## chapter 5

# The Use of Animals in Research

*I know that half of what I teach as fact, " said a wise medical pedagogue, "will be proved false in 10 years. The hard part is that I don't know which half. " His statistics may not be exact, but the notion is right enough. No one knows which half, and it is impossible to know except in retrospect.*

*That is what research is—the reason for the prefix. The half that is wrong is at least as important as the half that is right, because the new questions come in ferreting out the errors-and new answers too.*

Kenneth L. Brigham
Vanderbilt University School of Medicine
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# Chapter 5

# The Use of Animals in Research

Research, as the word denotes, is an ongoing search—a search for new information and for novel ways to apply existing information. Research assumes a multitude of directions in a wide variety of disciplines. It is not surprising, then, that the use of animals in research—and the potential for alternatives to using them—mirrors the multifaceted nature of research itself.

Viewed broadly, almost any research investigation involving members of the animal kingdom, including humans, and sometimes even members of the plant kingdom, can be categorized as biomedical research. In this sense, biomedical research covers a long list of disciplines: anatomy, anesthesiology, behavioral biology, biochemistry, biomedical engineering, biophysics, cardiology, cell biology, dentistry, developmental biology, endocrinology, entomology, epidemiology, genetics, gerontology, histology, immunology, metabolism, microbiology, molecular biology, neurology, nutrition, oncology, parasitology, pathology, pharmacology, physiology, psychology, radiology, reproductive biology, surgery, teratology, toxicology, veterinary science, virology, and zoology.

When considering animal use—and alternatives to animal use—in research, it is useful to isolate behavioral research from the broader category of biomedical research. Behavioral research is a part of biomedical research, yet is distinguished from the larger topic by the nature of the experiments, the identity of the researchers, and the kinds of alternatives available (see ch. 6).

This chapter defines and describes animal use in biomedical and behavioral research. Also included are the results of a brief survey done by OTA of the use of animal and nonanimal methods in published research reports in selected disciplines of biomedical and behavioral research.

## THE ROLE OF ANIMALS IN BIOMEDICAL RESEARCH

To discuss alternatives to using animals in biomedical research, it is important to review the context in which animals are presently included. A comprehensive review of this subject (see ref. 41) is beyond the scope of the present assessment. However, animals' broad role in contemporary biomedical research can be at least partly delineated by considering:

- the manifold contributions to biomedical research of a single group of animals—nonhuman primates;
- the role of experimental animals in the development of a single medical procedure, namely coronary artery bypass surgery; and
- the reasons multiple species are used in biomedical research.

These perspectives illustrate two fundamental principles of animal use in biomedical research. First, a single species or group of animals often serves a multitude of purposes in widely varying research enterprises. Second, a single advance in applied research often represents results generated from many species.

### *Nonhuman Primates in Biomedical Research*

Primates—humans, monkeys, and apes—share a common genetic basis and anatomical, physiological, biochemical, and behavioral traits that provide unique research opportunities. As a consequence, humans and other primates are susceptible to many of the same diseases and have many of the same disease-fighting capabilities. Reviewing the use of nonhuman primates is also appropriate because they are relatively expensive" research animals (e.g., a rhesus monkey costs from $600 to $2,000) and the object of much public interest. Two recent reports describe the role of primates in biomedical research (29,45). Those



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reports are summarized in table 5-1; highlights of the studies follow.

## Polio

The development of the polio vaccine exemplifies the key role of primates in the research laboratory. Many thorough studies of polio in humans had been made by the early 1900s, but the cause of the disease was still unknown. A breakthrough occurred in 1908, when scientists experimentally transmitted the poliovirus to monkeys for the first time. Studies in rhesus and cynomolgus monkeys and in chimpanzees followed isolation of the virus, but a vaccine remained elusive. After nearly a half-century, researchers were able

**Table 5-1.—Some Uses of Nonhuman Primates in Research on Human Health and Disease**

| Human health concern | Primate experimental model |
|---|---|
| Acquired immune deficiency syndrome (AIDS) | Chimpanzee, African green monkey |
| Atherosclerosis | Cynomolgus monkey |
| Balding | Stumptail monkey |
| Cancer from solid tumors | Chimpanzee |
| Cholesterol gallstones | Squirrel monkey |
| Circadian rhythms | Squirrel monkey |
| Cornea transplant | Rhesus monkey, African green monkey, Stumptail monkey, Patas monkey, Cynomolgus monkey |
| Dental implants | Pig-tailed monkey |
| Diabetes | Celebes black macaque |
| Dietary fats and heart disease | Cynomolgus monkey |
| Embryo transfer | Rhesus monkey, Cynomolgus monkey |
| Eye damage from ultraviolet radiation | Rhesus monkey |
| Eye disorders in children | Rhesus monkey |
| Fetal alcohol syndrome | Pig-tailed monkey |
| Fetal surgery | Rhesus monkey |
| Genital herpes | African green monkey |
| Gilbert's syndrome | Bolivian squirrel monkey |
| Glaucoma | Rhesus monkey |
| Hearing impairment | Rhesus monkey |
| Hepatitis B | Rhesus monkey, Chimpanzee, African green monkey |
| Herpes-virus-induced cancer | Owl monkey, Marmoset |
| High blood pressure | Cynomolgus monkey |
| Hyaline membrane disease in newborns | Rhesus monkey, Pig-tailed monkey |
| In vitro fertilization | Rhesus monkey, Chimpanzee, Baboon, Cynomolgus monkey |
| Infertility | Rhesus monkey |
| Inflammatory bowel disease | Marmoset |
| Laser surgery on damaged nerves | Baboon |
| Leprosy | Sooty mangabey |
| Liver disorders | Rhesus monkey |
| Malaria | Chimpanzee, Owl monkey, Rhesus monkey |
| Male and female behavior patterns | Rhesus monkey |
| Male birth control | Rhesus monkey, Cynomolgus monkey |
| Menopausal problems | Rhesus monkey, Stumptail monkey |
| Mother-infant behavior | Rhesus monkey |
| Motion sickness | Squirrel monkey |
| Nonhormonal fertility regulation | Bonnet monkey, Chimpanzee |
| Obesity | Baboon |
| Parkinson's disease | Rhesus monkey |
| Polio | Rhesus monkey, Cynomolgus monkey, Chimpanzee |
| Premature labor | Rhesus monkey, Baboon |
| Rh factor disease | Rhesus monkey |
| Slow viruses | Owl monkey, Squirrel monkey, Stumptail monkey |
| Systemic lupus erythematosus | Cynomolgus monkey |

SOURCES: Adapted from "Toward Better Health: The Role of Primates in Medical Research," Primate News 21(1):1-24, 1984; and F. A. King and C. J. Yarbrough, "Medical and Behavioral Benefits From Primate Research," *Physiologist* 28:75-87, 1985.

to grow the poliovirus in human tissue culture (15), and an effective vaccine became available to the public in 1955. When the vaccine was developed, monkey kidney tissue was essential for production of pure virus in great quantities, and live monkeys were essential for safety and effectiveness testing. Today, noninfectious polio vaccine can be produced in continuously propagating cells without the need for monkeys, although monkeys are required to test for safety. The impact of the polio vaccine has been dramatic: In 1952, at the height of one epidemic, 58,000 cases of polio occurred in the United States; in 1984, just 4 cases were reported (39).

### Hepatitis B

Hepatitis B is the most dangerous form of hepatitis, a debilitating liver disease characterized by fever, weakness, loss of appetite, headache, and muscle pain. There are nearly 1 million hepatitis B virus carriers in the United States today, and the infection is estimated to cost $1 million per day in this country. Worldwide, there are some 200 million carriers, primarily in Asia and Africa. Up to 1 percent of those infected with hepatitis B die of the disease, and 5 to 10 percent become chronic carriers of the virus who can remain infectious indefinitely (21). Since there is no known treatment for hepatitis B infection, prevention is essential.

Research with rhesus monkeys and chimpanzees led to the development just a few years ago of a vaccine, derived from human plasma, against hepatitis B infection. In 1981, the Food and Drug Administration (FDA) licensed this vaccine for human use. In 1984, recombinant DNA technology was used to prepare a hepatitis B vaccine from yeast cells (the first vaccine for human use so produced). Prior to its trial in 37 human volunteers, this yeast recombinant hepatitis B vaccine was administered to African green monkeys in order to gauge its effectiveness (52). These new vaccines are expected to have a worldwide impact on the disease, and they may also reduce the incidence of hepatocellular carcinoma, a form of liver cancer associated with chronic hepatitis B infection (40).

### Herpes

Estimates of the number of persons afflicted with recurrent genital herpes virus infections range from 5 million to 20 million worldwide (61). A new antiviral drug, acyclovir, was recently licensed for use against human genital herpes infections and appears to yield antiviral and clinical benefits when taken orally (48). Acyclovir was extensively tested in African green monkeys. The opportunity to run such tests arose because of a natural outbreak of a virus closely related to that causing both chickenpox and shingles (i.e., herpes zoster) in humans. The infected monkey colony at the Delta Regional Primate Research Center in Louisiana enabled scientists to study the herpes disease process and test antiviral drugs. In 1984, researchers reported an in vitro model system for studying the herpes simplex virus, using human fetal nerve cells as the host. This in vitro model is expected to enable analysis of the state of the herpes virus as it establishes and remains latent in human nerve cells (62).

### High Blood Pressure

High blood pressure, when untreated, increases the risk of stroke, heart disease, and kidney failure. In most cases, the cause or causes of high blood pressure remain unknown, and the condition is a public health problem of immense proportions. Data from the early 1980s indicate that fully one-third of Americans use medication to control blood pressure. From 1971 to 1981, visits to physicians for diagnosis and therapy of high blood pressure increased by 55 percent, while visits for all other causes decreased by approximately 5 percent (32).

Monkeys are used to examine mechanisms of high blood pressure because the natural hormone molecules controlling blood pressure (e.g., the kidney hormone renin) are identical in humans and other primates. In contrast, the renin molecules of humans and nonprimate species are dissimilar. In addition to using monkeys to study the effects of diet and drugs on high blood pressure, researchers are examining the genetic transmission of high blood pressure. One breeding colony of cynomolgus monkeys exhibiting high blood pressure has been monitored for 5 years; this permits the study of high blood pressure in parents, offspring, and future generations to analyze the tendency to inherit the condition.

### Parkinson's Disease

Parkinson’s disease is a neurological disorder of older adults characterized by palsy and rigid muscles. Progress in understanding the cause and development of the disease and in refining methods of long-term drug therapy has been hampered by lack of an adequate animal model. Attempts to induce the disease in rats, guinea pigs, and cats either have failed to produce all the symptoms or have yielded symptoms that do not last long and so cannot be effectively researched.

In 1983, the first animal model of Parkinson’s disease was developed. Scientists at the National Institute of Mental Health (NIMH) induced a form of parkinsonism in eight rhesus monkeys by giving them a drug, l-methyl-4-phenyl-1,2,3)6-tetrahydropyridine (MPTP), that selectively destroys specific cells in the substantial nigra, a region of the brain destroyed in humans by Parkinson’s disease. The monkeys exhibited all the major clinical features of Parkinson’s disease in humans. They also responded dramatically to L-dopa, the standard medication for people with this disease (8). NIMH researchers have speculated that the availability of this new animal model may lead to understanding the reason Parkinson’s disease occurs in older adults, the course of the disease, and drug therapy and its side effects (30).

In 1984, squirrel monkeys were used to shed further light on the mechanism of MPTP-induced parkinsonism. Pargyline, a drug currently prescribed for high blood pressure in humans (Eutonyl, Abbott Laboratories, North Chicago, IL), was used to prevent the neurotoxic effects of MPTP (31). These results in squirrel monkeys suggested that MPTP itself may not be the actual neurotoxic agent. Instead, attention is now focused on an MPTP metabolize and on the mechanism of MPTP metabolism in the brain (33).

### Baldness

Like many men, stumptail monkeys become bald as they age. This trait has made the stumptail monkey the animal of choice in baldness research. Although it is not life-threatening, baldness is a matter of concern for many people: Hair-combing patterns suggest that many men desire to have hair where there is none, and advertisements for hair restoration abound in the popular media. The public spends large sums on hair-restoration nostrums, and in 1985 the FDA proposed banning the sale of all nonprescription drug products sold to prevent or reverse baldness, having concluded there is no scientific evidence that such lotions and creams are effective (50 FR 2191).

A drug originally developed to manage high blood pressure, minoxidil, has the unexpected side effect of causing thick hair growth from follicles that normally produce only fine, downy hair. To test the potential of minoxidil for hair growth, researchers applied it externally to the bald front scalp of stumptail monkeys. The results with monkeys showed promise, and clinical trials are now in progress with bald men across the United States. Monkey studies are continuing to assess the effects and safety of minoxidil as a means of counteracting hair loss.

### Menopausal Hot Flashes

Of the 30 million postmenopausal women in the United States, as many as 75 percent have experienced or will experience hot flashes brought on by increased blood flow to the skin. Hot flashes produce a feeling of warmth for several minutes, and they are often followed by sweating. These physical symptoms may be accompanied by nervousness, irritability, and depression. At present, physicians can treat the symptoms of menopause, but the causes of the symptoms remain unknown. Research into the mechanisms of menopause and the development of therapy for menopausal problems has been hampered by the difficulty of studying this condition in animals. This difficulty stems from three facts: only primates, and no other nonhuman species, have menstrual cycles; monkeys do not exhibit symptoms of menopause until at least age 25; and monkeys brought into the laboratory from the wild are rarely of menopausal age.

Throughout the last decade, researchers have studied the menstrual cycle and its cessation in

*Left:* Bent, flexed posture and absence of movement exhibited by a rhesus monkey treated with the drug MPTP to induce Parkinson's disease. Other symptoms in both monkeys and humans include tremor, eyelid closure, difficulty swallowing (drooling), and difficulty with vocalization and speech.

*Right:* Reversal of abnormal posture and return of normal movement following treatment with L-dopa. The *right* photograph was taken 2 hours after the *left* one.

*Photo credit: f?.* **Stanley** Bums, National Institute *of* **Mental Hea/th**

First animal model of Parkinson's disease, developed in 1983

a limited number of rhesus monkeys reaching 25 to 30 years of age (11). In 1984, hot flashes were described in another primate, the stumptail monkey (25). The aim of developing an animal model for hot flashes is to determine the role of the brain and of hormones in the control of this problem. Once the underlying mechanisms that produce hot flashes are better understood, more effective treatments may be developed for women who suffer from menopausal problems.

## *Experimental Animals' Contribution to Coronary Artery Bypass Graft Surgery*

A second way to describe the role of animals in biomedical research is to review the ways in which a single advance in applied biomedical research came about. As an illustration of this process, the development of the coronary artery bypass graft operation, recently recounted (9,46), is summarized here.

Coronary or arteriosclerotic heart disease, often caused by a narrowing or blocking of the arteries supplying blood to the heart, is the number one cause of death in the United States. In 1982, it was responsible for approximately 500,000 deaths (59). Coronary artery bypass graft surgery was introduced in the early 1970s. In this procedure, which has become the primary surgical approach to treatment of coronary artery disease, a grafted vessel is attached to the coronary artery to circumvent the constricted portion. The graft improves the blood and oxygen supply to the heart muscle. The growth of the procedure has been quite rapid: Approximately 70,000 operations were performed in 1977; 160,000 in 1981 (7); and 191)000 in 1983 (38).

Coronary artery bypass graft surgery is now the most commonly performed major operation in the United States (7). It is accepted as far more effective than medication in relieving the severe chest pain, or angina pectoris, associated with coronary heart disease (47). The long-term benefit of this procedure, in terms of mortality, varies among patient groups (60).

The experimental steps leading to the successful coronary artery bypass graft operation are depicted in figure 5-1, in which the cardiac surgeon stands at the summit of Mt. Coronary Artery Bypass. In the early stages of research—that is, in the foothills of the mountain—there was a great deal of variability in the kinds of animals required. Studies in frogs, reptiles, horses, cats, dogs, sheep, and deer contributed to scientists' understanding of the fundamental principles of circulation, blood pressure, and temperature regulation. As problems became more specialized, the choices of animal species became more restricted. Dogs, chimpanzees, and, ultimately, humans contributed to the later stages of research leading to the coronary artery bypass. Virtually every step up Mt. Coronary Artery Bypass required initial stages of study on living animal models of various species.

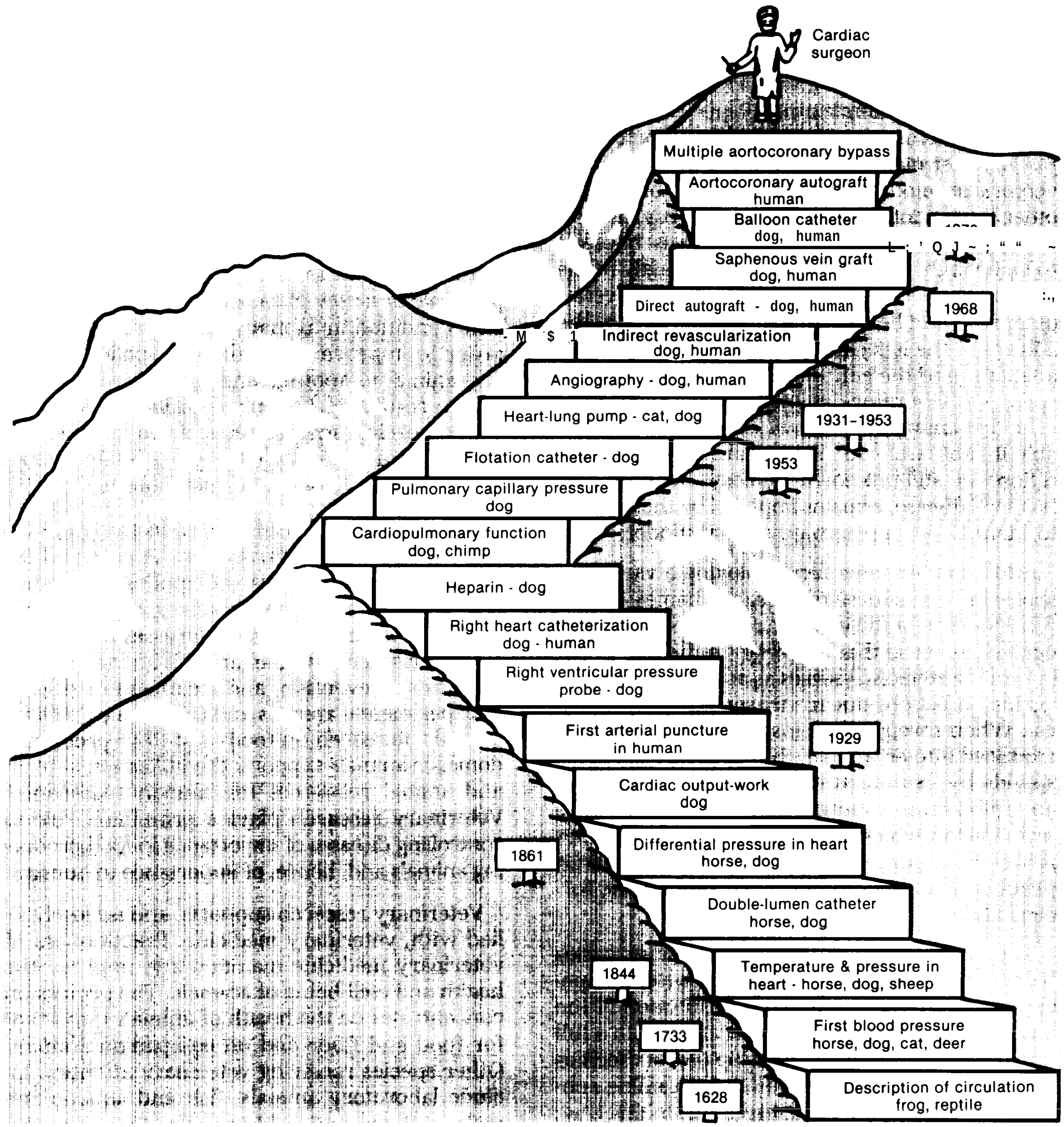
Today, in retrospect, the experimental steps leading to this surgical procedure appear as a simple and logical progression. In this sense, figure 5-1 is deceptive. It is important to note that the first step was not predictive of the second step, the second not predictive of the third, and so on. The advance from each step involved uncertainty, missteps, and serendipity. All are inherent in the process of basic biomedical research. Moreover, only a poor understanding exists of the path leading from basic to applied biomedical research. Although Mt. Coronary Artery Bypass stands as a bona fide illustration of the integration of data drawn from several species, it was formed without a blueprint.

## *Use of Multiple Species in Biomedical Research*

The contributions of animals are an important part of the history of human health, disease, and medicine. It is noteworthy that animals have not only contributed to human welfare, but deterred from it as well. The benefits and detriments derived from animals involve numerous species.

The number of animal diseases labeled zoonoses-diseases transmissible from animals to humans–now stands at about 200. These exact a heavy toll of human morbidity and mortality on a worldwide scale. Research to combat zoonoses logically focuses on the species that are the principal sources of the diseases. And the more species that are infected by a particular agent, the greater are the biological resources available for research to overcome it. Numerous animal vectors of an infectious agent provide increased opportunities for the study of variation among species in the incubation of, transmission of, and susceptibility to the infectious agent. Most of the threats to humans from animals—including rabies, tuberculosis, brucellosis, toxoplasmosis, anthrax, and dengue fever—infect a sufficient va-

**Figure 5-1.—Steps in Biomedical Research That Preceded Successful Coronary Artery Bypass Graft Surgery**




SOURCE: Redrawn from W, C Randall, "Crises in Physiological Research," Physiologist 26:351-356, 1963, after J. H. Comroe, Jr., and R. D. Dripps, "Ben Franklin and Open Heart Surgery," *Circ Res.* 35:661-669, 1974 riety of species that effective research on their control has been possible (19). Perhaps ironically, the same diverse mix of species that transmits disease to humans forms the substrate for research to ameliorate human disease.

Infection of multiple animal species has led to virtual control in industrial countries of the plagues just mentioned. Yet a paucity of animal vectors or models hampers control of certain other human infectious diseases. Leprosy, herpes, and gonorrhea (which are not zoonoses) have yet to be brought under control, owing partly to the lack of effective animal models. Recent discoveries of leprosy and herpes infections in primates, the culture of the leprosy bacillus in armadillos, and adaptation of the gonorrhea organisms to some species of laboratory animals offer promise that effective animal models will soon become available for research (19). Yet research on other conditions of still-unknown etiology, such as Alzheimer's disease, remains impeded by the inability to identify an appropriate animal model.

Additional impetus for employing a variety of species in the course of research comes from a consideration of the immune response, which recognizes material that is foreign to the body. The immune system thus serves as an animal's defense against infections due to viruses, fungi, or bacteria. When foreign proteins, or antigens, are introduced into an animal, the immune system responds by manufacturing a protein of its own, an antibody, to counter the invader. This is the principle on which the development of vaccines is based: An antigen is injected, and it stimulates production of an antibody that combats the foreign antigen.

The strength of an immune response varies from species to species, and even within a species, according to the genetic constitution of the animal used. Researchers often cannot gain a full understanding of how to develop useful vaccines unless they test several species to examine subtle differences in immune responses. In this way, species differences in response to foreign antigens are found and can be exploited in the production of effective vaccines for humans and animals. It is this use of the immune system that has controlled most of the major infectious viral diseases, including smallpox, which was controlled through the use of the cowpox, or vaccinia, virus.

No one animal species is the complete research model for the human. In general, nonhuman primate species have the greatest anatomical, physiological, and metabolic similarities to humans. Yet, as table 5-2 indicates, much important biological information can be provided by using dissimilar organisms. (This table oversimplifies the use of various animals in studying human health and disease because it does not rate the closeness of the similarity of the conditions between humans and animals (19).)

It is important to establish any new biological principle or a new phase of understanding a disease condition in as many species as possible in order to improve safely the extrapolation from one animal to another and to humans (19). Research results derived from multiple systems in varied species, such as those listed in table 5-2, complement each other to approximate human anatomy, physiology, and metabolism.

Some biomedical research, collectively known as veterinary research, seeks to understand the life processes of animals and applies this knowledge to serve animals themselves, as well as humans. Veterinary research addresses the normal structure and function of animals and the causes, diagnosis, prevention, and treatment of disease in experimental animals and clinical (i.e., patient) animals. Research on food- and fiber-producing domestic animals supports the utilization of plant and animal resources for human sustenance. Veterinary research plays a prominent role in controlling diseases of importance in food-producing animals and, hence, of importance to humans.

Veterinary research supports, and is closely allied with, veterinary medicine. Practitioners of veterinary medicine maintain and improve the health and well-being of animals. The profession concentrates on the health of animals important for food and fiber and on companion animals. other species receiving veterinary attention include laboratory animals, fish and aquatic animals, and zoo and wild animals, Thus, the majority of veterinary medicine addresses 30 to 40 different species of economic, ecologic, and environmental importance. These include:

- domestic animals (e.g., cats, cattle, chickens, dogs, donkeys, goats, horses, sheep, and turkeys);

**Table 5-2.—Some Anatomical, Physiological, and Metabolic Similarities and Differences Between Humans and Various Laboratoy Animals**

| | Conditions, systems, or structures | |
|---|---|---|
| Animal | Similarities to humans | Differences from humans |
| Cat | Splenic vasculature<br>Sphenoid sinus in skull<br>Liver<br>Middle ear and ear drum<br>Epidermis | Spleen<br>Reaction to foreign protein<br>Laryngeal structures<br>Sweat glands<br>Mediastinum (interior chest tissue)<br>Development of embryonic gonads<br>Sleep<br>Heat regulation |
| Cattle | Ascending colon<br>Electrolyte excretion | Digestion<br>Plasma gamma globulins in newborn<br>Sleep<br>Heat regulation<br>Vomiting<br>Sweat glands |
| Chicken | Palate | Retinal vessels<br>Lymphoid tissue in liver<br>Pituitary gland<br>Respiratory system<br>Oviduct<br>Reproductive system<br>Acetate metabolism |
| Chinchilla | Inner ear structures | |
| Dog | Pituitary gland vasculature<br>Renal arteries<br>Splenic vasculature<br>Sphenoid sinus in skull<br>Superficial kidney vasculature<br>Liver<br>Epidermis<br>Adrenal gland innervation | Intestinal circulation<br>Anal sacs<br>Sweat glands<br>Pancreatic ducts<br>Heat regulation<br>Sleep<br>Laryngeal nerves<br>Mediastinum |
| Goat | Embryonic blood circulation | Stomach and digestion<br>Heat regulation<br>Sweat glands<br>Vomiting<br>Sleep<br>Plasma gamma globulins in newborn |
| Guinea pig | Spleen<br>Immune system | Sweat glands |
| Horse | Pulmonary vasculature<br>Bile duct<br>Pancreatic duct<br>Lung | Carotid body<br>Spleen<br>Cecum and colon<br>Gall bladder<br>Plasma gamma globulins in newborn |
| Mouse | Senile hepatic changes | Spleen |
| Pig | Maturation of red blood cells<br>Cardiovascular tree<br>Teeth<br>Adrenal gland<br>Skin<br>Penile urethra<br>Retinal vessels | Spleen<br>Liver<br>Plasma gamma globulins in newborn<br>Sweat glands |

**Table 5-2.—Some Anatomical, Physiological, and Metabolic Similarities and Differences Between Humans and Various Laboratory Animals (Continued)**

| | Conditions, systems, or structures | |
|---|---|---|
| Animal | Similarities to humans | Differences from humans |
| Nonhuman primates | Brain vasculature<br>Intestinal circulation<br>Placenta<br>Pancreatic duct<br>Adrenal gland<br>Innervation<br>Nucleic acid metabolism<br>Teeth and mandible<br>Brain<br>Larynx<br>Kidney<br>Reproductive performance<br>Menstrual cycle<br>Spermatozoa | Inguinal canal |
| Rabbit | Splenic vasculature<br>Spleen<br>Immunity<br>Innervation<br>Middle ear and ear drum | Liver<br>Sweat glands<br>Lung elasticity |
| Rat | Spleen<br>Senile splenic changes<br>Senile pancreatic changes | Cardiac circulation<br>Abdominal circulation<br>No gall bladder |
| Sheep | Splenic vasculature<br>Sweat glands | Stomach and digestion<br>Heat regulation<br>Breeding<br>Vomiting<br>Sleep<br>Plasma gamma globulins in newborn |

SOURCES: Adapted from B.M. Mitruka, H.M. Rawnsley, and D.V. Vadehra, *Animals for Research, Models for the Study of Human Disease* (New York: John Wiley & Sons, 1976); and W.I. Gay and J.D. Willett, "The Spectrum of Biological Systems and the Selection of Models," in *National Symposium on Imperatives in Research Animal Use: Scientific Needs and Animal Welfare,* NIH Pub. No. 652746 (Bethesda, MD: National Institutes of Health, 1965).

- laboratory animals (e.g., mice, rats, guinea pigs, rabbits, hamsters, and ferrets);
- nonhuman primates (e.g., baboons, new-world monkeys, and old-world monkeys);
- exotic birds (e.g., parakeets, parrots, cockatiels, and cockatoos);
- birds of prey (e.g., falcons, hawks, and eagles);
- freshwater and marine fish;
- marine mammals (e.g., porpoises and whales);
- large terrestrial mammals (e.g., deer, antelope, elk, lion, tigers, elephants, and llamas); and
- assorted reptiles and amphibians.

## *Choice of Species*

The variety of animal species used in research spans the animal kingdom, and some species are used more often than others (see ch. 3). Various reasons exist for using particular species in research:

- Some species are more available than others. For example, certain primate species are in chronic short supply. Conversely, in the case of rats and mice, large numbers of commercial breeding businesses can supply particular strains, ages, and sex on the purchaser's demand.
- Existing databases and literature have been built on a particular species. Additional work, in order to contribute to the field in a direct way, needs to be based on the same species.
- For most research purposes, nonendangered, commercially available animals are preferred over endangered ones.
- Some species exhibit the physiology or behavior of interest in a more vivid and robust form than do other species. For example, the desert-adapted kangaroo rat is the species of

choice for studies of the kidney's role in water conservation,

- Certain aspects of physiology or behavior are exhibited by only a limited number of species. For example, studies of echolocation are best done with bats, which emit sounds in radar-type fashion.
- The costs of acquisition vary widely among species. For example, a mouse costs approximately $2, a hamster approximately $5, and a guinea pig approximately $19. (The actual cost for a particular species varies with the sex, strain, weight, age, quantity ordered, method of shipping, and distance shipped.)
- Maintenance costs vary widely among species. Depending on the laboratory lifetime of the animal, maintenance expenses can quickly exceed acquisition costs. For example, maintaining a mouse in a research laboratory costs approximately 5 cents per day, a hamster approximately 11 cents per day, and a guinea pig approximately 40 cents per day. (The actual per diem cost varies among different animal facilities, depending, for example, on accounting practices and local labor costs.)
- Results obtained from different species varv in their ability to be generalized, both among animals and between animals and humans. Generalizations are more readily made among species that are more closely related than among species that are less closely related.

Attempts to identify alternatives to using animals in research are likely to be influenced by these considerations.

## THE ROLE OF ANIMALS IN BEHAVIORAL RESEARCH

Like all of biomedical research, behavioral research relies on animals to identify models for and aid in the understanding of human phenomena. Behavioral research has the further goal of understanding the behavior of animal species of economic or intrinsic interest to people.

Behavior encompasses all the movements and sensations by which organisms interact with both the living and nonliving components of their environment (2). The environment includes not only objects and events external to the organism, but internal events as well (e.g., visceral cues, motivations, and emotions). Behavior is not an object or a thing. It is a process that continues in most organisms until they die. Even sleep is a form of behavior. Unlike coloration or size, behavior is a dynamic property that functions primarily to enable an organism to adapt to changing environmental conditions.

### *What is Behavioral Research?*

#### Classes of Behavioral Research

There are several classes of behavioral research, each with a distinct focus:

- **Abnormal Behavior.** In the broadest sense, abnormal behavior is any that deviates from normal patterns. Instances among animals include seemingly suicidal, self-induced beachings by whales, phobic and neurotic problems in pets, and various laboratory-induced animal models of human psychopathology (e.g., depression, drug addiction, or obesity).
- **Aggression** Aggression can be defined as an organism's threatening to inflict, attempting to inflict, or actually doing physical harm to another organism.
- **Animal Movements** Animal movements represent major changes in location over time and space, such as patterns of migration, herding, homing, navigation, orientation, and dispersal.
- **Body Maintenance.** Behaviors that function to provide body maintenance and homeostasis include hunger, thirst, respiration, thermoregulation, excretion, grooming, preening, and parasite removal.
- **Cognition** Although this label has been used indiscriminately to encompass practically all aspects of learned behavior (36), the term is more strictly applied to instances of apparentmentalistic activity in animals (e.g., consciousness, thinking, imagery, self-awareness, intention, or attribution).
- **Communication.** Communication consists of an exchange of information between two

or more organisms that results in a change in behavior. Instances of this range from those that are stereotyped and instinctive, such as the dance "language" of honey bees, to those that might appear to have a symbolic basis, as in the case of the recent attempts to teach chimpanzees various forms of sign language. Depending on species, communication can involve visual, auditory, olfactory, or tactile cues.

- **Exploration and Activity.** In addition to instances of curiosity and exploratory behavior, patterns of activity included in this discipline are circadian rhythms, sleep, hibernation, roost-time restlessness, and different patterns of locomotion (e.g., swimming, swinging, or flying).
- **Habitat and Food Selection.** Habitat and food selection refer to the areas where animals live under natural conditions (e.g., freshwater streams, forests, or deserts) and the ways they exploit resources. Areas of inquiry by behavioral researchers include competition between species and optimal foraging strategies.
- **Learning Memory, and Problem Solving.** These behaviors are represented by the acquisition and retention of new information that allows organisms to anticipate recurring environmental events, as well as changes in behavior that maximize or minimize certain outcomes. Included in this discipline is the cultural transmission of information from one generation to the next and imitation.
- **Motivation and Emotion** The study of motivation looks at mechanisms and manipulations that activate and sustain behavior. Emotion typically includes reactions that accompany different motivational states and is often associated, for example, with fear, anxiety, apprehension, pleasure, and rage.
- **Predator-prey Relations** As a consequence of selective pressure associated with predation, many prey species have developed an extensive and elaborate array of predator defenses couched in terms of sensory and/or behavioral adaptations, such as burrowing or voluntary immobility. Likewise, predators use a variety of behavioral strategies in prey identification and capture.
- **Reproduction and Parental Care.** Patterns of courtship, mate selection, copulatory behavior, nest building, nurturing, and care of offspring all fall within this discipline.
- **Sensation and Perception.** Sensation and perception refers to the ways in which organisms detect and interpret their environment. Topics included in this discipline include studies of sensory mechanisms, the development of search images, and highly specialized sensory mechanisms, such as echolocation.
- **Social Behavior.** Social behavior is defined by a situation in which the behavior of one organism serves as a stimulus for the behavior of another, and vice versa. Instances of social behavior range from simple forms of aggregation to complex exchanges among individuals (e.g., dominance, cooperation, and reciprocal altruism).
- **Spacing Mechanisms** Spacing mechanisms are intimately tied to social behavior, and range from such topics as individual distance to the maintenance of territories.

### Behavioral v. Biomedical Research

Distinctions between behavioral and biomedical research, although they are commonly made (and are followed in this assessment), frequently break down. Behavior, in the final analysis, is a biological phenomenon, Behavior presupposes a living organism, and the way that organism behaves is influenced in complex ways by its genetic makeup, hormonal status, physiology, and neurochemistry. Intervening between the input of environmental events and the output of behavioral events are complex neuroanatomical networks involving receptors, electrochemical reactions, nerve impulses, and effecter organs. Behavior does not occur in a vacuum. The biology of the organism provides the foundation that makes behavioral events possible.

It is increasingly apparent that many aspects of behavioral research must be viewed in conjunction with biomedical research. Strong components of both behavioral and biomedical research are evident, for example, in the study of obesity, hypertension, drug addiction, headaches, aggression, alcoholism, sexual dysfunction, brain damage, epilepsy, schizophrenia, depression, learning disorders, smoking, anorexia nervosa, stomach ulcers, mental retardation, and a variety of other psychological disorders.

## *Why Are Animals Used in Behavioral Research?*

### Control

The use of animals under laboratory conditions enables the manipulation and control of a variety of factors that in different settings would confuse, contaminate, and confound any attempt to interpret a behavioral outcome. Animal models also allow the control of genetic background, prior experience, temperature, humidity, diet, and previous social encounters. When these variables are uncontrolled, observed behavioral responses can be virtually impossible to interpret.

### objectivity

Two prerequisites to any research are objectivity and impartiality. When humans study humans, as can be the case in behavioral research, unique problems may arise. Not only can it be difficult for the investigator to remain objective in interpreting behavioral phenomena, but a variety of other complications can arise from the social relationship among those conducting the research and those participating as subjects (50). The use of nonhuman species partially ameliorates this problem.

### Developmental Effects

Among many species behavior changes as a function of age. The problem this poses for human research is one of time. Human development continues for many decades. To chart behavioral changes within the same persons would take many years, involving exhaustive followup studies and the ever-present danger of losing research subjects, for example, because of death or relocation. The alternative to such longitudinal work is to conduct cross-sectional studies, where simultaneous samples are drawn from different age groups. A problem in this case is that sociological and cultural changes over time (e.g., 50 years ago, an eighth-grade education was the norm) confound apparent differences between people of different ages. Because a range of lifespans is available among laboratory species, the use of animal models can minimize or circumvent altogether some problems associated with the study of behavior over time.

### Genetic Effects

There is growing evidence of a variety of genetic effects on behavior (23). With animal models, selective breeding studies can establish, pinpoint, and quantify genetic effects on behavior. The opportunity for human research in this area, apart from studies of identical twins, is limited.

### Methodology

The fact that animals cannot talk seems at first to constitute a serious disadvantage to conducting behavioral research with animals. Yet, the stark limits of trans-species communication help to keep human investigators unbiased in their work. The use of animal models forces the behavioral scientist to develop objective, operational definitions and research techniques that may later be applied to humans.

### Lower Complexity

Behavior, notably human behavior, can be extremely complex. The use of animals that appear to be structurally and functionally less complex presents a way to identify some of the basic elements and principles of behavior that might otherwise remain inextricably embedded in a mosaic of other factors.

### Species-Specific Behaviors

Certain behavioral phenomena fall outside the realm of human sensory or motor abilities. For example, flight, echolocation, infrared detection, and homing require the use of nonhuman species as subjects for research purposes.

### Heuristic Value

Research on the behavior of animals has been an important source of hypotheses about human behavior and an impetus to research on humans (35). Much of what is now known about the principles of learning, for example, was initially derived from research on animals. Likewise, a variety of therapeutic techniques (e.g., desensitization) were derived from work with animals, Human studies were done to verify what was learned from animal research and to gauge the limits of extrapolation from animals to humans.

### Practical Application to Animal Species

In addition to providing models of a variety of biomedical and psychological problems in humans, research on animal behavior is in many instances focused on benefits to the animals themselves. For example, an understanding of behavior has proved crucial for designing optimal captive environments for the protection and breeding of endangered species (55). Increased attention has also been paid to the behavior of farm animals. The study of mother-infant attachments, social behavior in groups, stress resulting from overcrowding and confinement, and habitat preferences has led to important insights into farm-animal welfare and husbandry (13,27,54).

It is also noteworthy in this context that knowledge gained about behavioral problems in humans through animal research is now being applied to animals. Effective treatments have been developed for aggressive problems in cats (5) and fears and phobias in dogs (24)58).

A knowledge of animal behavior has helped identify and solve ecologic problems. The discovery and subsequent synthesis of insect sex attractants, or pheromones, has important implications for the control of agricultural pests. Rather than having to use toxic pesticides applied over vast areas, there is already some application and much future potential in baiting traps with specific pheromones, which precludes environmental contamination.

One unique application of laboratory findings to the solution of ecologic problems involved studies of taste-aversion conditioning in rats (18). Researchers paired unpleasant, chemical- or radiation-induced illness with different flavors. After just one or two trials, rats developed highly durable aversions to the flavors paired with unpleasant stimuli. outside the laboratory, by pairing lithium-chloride-induced illness with the flesh of various prey species, it is now possible to control coyote attacks on sheep and turkeys (14). Indeed, one or two trials is sufficient to eliminate attacks on specific domestic farm animals but leave the coyote free to feed on alternative prey (22).

This procedure has recently been extended to reducing crop damage by crows and even appears to have promise for dealing with cancer patients undergoing radiation therapy (l). (A frequent complication of radiation therapy has been unpleasant gastrointestinal illness that the patient generalizes to all food; the patient may be unable to eat. Using the principles of conditioned taste aversion developed in rats, it is now possible to circumvent the problem by restricting patients to one particular kind of food during radiation treatment, so that the aversion that develops is specific to that food alone.)

### Individual Animals in the Service of Humans

Behavioral research occasionally centers on a trait of a particular species that maybe especially well suited to assist humans. For example, using animals to help handicapped persons has required a knowledge of animal behavior. Seeing eye guide dogs, usually German shepherds or golden retrievers, assist the blind (20), and trained capuchin monkeys perform as aides for quadriplegics (63). Pet dogs and cats have been shown to have therapeutic value for psychiatric patients (10), the handicapped (12), and the elderly (49), and they may even hold promise for alleviating depression resulting from loss of a child (57).

## *Methods of Behavioral Research*

The methods of behavioral research are as varied as the disciplines, but most fall into one of three general categories: field studies and naturalistic observation; developmental studies; and laboratory studies.

Field studies represent an attempt to examine the behavior in question as it occurs under natural circumstances, Such studies do not typically involve attempts to manipulate or control the conditions of observation. watching animals in natural conditions has frequently been suggested as an alternative to using them in laboratory research (6,44). The following benefits and limitations of naturalistic observation have been recognized:

- Naturalistic observation is frequently a starting point. Observation of animals in the field provides a base of descriptive information and serves as a source of hypotheses to be subsequently tested under laboratory conditions,
- Naturalistic observation can be used to compare behavior observed in the field with that occurring in the laboratory to assess the extent to which an artificial environment may alter behavior, and whether the results can be generalized.
- Field studies can increase the efficiency with which animals are used by providing important information on natural species variables and biological constraints on behavior.
- The principal drawback to naturalistic observation is the absence of control. Under natural conditions, events frequently change in both important and spurious ways, often making it impossible to establish cause-and-effect relations (37).

Behavioral research often requires study of one animal or a group through time, as development proceeds. Among many species the emergence of different patterns of behavior is a reflection of both maturational and experiential factors. Developmental variables have been identified as being important in the expression of such diverse behaviors as aggression, communication, activity, learning, and social behavior.

Laboratory studies undertake to manipulate and control the condition of observation so as to specify more precisely the variables and conditions that influence the behavior in question. Most laboratory studies of behavior can be subdivided into those that attempt to identify the environmental determinants of behavior and those concerned with the organic basis for behavior. Within the latter category are a number of approaches involving attempts to identify the neuroanatomical, neurochemical, endocrinological, and genetic underpinnings for behavior.

### *Use of Multiple Species in Behavioral Research*

Many behavioral phenomena appear common to different species. Patterns of migration, for example, are common to such diverse groups as insects, fish, birds, and even some species of mammals. Much the same appears true for learning, motivation, and bodily maintenance. Yet, generalizations about categories of behavior (e.g., parental care or hoarding) in unrelated species may be misleading, because the species evolved independently (34). Moreover, comparing the performance of different species on a simple task may have no bearing on larger issues such as intelligence (26). What used to be seen as general principles and "laws" of learning, for example, now turn out to be specific to certain species under certain situations (3,4,53).

There are some behaviors that are of limited scope across species but of profound importance in terms of their bearing on the question of human behavior. For example, the capacity to recognize one's own reflection in a mirror has only been found in humans, chimpanzees, and orangutans, and much the same may apply to instances of intentional deception, gratitude, grudging, sympathy, empathy, attribution, reconciliation, and sorrow (17).

## PAIN AND DISTRESS IN RESEARCH ANIMALS

There are two general kinds of animal experimentation in which pain may occur. First, there are studies that investigate the nature of pain itself and the anatomical, behavioral, chemical, pharmacological, and physiological mechanisms responsible for it. In such studies, the infliction of pain and the monitoring of the responses to pain are usually integral parts of the experimental procedure. The goal is the prevention, treatment, and amelioration of human and animal pain. The second, and much larger, class of animal experimentation in which pain may occur consists of those studies in which pain is but a byproduct of the procedures used (28).

When indices of pain are observed or anticipated in living research animals as byproducts of an experimental protocol, the investigator is both informally and formally obliged to supply pain relief. (For a further discussion of the investigator's responsibilities in this area, see chs. 4, 13, 14, 15, and 16.)

Pain relief for a laboratory animal is usually accomplished by one of three means. An **analgesic** is an agent that relieves pain without causing loss of consciousness. The most frequent use of analgesic drugs in laboratory animals is likely to be in the postoperative period. An **anesthetic** is an agent that causes loss of the sensation of pain, usually without loss of consciousness. An anesthetic may be classified as topical, local, or general, according to the breadth of its effect. Topical anesthetics find only limited use in animal research, usually as components of ointments applied to minor injuries, whereas local anesthetics are used for many minor surgical procedures. The use of local anesthetics requires post-surgical care, because anesthetized surfaces are particularly liable to accidental and self-inflicted damage (43). General anesthetic, either injected or inhaled, is widely used in research. A **tranquilizer** is an agent that quiets, calms, and reduces anxiety and tension with some alteration of the level of consciousness and without effecting analgesia. Tranquilizers are particularly useful in reducing distress and resistance to confinement.

The perception of pain is largely subjective. It is best described as an awareness of discomfort resulting from injury, disease, or emotional distress and evidenced by biological or behavioral changes. A frequent companion to pain is distress—the undesirable stress resulting from pain, anxiety, or fear (51). Distress can also occur in the absence of pain. An animal struggling in a restraint device may be free from any pain, but it may be in distress.

Despite the difficulty associated with objectively defining pain, it can usually be recognized. The most obvious sign is an animal's behavior (16)42, 56), Signs of pain include the following:

- **Impaired activity.** Animals may be relatively inactive or may remain completely immobile within their pen or cage. If they do move, it is often with an abnormal gait, such as limping or not using a leg.
- **Change in personality.** Pain may result in guarding behavior (attempting to protect or move away). Animals may also be uncharacteristically aggressive.
- **Restlessness.** Animals may move about continually or may rise up and lie down repeatedly.
- **Decreased intake.** Food and water consumption are usually severely retarded, often to the extent that moderate or severe dehydration can occur.
- **Abnormal vocalization.** Dogs may whine or whimper, rats and hamsters may squeak at a high pitch, and primates may scream or grunt.
- **Abnormal posture.** Dogs, cats, and rodents may tense the muscles of the back and abdomen to effect a "tucked-up" appearance.
- **Self-mutilation.** Dogs and rodents may gnaw at the site of a lesion on their own flesh or, for example, remove their own tumor.

In identifying pain, all these criteria must be considered in conjunction with the nature of the experimental procedure and the previous normal behavioral characteristics of the animal. Also, it should be noted that no one criterion is a wholly reliable indicator of pain.

An experimental procedure probably involves pain if it includes, for example, induction of any pathological state, administration of toxic substances, long-term physical restraint, aversive training, or major operative procedures such as surgery and induction of physical trauma. Various procedures employed in the research laboratory can be compared, ranking each for the estimated degree of pain for the animal subject (see table 5-3). Educated estimates of pain perception in animals can be made by understanding animal behavior; by drawing analogies based on compar-

**Table 5-3.—Classification of Research Experiments and Procedures According to the Degree of Pain or Distress for the Animal**

| Level of pain/distress | Examples of types of experiments | Examples of procedures |
|---|---|---|
| Absent or negligible | • Noninvasive behavioral testing<br>• Studies of migration or homing<br>• Dietary preference studies | • Banding for identification or tracking<br>• Field observation<br>• Fecal examination<br>• Conditioned learning with food reward |
| Low | • Determination of pain threshold<br>• Manipulation of blood chemistry<br>• Experiments carried out on anesthetized animals that do not wake up again | • Flinch or jump response<br>• Injections<br>• Tube feeding<br>• Tattooing<br>• Administration of anesthetic<br>• Surgery under deep anesthesia and subsequent sacrifice<br>—Removal of organs for histological or biochemical investigation<br>—Culture of surviving organs<br>• Blood sampling |
| Moderate | • Behavioral study of flight or avoidance reactions<br>• Operations carried out under anesthesia or analgesia, with the animal waking up or experiencing the cessation of the action of the painkiller (postoperative pain) | • Stimulation of unanesthetized animal<br>• Biopsies<br>• Implantation of chronic catheters<br>• Castration<br>• Mild electric shock<br>• Implantation of electrodes<br>• Central nervous system lesions<br>• Exposure of internal organs<br>• Food or water restriction for more than 24 hours |
| High | • Chronic stress studies<br>• Drug withdrawal studies<br>• Studies of certain infectious agents<br>• Experiments on mechanisms of pain in conscious animals<br>• Experiments on mechanisms of healing<br>• Studies of radiation toxicity | • Prolonged physical restraint<br>• Chronic sleep deprivation<br>• Intense electric shock<br>• Production of pain clearly beyond threshold tolerance<br>• Induction of burns or wounds<br>• Surgery on conscious animal |

SOURCE: Office of Technology Assessment.

ative anatomy, physiology, and pathology; and by basing inferences on subjective responses to pain experiences by humans. Careful attempts to estimate and categorize the degree of pain experienced by laboratory animals—ranging from absent or negligible to high-can provide a basis for efforts to minimize the pain or distress caused by research procedures.

## ANIMAL AND NONANIMAL PROTOCOLS IN BIOMEDICAL AND BEHAVIORAL RESEARCH REPORTS

One way to measure the balance of animal and nonanimal methods in research is to survey the end-product of experimentation—the published literature. OTA examined approximately 6,000 research reports published from 1980 through 1983 in an effort to document the prevalence of animal and nonanimal protocols in contemporary research.

Fifteen leading scientific journals were selected to represent disciplines within biomedical and behavioral research, These journals were chosen because of their primary emphasis on research done in the United States by American scientists and because of the respect accorded them by scientists in each discipline. The editors of all 15 subject manuscripts to independent peer review prior to publication.

For each year from 1980 through 1983, OTA examined the first 100 research papers published in each journal; in a few cases, fewer than 100 papers were published in a given year. Short communications and review articles were not included. In each report, OTA checked whether animals were used. Thus, the materials and methods employed in each article were categorized as either use of animals, no use of animals, or use of humans. "Animal" is defined as described earlier (see ch. 2), any nonhuman vertebrate. "Use" of animals is defined conservatively as **any** use of an animal in an experiment. Table 5-4 lists some examples of the ways specific protocols were categorized by OTA.

## *Survey Findings*

The results of this survey indicate that the research journals—and perhaps the disciplines they represent—fall into two categories:

**Table 5-4.—Classification of Pubiished Research Protocois in OTA Survey of 15 Journais**

| |
|---|
| ***Examples of protocols classified as use of animals:*** |
| Whole animals used as experimental subjects |
| Animals used to obtain cell, tissue, or organ of interest |
| Animals used in the establishment of new cell, tissue, or organ cultures |
| Extraction of protein or other biological molecule from animals |
| Production of antibodies by whole animals or animal components |
| Use of egg, sperm, or embryo from animal source |
| Use of animal epidemiologic data |
| ***Examples of protocols classified as no use of animals:*** |
| Use of invertebrate organisms |
| Use of computer systems |
| Use of previously established cell lines |
| Acquisition of biological molecules from a commercial manufacturer |
| Use of physical or chemical systems |
| ***Examples of protocols classified as use of humans:*** |
| Use of living human subjects |
| Use of cadavers |
| Use of human placenta |
| Use of human blood cells or components |
| Use of human epidemiologic data |

SOURCE: Office of Technology Assessment.

- journals representing disciplines that have already largely incorporated nonanimal methods into the research process; and
- journals representing disciplines that either have not incorporated, or may not have available, nonanimal methods.

For most of the 15 journals (see table 5-5), published protocols fall predominantly into just one of the three categories of methods; in many cases, over 80 percent of the protocols are in one category. Only Cell, representing cell biology, had a majority of articles using nonanimal methods. The ***American Journal of Cardiology*** contained a majority of articles using humans or human materials as research subjects. All the remaining journals except ***Developmental Biology*** and the ***Journal of Biological Chemistry*** included a majority of articles using animals. ***Developmental Biology*** and the ***Journal of Biological Chemistry*** contained approximately equal percentages of articles employing animal and nonanimal methods.

The 12 biomedical research journals included in this survey cover a diverse array of disciplines under this one rubric. The differing patterns of animal, nonanimal, and human use make generalizations misleading at best and perhaps impossible. In the same way that biomedical research itself is not monolithic, the patterns of animal use among disciplines of biomedical research are not uniform. Perhaps not surprisingly, veterinary research, insofar as it is represented by two journals, relies primarily on animals, a minimal percentage of nonanimal methods, and no protocols with humans.

The three behavioral research journals included in this survey registered a predominance of animal methods—more than 90 percent of the protocols in each case. The research reported in these journals involved minimal use of humans or nonanimal methods. Other behavioral research journals, for example those reporting on clinical psychology, largely publish reports of research with human subjects.

## *Survey Limitations*

This attempt to gauge the implementation of nonanimal methods in selected areas of biomedical and behavioral research had certain limita-

**Table 5-5.–Percentage of Papers (Average, 1980-83) Using Animal, Nonanimal, and Human Subjects in 15 Biomedical and Behavioral Research Journals Surveyed by OTA**

| | Percentage of papers using: | | |
|---|---|---|---|
| Journal | Animals | Nonanimals | Humans |
| ***Biomadical research:*** | | | |
| American Journal of Veterinary Research | 96 | 4a | 0 |
| Journal of Animal Science | 96 | 4[b] | 0 |
| Endocrinology | 91 | 8 | 1 |
| American Journal of Physiology | 90 | 6 | 4 |
| Anatomical Record | 88 | 3 | 9 |
| Proceedings of the Society of Experimental Biology and Medicine | 83 | 10 | 7 |
| Journal of Immunology | 71 | 10 | 19 |
| Journal of the National Cancer Institute | 60 | 9 | 31 |
| Developmental Biology | 54 | 46 | 0 |
| Journal of Biological Chemistry | 39 | 52 | 9 |
| Cell | 31 | 67 | 2 |
| American Journal of Cardiology | 12 | 0 | 88 |
| ***Behavioral research:*** | | | |
| Behavioral and Neural Biology | 96 | 4 | 0 |
| Journal of Comparative and Physiological Psychology | 96 | 3 | 1 |
| Phvsioloav and Behavior | 93 | 1 | 6 |

[a]Primarily virus research.
[b]Primarily computer modeling or grain fermentation applicable to ruminant nutrition.

SOURCE: Office of Technology Assessment.

tions. The conservative scoring procedure tended to underestimate the use of alternatives to animals as defined in this assessment (see ch. 2). For instance, if an experimental protocol used both animal and nonanimal methods, it was categorized under use of animals. If a study involved both nonanimal methods and humans, it was counted as use of humans. Further, if a study involved both animal methods and humans, it was counted as use of animals. The approach used to categorize protocols took into consideration only the replacement, not the reduction or refinement, of animal methods. Whether a protocol involved 1 or 100 animals, it still fell under the category of "use of animals, " and all reports bore equal weight in determining percentage of protocols using humans or animal or nonanimal methods. In addition, there was no attempt to quantify the pain or stress of an animal in an experiment or to distinguish between different vertebrate species. Any alternative protocol, therefore, that tended to reduce or refine an existing animal procedure was still categorized as "use of animals. "

An example of the problem of overestimation of animal use by a survey such as this exists in immunology. Today, antibodies, needed in most immunology research, can be obtained by injecting rabbits with foreign proteins, or antigens, and extracting the antibodies that the rabbit produced or by using mouse spleens and the monoclinal antibody technique to produce antibodies to an antigen. Each process requires animals. Once the monoclinal cells are in culture, however, there is a virtually unlimited supply of the needed antibody, and there is essentially no further need for animals. Thus the monoclinal technique can decrease animal use, as was the case in many of the most recent articles surveyed in the ***Journal of Immunology.*** These articles, though, were still coded under the "use of animals" category because the primary methods and materials involved animals. But the total number of animals in a given experiment decreased, for they were used in just one aspect of the experiment instead of two. The monoclinal antibody technique is being used as an alternative to the repeated use of rabbits, yet its impact is underestimated in a survey such as this. The OTA scoring of protocols published in the ***Journal of Immunology*** did not reflect certain reductions that are currently being implemented.

Along with underestimating the implementation of nonanimal methods, the boundaries within which the OTA survey was carried out also tended to overestimate the use of animals as experimental subjects. This was due principally to two factors included in the scoring procedure under animal use-epidemiologic studies and the study of biological molecules obtained from animals.

Epidemiologic data are the primary sources in some articles in the ***American Journal of Cardiology,*** the ***Journal of the National Cancer Institute,*** and in many veterinary studies. These protocols were included under "use of animals," yet they did not manipulate animals in any way as experimental subjects.

Obtaining many biological molecules that are studied experimentally requires that they be extracted from animals who produce them. Subsequent experiments on these molecules themselves (reported, for example, in the ***Journal of Biological Chemistry)*** do not involve animals at all. In such cases, animals may be used in preparation for an experiment but are not actually involved in the experiment being performed. Therefore, protocols that involved animals as donors of biological molecules (e.g., bodily fluids) for an experiment prior to its initiation were also included under use of animals, and this tended to overestimate the use of animals as research subjects.

It is important to distinguish between the number of published articles involving animal methods and the actual number of animals used in research. The OTA survey provides no information on the latter. Some protocols may involve only a few animals, while others may employ tens or hundreds. Moreover, depending on the species and type of research, some subjects might be used in multiple experiments. In primate research, for example, it is not uncommon for animals to be used in a succession of either related or unrelated studies over a period of years; this would not be the case for rodents.

## SUMMARY AND CONCLUSIONS

Biomedical and behavioral research center on the understanding of human health and disease and rely on animals to achieve this goal. They use animal subjects to understand not only human phenomena, but animal phenomena as well. The broad spectrum of enterprises involved in these fields of research includes disciplines ranging from anatomy to zoology. Although the varied disciplines that make up biomedical and behavioral research have distinct foci, they often overlap.

Animals are used throughout these disciplines to address an array of questions. Nonhuman primates, for example, have contributed to an understanding of polio, hepatitis B, high blood pressure, Parkinson's disease, baldness, menopausal hot flashes, and other human conditions. Beyond the nonhuman primates, diverse species are used in biomedical research because of their anatomical, physiological, and metabolic similarities to or differences from humans. Principles and techniques developed in varied animal species (e.g., dog, horse, and sheep) may combine to support a single application to humans, as in the case of coronary artery bypass graft surgery. In behavioral research, different animal species may also be used to learn about characteristics unique to the species under study, usually one of economic importance or intrinsic interest to humans.

Animals may suffer pain or distress in the course of research on the mechanism of pain, or, more generally, as a byproduct of experimental procedures. In such cases, the investigator is obliged to supply pain relief to the animal or to justify withholding pain-relieving drugs as necessary to the experiment. Institutional animal care and use committees play an important role in overseeing this process (see ch. 15). Pain relief is usually effected by the administration of analgesic, anesthetic, or tranquilizing agents. Indices of pain can usually be recognized in experimental animals, and experimental procedures can be ranked according to estimates of the degree of pain produced. Such a ranking provides a basis for efforts to minimize the pain caused by research procedures.

An OTA survey of published research reports in 15 scientific journals documented the prevalence of animal v. nonanimal protocols in contemporary research. Each research journal, and perhaps the discipline it represents, can be identified by a characteristic balance of protocols using animals, nonanimals, and humans. The data permit research journals to be classified as representing disciplines that either rely on nonanimal methods or that do not incorporate such methods (or do not have them available). In the same way that research itself is not monolithic, patterns of animal use and the use of nonanimal methods among research disciplines are not uniform.

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