm to the patient. Animals also are essential to measure a drug's beneficial or harmful effects on organs and tissue. Moreover, data documenting efficacy and safety is required by the Food and Drug Administration (FDA) before a new drug is approved for testing in clinical trials on humans. Such testing remains the best predictor of adverse risks such as cancer, reproductive disorders and birth defects.

Two of the most controversial tests are the Lethal Dose 50 (LD50) and Draize tests. The LD50 test provides data on how toxic a substance is by determining the dose needed to kill 50 percent of a test group of rodents. The classical LD50 test using large numbers of animals is rarely used today. The maximum tolerable dose is important information for some cancer chemotherapeutic agents where the clinically effective dose is near the lethal dose. The doses that animals tolerate on an acute basis provide information for risk assessment and also determine doses for further studies. Many toxicologists believe that fewer animals can be used to achieve sufficient data, and work is being done to develop nonanimal methods.

There are two Draize tests: one for the eye and one for the skin. The Draize eye irritancy test measures how safe a substance is to the eye by putting drops of a substance on rabbits' eyes. While modifications of this test and alternatives are being explored, many scientists believe that this is still one of the best predictors of the effects a chemical would have on the human eye. The skin test is performed in a similar fashion, by exposing a chemical substance to an animal's skin to measure possible irritancy.

Duplication and Validation of Research

Both government and private research institutions practice stringent review processes when approving research projects because of concern for the number of animals used and because of the cost of research. Experts review research proposals to measure the importance of a project, its scientific merit, the competence and the appropriateness of research models.

NIH, the major single source of funding for U.S. biomedical research, requires each grant application to include a bibliography of all relevant scientific literature to avoid unnecessary duplication of research. The cost of research plays a significant role in deciding appropriate ventures. The NIH, for example, is able to fund only about one-third of all research proposals judged worthy of support, and...
The overwhelming majority of lab animals are rats and mice bred for this purpose by licensed suppliers. Large animals, such as swine, cattle, and sheep, are raised on agricultural sources. Most nonhuman primates used in research are from scientific breeding centers, not from the wild.

Many cats and dogs necessary for research are bred for this purpose and others have been abandoned in public pounds and animal shelters. Estimates vary widely, but of the approximately 16.2 to 27 million cats and dogs left in pounds and shelters each year, only about 138,000 dogs and 50,000 cats are used in research annually. The majority of these pound animals, between 10.1 and 16.7 million dogs and cats, are put to death by animal care and control agencies each year, according to the American Humane Association’s 1989 statistics. The remaining animals are claimed by their owners or adopted.

While the majority of lab animals are rodents, other species are used in small numbers to provide data not fully available by using rodents. The dog model, for example, continues to assist scientists in discovering new therapies for cardiovascular disease, and many surgical techniques. Nonhuman primates, also used in small numbers, help scientists investigate reproductive disorders, hepatitis, deafness, head injuries, and eye disorders. Research conducted today, however, includes the use of mice to study immunology and calves to help improve the performance of artificial heart valves.

Whether animals used by researchers administered by the FDA do not specify the use of animal testing,” said Dr. John Augsburg, assistant to the director of the Center for Veterinary Medicine at the FDA. “However, the FDA position is that the use of animal tests by industry to establish the safety of regulated products is necessary to minimize the risks from such products to humans and animals. Consideration should be given to the use of validated and accepted alternatives and, if necessary, to the replacement of many procedures intended to replace animal tests are still in various states of development and it would be unwise for the FDA to urge manufacturers not to do any further animal testing. This appears to be little chance of replacement of animal testing in the foreseeable future.”

Care of Lab Animals - Laws and Regulations

The care of lab animals in universities, medical schools and hospitals, pharmaceutical companies and other research facilities is monitored by the U.S. Department of Agriculture (USDA), under the provisions of the Animal Welfare Act (AWA). The AWA has been amended three times since its passage in 1966. USDA officials make periodic unannounced inspections to ensure compliance with stringent standards for housing, feeding, and watering, cleanliness, ventilation and veterinary medical care.

The U.S. Public Health Service (PHS) has an Animal Welfare Policy that applies to all NIH-funded projects involving animals. The NIH requires that the institutions follow the Guide for the Care and Use of Laboratory Animals, prepared by the Institute of Laboratory Animal Resources of the National Research Council. The organization also serves as a scientific forum for laboratory animal medicine and care.

The American Association for the Accreditation of Laboratory Animal Care (AAALAC) offers a lab accreditation program. In addition, the FDA and the Environmental Protection Agency (EPA) have Good Laboratory Practices regulations (GLPs).

The AWA calls for the use of anesthetics and analgesics for potentially painful procedures and for postoperative care. These regulations, along with animal care regulations within each facility, ensure that animals receive the best care and the least pain and distress. USDA statistics state that approximately 95 percent of all lab animals in federally protected facilities are not exposed to pain or distress. Of the remaining percentage, many animals are involved in studies of pain itself, and pain-relieving drugs or analgesics are administered as specific procedures during the study.

Dr. M.H. Cook, of the USDA’s Animal Plant Health Inspection Service (APHIS), said most of the 1,100 USDA-regulated research facilities consistently comply with federal standards, and have often initiated improvements for animal care called for in the AWA amendments before they have become law. APHIS inspectors follow strict guidelines to ensure air temperature, humidity and the study area, and other regulations are met. “We find that, in general, the scientific community does a good job and is concerned about the care of lab animals,” Dr. Cook said.

Animals and Research Statistics

- There are approximately 56 million cats and 54 million dogs in the U.S.
- It is estimated that every hour more than 2,000 dogs and 3,500 cats are born.
- Animal shelters take in 16.2 to 27 million dogs and cats annually.
- Between 10.1 and 16.7 million dogs and cats are put to death in pounds and shelters annually because they were not claimed by owners nor adopted.
- Approximately 1.1 percent of the dogs and cats from pounds and shelters, that would otherwise be euthanized, are put to death.
- Rats, mice, and other rodents comprise 85 to 90 percent of all research animals.
- Only 1 to 1.5 percent of research animals are dogs and cats, and 0.5 percent are nonhuman primates.
- There has been a 40 percent decrease in the number of animals used in biomedical research and testing in the U.S. since 1968.
- Approximately 17 million to 22 million animals are used in research each year.

(Source: The American Humane Association, USDA, Foundation for Biomedical Research, Newsweek)

**The Three R’s** and Trends in Alternatives

Most research organizations and scientists are following a practice known as the “Three R’s,” which stands for replacement, reduction and refinement.

Replacement refers to the use of nonanimal techniques instead of animal models or a lower species of animal when possible. For example, rabbits are no longer used for pregnancy testing, and some preliminary drug toxicity testing can be done using cell cultures, rather than animal species.

Reduction refers to areas where the number of animals used can be reduced. The number of animals used in acute toxicity testing has been reduced as scientists have discovered ways to obtain accurate toxicity data using fewer animals. In addition,
Dr. Galligan for more than a year. He has a ration sheet and feeds each cow individually according to her production. The rations formulated for his farm save him about $400 to $500 a month. Dr. Galligan visits the farm periodically to check and to revise the feeding program and to discuss other herd-related problems that might arise.

The interactive computer program has five subunits: 1. a nutrient requirement section; 2. a feed bank section that stores the composition of available feed; 3. a computational section where rations are evaluated or formulated; 4. a feeding recipe section, which displays or prints grain mix, mineral mix, total mixed ration, or stanchion barn recommendations; and 5. a comparative economic evaluator, which ranks feeds by a nutritional cost and benefits algorithm.

"We can select up to 12 fixed feed ingredients from a bank of up to 100 feeds," explained Dr. Galligan. "The basis of selection is farm availability and nutrient constraints. Selected variable ingredients are used to balance the ration for dry matter, crude protein, bypass protein, soluble protein, acid detergent fiber, and neutral detergent fiber. Calcium and phosphorus are balanced using a combination of mineral sources. Trace minerals are either custom composition of formulated or selected from a bank of proprietary supplements on the basis of limited trace elements in the ration.

The spreadsheet allows individual calculations for the various components. "We can determine what kind of hay to feed if soy meal is high in price," said Dr. Galligan. "If soy meal is low in price, then it will make up a greater part of the ration and the farmer can use first-cutting hay which does not have that great a nutrient value. However, if soy meal is expensive, then we put it in the ration formula and recommend that high quality hay be used." This kind of ration formulation requires that farmers change their habits. It used to be that hay was fed in reverse order of harvesting, meaning that the last cut hay was fed first. Now Dr. Galligan recommends that the cuttings be stored separately so the hay can be accurately matched to the other feed ingredients to provide the proper nutrition for the least price.

If one kind of fiber is high priced, then another may be selected. Further, Dr. Ferguson and Dr. Galligan have encouraged farmers to buy feeds by purchasing them as a group.ショットバジャー purchases minerals and other feed ingredients jointly with other producers also enrolled in the Production Medicine Services, obtaining a bulk price. Stolzhus and his neighbor too combine their orders to get a better purchase price.

Dr. Galligan and Ferguson and their colleagues are continually refining the program and the service formulations. They are also attempting to create systems and are making calculations as to whether it is advantageous to buy a three-month's supply, versus a six-weeks' supply when considering the interest the money could earn if invested alternatively. "If all this sounds a bit farfetched coming from veterinarians, it really is not as the contemporary veterinarian has moved beyond being a mere healer. "We have to look at the total farm picture," said Galligan. "While disease prevention is an important part of herd health, management programs like this rationalize the time and cost. The veterinarian can take a look at the overall picture and then advise the client. By increasing the feed efficiency and advising the farmer about ration formulation, we can save him more money than through many traditional veterinary services."

The members of the Center for Animal Health and Productivity have been spreading this word at bovine practitioner's meetings and now about 1,000 veterinarians use the program to advise their clients. It costs $100, this includes the spreadsheet, a tutorial and a user's manual as well as a year's subscription to the University's on-line bulletin board. Here users find out about updates and improved features of the program.

The program is also an important teaching tool for Penn's veterinary students, familiarizing them with feed rations and formulation of the most economic ration without sacrificing production yield. And what is in the future? "We will be looking at the futures market to see if feed expenses can be reduced further," said Dr. Galligan. "We are employing economic principles and modeling being used in industry and are applying them to agriculture to help the dairy farmer to remain profitable."

Dr. Galligan is an associate professor in animal health economics and holds an MBA degree from the Wharton School. Dr. Ferguson is an assistant professor in nutrition and is board certified in nutrition and reproduction. The ration formulation program was chosen by Analy Magazine as one of the five best applications of Lotus 123 for 1990. The research to develop the program was funded in part by the Pennsylvania Department of Agriculture.