with LAV showed "productive lentivirus infection."

Swire, who says he has had a copy of Gonda's letter "for some time," alleged in the suit filed last December that Gallo's group had not successfully isolated the AIDS virus before December 1983. Gallo insists, however, that Gonda's letter should not be interpreted this way. "It can be conclusively documented," says Gallo, that he had electron micrographs, taken by a different laboratory, Electro-Nucleonics, well before the sample of LAV arrived at his lab. (Gallo's lab sent samples for electron microscopy to Electro-Nucleonics until September 1983, when they switched to Gonda's lab.)

Popovic says that the cell lines infected with LAV were killed by the virus in 2 or 3 weeks, and he again froze the material. However, he subsequently reexamined the cultures and on 13 February 1984, he sent five more samples to Gonda for electron microscopy. According to a letter from Gonda dated 22 February, all were negative for virus particles. Asked why he reexamined the LAV cultures in February, Popovic says he wanted to compare the susceptibility of the H9 line to infection with different isolates, including LAV. Gallo points to Gonda's results as confirmation that infection of the HUT-78 and T-17.4 lines was transient and that they could not infect the H9 line with LAV.

One of the allegations in the Pasteur suit is that HTLV-III "is, or is substantially identical to, the LAV strain . . . " The implication is that HTLV-III may be the French virus. Gallo indignantly denies this, pointing out that the genetic sequences of the two viruses differ by about 1.5%, a variation that, he argues, would not have come about by passage in culture. Gallo also points out that the patent application contained details of H9 cells infected with virus from single patients. Since he had these cultures, he asks, why would he sequence the virus from the culture he allegedly infected with LAV?

The electron micrographs of LAV were apparently mistakenly used instead of photographs of HTLV-III when Gonda's lab prepared a composite picture of HTLV-I, HTLV-II, and HTLV-III for Gallo's publication. The mistake came to light recently after a meeting between Gonda and Swire.

Gonda told Gallo and other U.S. officials that he was invited to a meeting to consult on some electron micrographs, but he did not realize until he got there that the meeting was with the Pasteur lawyers. Gonda declined to be interviewed for this article, but Swire admits that the lawyers did not identify themselves when they called Gonda. He says, however, that he told Gonda who he was at the start of the meeting, and Gonda "was free to leave at any time."

The lawyers showed Gonda copies of the letters he sent to Popovic and asked him about the electron micrographs in the Gallo papers. This prompted the U.S. group to check that the correct pictures were used, and to their embarrassment they found that one series was in fact pictures of LAV. ■

COLIN NORMAN

Tight Money Squeezes Out Animal Models

Certain animal models have been lost, in many cases because of funding priorities. Researchers think the issue warrants close scrutiny and careful planning

As Linda Cork of Johns Hopkins School of Medicine described her research on Rottweiler dogs at a recent National Institutes of Health meeting about diseases that affect nerve axons,* she gave no indication that the experiments would be her last with that particular genetic model. Later, in an interview, Cork explained that restricted funding had forced her to terminate not just one, but two, colonies of dogs carrying genes for degenerative neuronal diseases that are models for human diseases.

Cork is not the only researcher to lose animal models in recent years. Colonies of large animals, including cats, dogs, horses, and primates, are expensive to maintain and seem to suffer most often from the budget axe, but too little money is not the only issue. An increasing number of research scientists think that pressures from animal rights groups will jeopardize the use of certain animals in research.

Concern from scientists that valuable animal models are being lost recently prompted the National Research Council (NRC) to establish a new committee on the preservation of laboratory animal resources. Cork is a member of the committee, which met last month for the first time.

Not everyone agrees that important animal models have been squeezed out by the current funding crunch. James Willett of the Research Resources Branch at NIH says, "If you look at the number of projects NIH supports, or the dollars spent over the period from 1977 to 1984, research depending on animal models received a flat percentage of total support money. I find it hard, in light of that information, to see reductions in mammalian models during the past 7 years." Willett does not know what that means in terms of individual animal systems, but NIH is working with the National Academy of Sciences to see how specific models are being affected.

At least two general categories of animal models are used in biomedical research—genetic models for particular diseases and nondisease models used to study normal body functioning. Some researchers think that endangered models fall into both categories.

Cork describes the first group. "There are specific animal models which duplicate human disease in every respect. But more often, we are dealing with an animal model which replicates only certain aspects of human disease." The latter includes Cork's former colony of Rottweiler dogs which develop a movement disorder that worsens as they age. The dogs were a model for human neuroaxonal dystrophy, a group of inherited diseases in which nerve axons in the brain and spinal cord degenerate.

Although normal aging brain and spinal cord neurons show some signs of axonal dystrophy, the cellular changes in the disease state are more pronounced. Typically the end regions of axons swell first, forming spheroid structures. Ultimately the entire cell is affected. Cork and her colleagues at Johns Hopkins University School of Medicine showed that spheroids form in many different kinds of nerve cells, a finding that disspelled the theory that only a single population of neurons was at risk.

*"Neuroaxonal Dystrophy and Axonal Transport," 19–24 February 1986, National Institutes of Health, Bethesda, MD. The symposium was organized by the Fogarty Center and the National Institute of Neurological and Communicative Disorders and Stroke.

Benefits of Animals in Research Described in New Publication

"As far back as 1500 to 500 B.C. there are indications in early Vedic (Hindu) records of animals being observed by man for scientific purposes. . . . Galen (130 to 200 A.D.) . . . was the founder of experimental physiology. His animal studies were designed to be applicable to humans; their accuracy and completeness improved markedly the understanding of the human body." Mildred Warfield, at the National Institute of Allergy and Infectious Diseases, and William Gay, director of the Animal Resources Program at NIH, offer this historical perspective of animal use in biomedical research in a new book, *Health Benefits of Animal Research.**

Today, six animal types—mice, rats, rabbits, cats, dogs, and nonhuman primates—account for more than 95% of the animals used in research. Researchers use all six groups in studies of aging, genetics, immunology, pharmacology, and cancer and as models for measuring normal structure and function of the body.

Albert Jonas of the Jackson Laboratory in Bar Harbor, Maine, describes how inbred strains of mutant mice have made it possible to identify marker genes for traits such as coat color that also signal the presence of a genetic disease. For instance, a "misty" coat is the marker for diabetes. Other inbred strains of mice are models for immune, convulsive, and hearing disorders.

Thomas Gill, of the University of Pittsburgh, and Gordon Harrington, of the University of Northern Iowa, describe the rat as "the major animal used in organ transplantation studies." Recently, scientists have begun to understand how the genes of the rat's major histocompatibility complex (MHC) function. Humans have MHC genes that are organized differently from those in the rat, but both code for some of the proteins that participate in graft rejection. In other studies, researchers use a spontaneously hypertensive strain of rats to assess the consequences of high blood pressure, develop rat models for studying infectious and autoimmune diseases, and explore behavioral mechanisms and the impact of brain lesions or implants in rats.

Warfield and Gay recall that in 1894 a French physiologist named Marey "used the motion picture camera to illustrate how the cat's body changed position when it was dropped from a height, eventually landing on its feet. This observation led other physiologists . . . to conclude that the brain and either the eyes or the balancing mechanism ('vestibular organs') in the ears were essential to accomplish the feat." Today, cats are used extensively in studies on the eye and ear and in research on the normal and diseased central nervous system. The tailless Manx cat may become a valuable model for the condition known as spina bifida in humans.

"One of the earliest recorded uses of the dog is in William Harvey's study of the movement of the heart. His research, done in the early 1600's was the beginning of the study of circulation," writes Gay. Later, Pavlov became "known throughout the world for identifying and defining the conditioned reflex." Dogs continue to be used for cardiovascular research and behavioral studies and are also the subjects of research into respiratory disorders, such as emphysema, asthma, chronic bronchitis, and obstructive airway disease, all of which affect humans in similar ways.

Frederick King and Cathy Yarbrough of the Yerkes Regional Primate Center of Emory University describe the value and necessity of using primates in biomedical research. The conquest of polio began in 1909 with the observation that polio could be transmitted from humans to apes and monkeys. Subsequent work on polio vaccines was first done in primates. King and Yarbrough note that "primates share more biological and behavioral characteristics with humans than do any other species." As a result, primates are the most valuable animals for studying many virally induced diseases, (including acquired immune deficiency syndrome), reproductive physiology, and the development and expression of learned behaviors.

"Recently, animal rights groups have declared the use of animals in research to be exploitation and have placed a high priority on its elimination. The consequences of such an action, were it to be successful, would be catastrophic and would herald the end of biomedical research as we know it," says Gay. ■ **D.M.B.**

**Health Benefits of Animal Research*, edited by William Gay, is available for $7.50 from the Foundation for Biomedical Research, Suite 303, 818 Connecticut Avenue, NW, Washington, DC 20006. The articles were first published in *The Physiologist* between June 1984 and April 1985.

Cork says that the National Institute of Neurological and Communicative Disorders and Stroke has been supportive of animal models, has held a workshop, and will sponsor two exhibits on the topic. "But," she adds, "research in cats and dogs takes more time and more money than research in rats and mice. You get fewer animals to work with so you do fewer experiments. In large animal models it may take longer to demonstrate productivity. And to keep a grant funded one has to have publications and show productivity."

When a grant typically lasts for 3 years and it takes 2 years for an animal model to develop its inherited disease, researchers are hard pressed to crank out enough papers to satisfy NIH study sections. "If you could be assured of 5 years of funding, it could be crucial to the success of the research," says Cork, who has recently received a 5-year grant to work on a different dog model.

Even researchers who work with rodents are having serious problems maintaining colonies. For example, Thomas Gill of the University of Pittsburgh says "I personally know of three major rat colonies that have been closed down and three investigators that have been put out of business."

Gill describes himself as "an immunogeneticist whose interest is in rat genetics." He and his colleagues study reproductive immunology and transplantation and have "discovered a set of genes linked to the major histocompatibility complex that causes malformations and small size in the newborns. These same genes predispose the animal to cancer if it has been exposed to chemical carcinogens." The major histocompatibility complex is a family of genes that regulates immune responses and determines whether an individual will reject transplanted tissue.

Gill's ability to do research has been adversely affected by funding because the increased costs of maintaining rats have not been accompanied by increased money to support them. His studies require large and diverse colonies of rats, and he says, "If you don't have the colony, you can't do the research. It is getting harder and harder to preserve animal models."

Gill's personal opinion about the preservation of animal models is that "the scientific community in this country has been too slow to respond to this issue." He is the chairman of NRC's Institute of Laboratory Animal Resources standing committee on animal models and genetic stocks and is also a member of the newly formed NRC committee on the preservation of laboratory animal resources.

A second category of animal models includes those used to study how the body

performs normal functions. Perhaps the animal models most at risk in this group, in terms of their vulnerability to funding pressures and as potential targets for animal rights activists, are primates.

For instance, Mortimer Mishkin and his colleagues at the National Institute of Mental Health use Old World monkeys to study how the brain works. Mishkin fears that he and other primatologists, along with researchers who use cats and dogs, are primary targets for animal rights groups because "this is the topic most likely to incite the public."

Furthermore, the cost of obtaining a monkey has skyrocketed from about $100 about 10 years ago to $1500 today. The animal is usually maintained for 1 to 3 years, adding food, housing, veterinary, and security costs to the total bill. Mishkin sees restricted money as an increasing source of pressure and says, "Surely there will come a time when NIH study sections will ask if a grant is really worth this tremendous financial outlay."

What are the research implications if the use of primates is priced out of existence? Mishkin says, "We won't be able to study the neurobiology of the thought process — that's the implication. We're not going to have good neurobiological models, not just of disease states, but of how the whole damn thing works."

Mishkin is also looking ahead to the next level of research on brain function in chimpanzees. "There will come a time when we will know enough to investigate how the brain works in the next higher species. We should be foresighted and plan now to start breeding colonies of chimpanzees. But will Congress and the public support it?"

Douglas Bowden, of the University of Washington School of Medicine in Seattle, is also a primatologist and neuroscientist. Like Mishkin, he thinks primates are essential for research in neurobiology and adds that "if research in primates were foreclosed, you would be foreclosing information about many aspects of human disease and normal function." For instance, monkeys are valuable models for studying AIDS (acquired immune deficiency syndrome). They are unique models for research in orthodontics and cranial structure and development, they are essential for certain kinds of vision research, and they are the best models for certain metabolic studies, such as atherosclerosis and diabetes.

Bowden conducted his own survey of the use of mammals, including primates, in neuroscience research over the 1973–85 period. By sampling 20% of the abstracts presented at the annual meetings of the Society for Neuroscience, he found "some interesting trends." The relative number of neuroscience studies based on mammals has been steady at about 80%. But within that statistic, the number of studies based on rodents increased from about 45% in 1973 to almost 70% in 1985. Bowden says this "is a trend people should be aware of—that more and more information is based on studies with rats and mice."

The number of neuroscience studies of primates dropped only slightly over the 12-year period, from about 11% in 1973 to 8% by 1985. It seems that research with cats and dogs was squeezed out most by rodent studies. But these statistics are only for research in neuroscience. Bowden says that "from the late 1960's to the present the number of primates imported from the wild has dropped by about 90%." Overall, monkeys are used much less in research, and the development of alternative animal models and in vitro systems for much drug and toxicity testing are significant factors.

William Gay, director of NIH's Animal Resources Program expresses another point of view about the danger, or lack of it, in losing valuable animal models. "They don't tend to go out of existence like the passenger pigeon. I'm hard put to identify any models that have been lost that I feel terribly bad about. The researchers have to get support for these models. It is true that some are lost and if you start looking for these tales, you will find them. But they are gone because not enough research was done to support them."

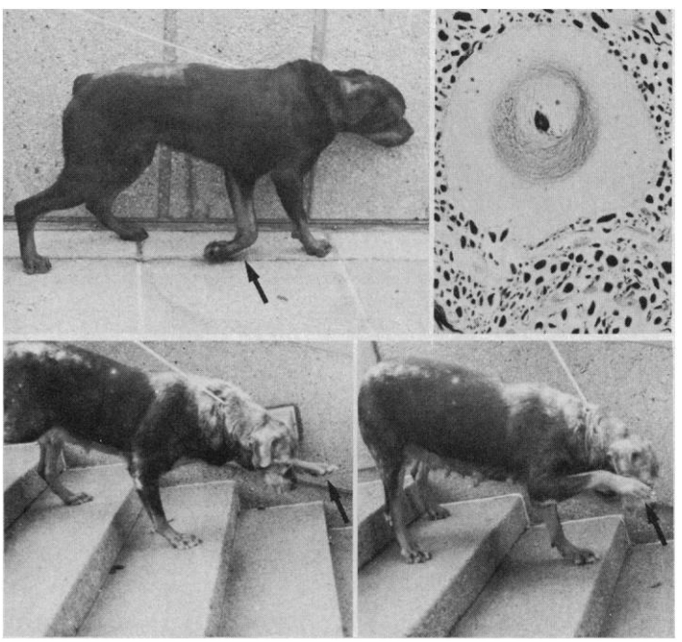
With respect to any influence the animal rights movement may have on the budget for animal models, Gay says, "It certainly isn't going to encourage NIH to spend more money for animal models. But I think NIH will continue to support animal models."

Wayne Grogan is the executive director of the NRC's Institute of Laboratory Animal Resources, which includes the standing committee on animal models and genetic stocks and the new committee on preservation of laboratory animal resources.† The new committee will study the current situation regarding animal models and issue an assessment within the next year or two. In response to scientists' concern that important animal models have been lost, Grogan says, "It's very compelling, but some argue that if the colony is so valuable, then why shouldn't it be supported by the normal funding mechanism? These are factors the new committee will have to consider in their deliberations"

Why, indeed? Perhaps the only point of general agreement is that there is simply not enough money to support all the animal models—genetic and normal—currently used in biomedical research. ■

DEBORAH M. BARNES

This is the second of a two-part series on animals in research. The first article appeared in the 11 April issue.



Rottweiler dog colony lost to funding pressures. *Dogs are unable to control the range of limb movement (arrows). Abnormal spheroid structure in a nerve axon from the spinal cord of an affected dog (top right).*

†Dorothy Greenhouse is the NRC staff officer for both committees.