Science, Medicine, and Animals

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NATIONAL RESEARCH COUNCIL
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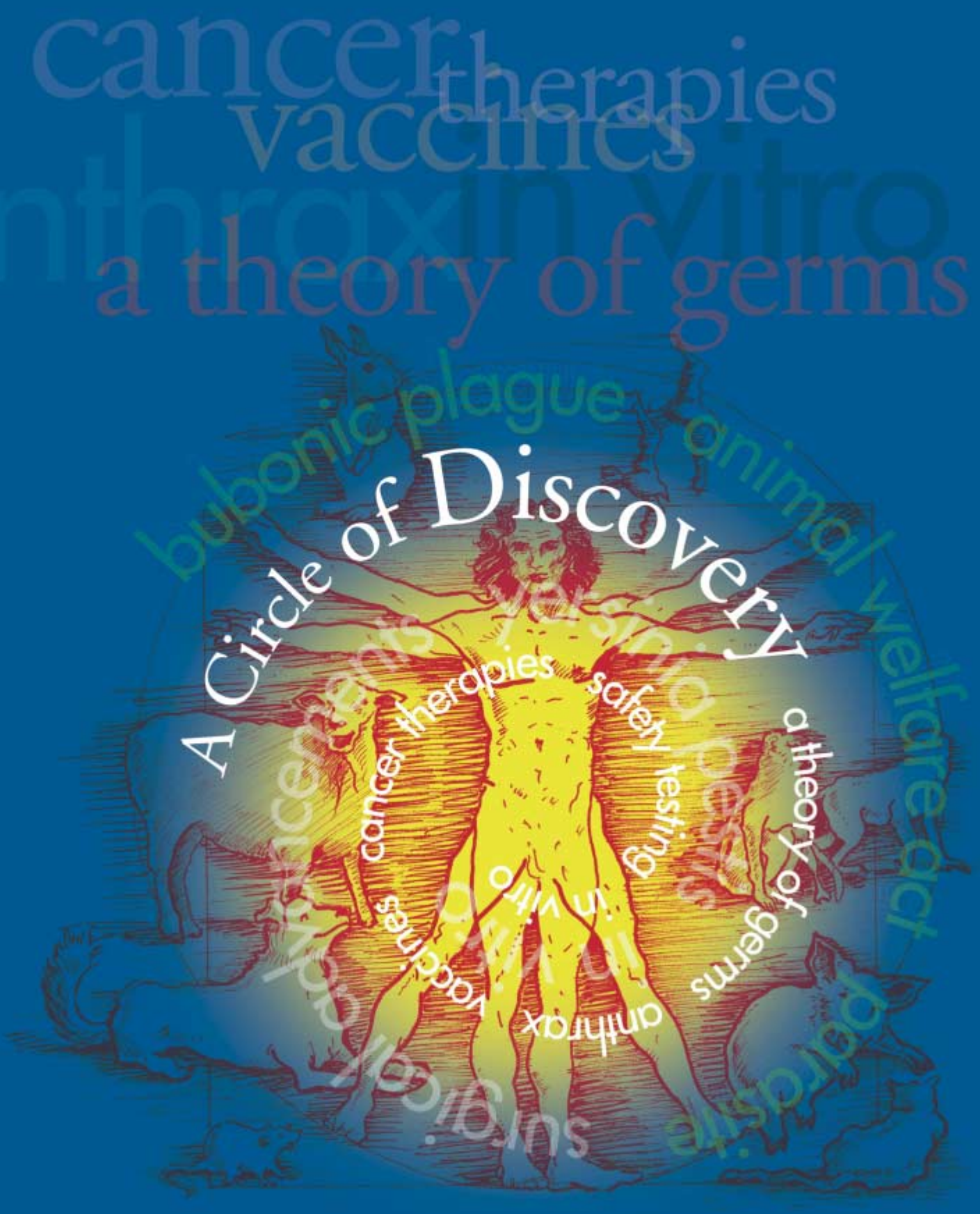

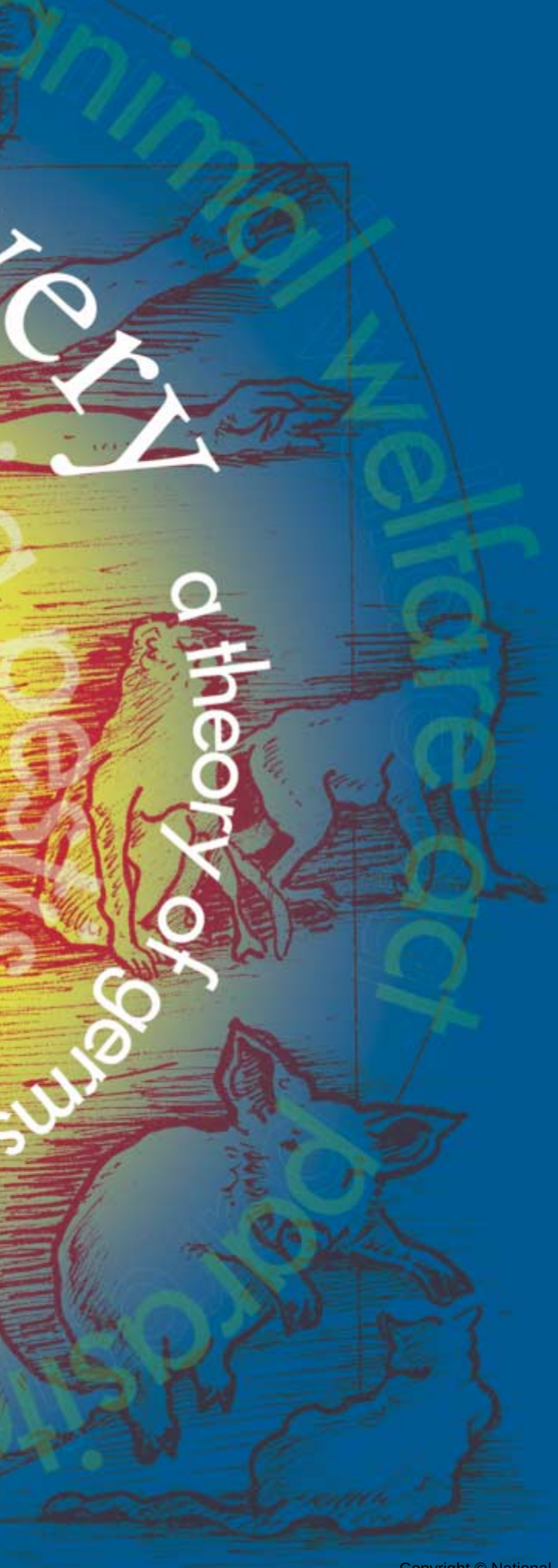

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science, and medicine, animals

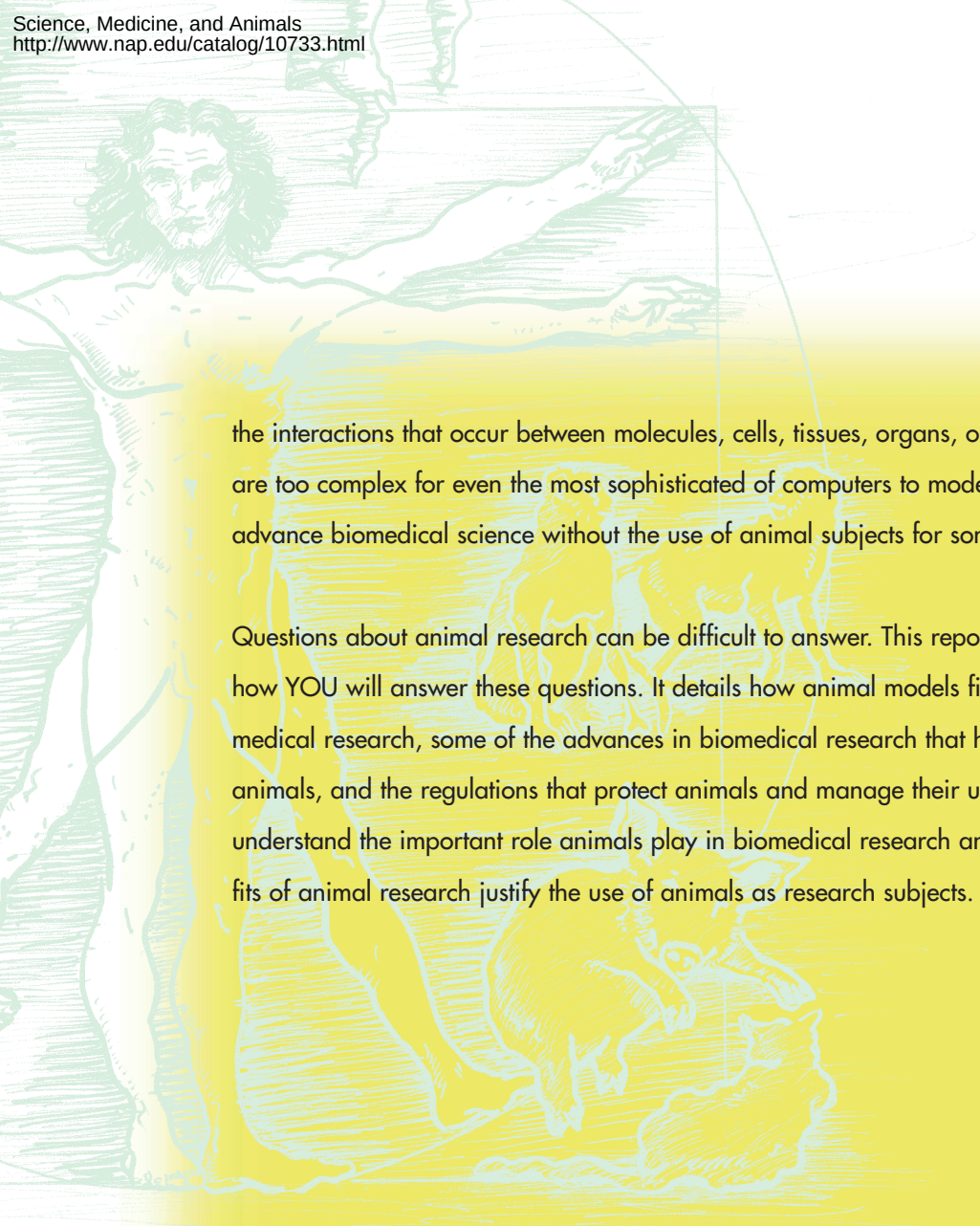
PREFACE

The lives of humans and animals have been intertwined since the beginning of civilization. Early humans learned to raise animals for food as well as to live alongside them as companions. Humans and animals develop strong interactions and lasting bonds to their mutual benefit. It is because of our close ties with animals that many people have mixed feelings about the use of animals in biomedical research—even scientists. In an ideal world, scientists would never need to use animals as research subjects. Because we do not live in an ideal world, some difficult ethical and moral questions arise.

First and foremost, is it ethical to allow humans and animals to suffer from injury and disease when treatments and cures can be discovered through animal research? Public opinion polls have consistently shown that a majority of people approve of the use of animals in biomedical research that does not cause pain to the animal and leads to new treatments and cures. However, another difficult question is whether it is morally acceptable to perform research on animals that is painful, if it leads to new and better treatments such as new anesthetics and painkillers. Or, is it acceptable to perform any research on animals if new treatments or cures resulting from the research might not be apparent for decades, if ever?

A minority ot people polled thought that experiments should be done on humans rather than animals. To some extent this does occur during clinical trials, but only after extensive animal testing to ensure that harmful drugs are not given to humans. In our society, most people consider it morally wrong to use humans as subjects for basic research, under the premise that humans deserve higher moral consideration than animals.

Some people also claim that it is unnecessary for animals to be used as research subjects and that computer or other nonanimal models could be used instead. In some cases this is true, and scientists strive to use computer models and other nonanimal methods whenever possible; however, many of



the interactions that occur between molecules, cells, tissues, organs, organisms, and the environment are too complex for even the most sophisticated of computers to model. At present, it is impossible to advance biomedical science without the use of animal subjects for some aspects of research.

Questions about animal research can be difficult to answer. This report is meant to help you decide how YOU will answer these questions. It details how animal models fit into the larger scheme of biomedical research, some of the advances in biomedical research that have been gained because of animals, and the regulations that protect animals and manage their use. This report will help you to understand the important role animals play in biomedical research and to decide whether the benefits of animal research justify the use of animals as research subjects.

INTRODUCTION

Diseases cause a staggering amount of suffering and death in both people and animals. As a result, human society has committed itself to alleviating the suffering caused by disease. Toward this goal, biomedical research has included the use of animals as one component of research to understand, treat, and cure many human and animal diseases. This publication (1) discusses how animals were and continue to be an important component of biomedical research, (2) presents the role animals play within the whole picture of biomedical research, (3) discusses the regulations and oversight that govern animal research, and (4) discusses continuing efforts to use animals more efficiently and humanely in biomedical research.

Throughout history, people have sought to reduce our vulnerability to the hardships and dangers of life. We have given up the wandering habits of our ancestors to settle in groups and cultivate the land to ensure a regular supply of food. We have built shelters to guard us from the weather and have crafted weapons to defend ourselves against predators. We have also tried to protect ourselves from a threat that is not always visible, but is often deadly—disease.

History is littered with examples of lethal diseases that strike and spread rapidly. Cholera, smallpox, polio, and influenza outbreaks have sickened, disabled, or killed hundreds of millions of people. The outbreak of the bubonic plague (caused by the bacteria *Yersinia pestis*) during the 14th century killed 25% to 50% of all people in Europe, the Middle East, China, and North Africa.

BUBONIC PLAGUE—A disease caused by the Yersinia pestis bacterium. Characterized by swollen lymph nodes and bleeding beneath the skin, often leading to death. Also called the "Black Death" during the 14th-century outbreak.

PARASITE—An organism that depends upon another organism (host) for its nutrients and protection, usually harming the host in the process.

why study animals?

Infectious diseases and those caused by parasites or malnutrition are not the only challenges to health we have faced. The ancients recognized epilepsy and called it "the sacred disease," believing that the seizures of epileptics were caused by gods or demons. Babylonian documents describe the symptoms of epilepsy, as do Greek and Roman medical texts. Cancer too was known and feared by our ancestors, who attempted to heal these diseases with remedies both natural and magical. Eventually doctors and scientists turned to the study of animals to help them understand the mysteries of anatomy and the riddles of disease.

So why do scientists study animals to understand human disease? They do so because people are vulnerable to many of the same or similar diseases as animals. Humans have 65 infectious diseases in common with dogs, 50 with cattle, 46 with sheep and goats, 42 with pigs, 35 with horses, and 26 with fowl. We have lived with and among these animals for thousands of years, so it is not surprising that we are susceptible to some of the same parasites, viruses, and bacteria as animals, including some that can be transmitted between animals and people such as rabies and malaria. Nor is it surprising that many chronic, noninfectious diseases such as epilepsy also afflict other species. The parallels between human and animal physiology and pathology were noted long ago, and the practice that we today call "animal research" has roots stretching back to ancient Egypt and Greece.

PHYSIOLOGY—All the functions of a living organism or any of its parts.

PATHOLOGY—The structural or functional manifestations of a disease.

epilepsy

cancer

why use animals?

Animals are just one type of model that scientists use in biomedical research to simulate biological functions and organizations:

Molecular models simulate the interactions and functions of molecules and how these molecules form larger structures like proteins and DNA. For example, molecular models help scientists understand how protein structures inside heart cells cause the heart to contract and pump blood.

Cellular models simulate how structures interact inside a cell and how a cell functions. For example, cellular models help scientists understand how cells produce an electrical charge that causes the heart to beat.

Tissue models simulate how cells interact to form tissues and how the tissues function. For example, tissue models help scientists determine how the many electrical cells in the heart synchronize to produce electrical charges at the same time.

Organ models simulate how multiple tissues organize and function as organs. For example, organ models help scientists understand how the four different chambers of the heart work together to pump blood throughout the body.

System models simulate how multiple organs interact and form a system. For example, system models help scientists understand how the heart, arteries, veins, and capillaries (called the cardiovascular system) all work together to move blood from the heart to the body.

Organism models simulate how different systems work together to allow an animal to respond to its environment. For example, organism models help scientists understand how stress causes high blood pressure.

Many questions about molecular, cellular, tissue, and even organ functions can be investigated using test tube, cell culture, and tissue culture models. But some questions, such as how the digestive system interacts with the cardiovascular system or how the environment affects an organism, can only be answered using animal models.

. . . why use animals? (cont.)

People Often Ask the Questions...

"How can the research be useful when animals are different from people?"

"People and animals suffer from different diseases, so how can scientists justify performing experiments on animals?"

Even though animals differ from people in many ways, they also are very similar to people in many ways. Animals develop many of the same diseases as people, including hemophilia, diabetes, and epilepsy. Animals are also susceptible to many of the same bacteria and viruses as people, such as anthrax, smallpox, and malaria. An animal is chosen as an "animal model" for research only if it shares characteristics with people that are relevant to the research. For example, Louis Pasteur was able to use dogs as an animal model for studying rabies. He was able to develop a rabies vaccine because (1) dogs and people can both develop rabies, and (2) the immune systems of dogs and people react to the rabies virus in the same way. For this research, it did not matter that humans and dogs differ in other ways; for example, dogs cannot develop AIDS or measles, diseases that do affect humans.

- ***ANIMAL MODEL—An animal in which normal biology and behavior or a disease or disability can be studied, and in which the normal or abnormal biology is similar to that in humans***

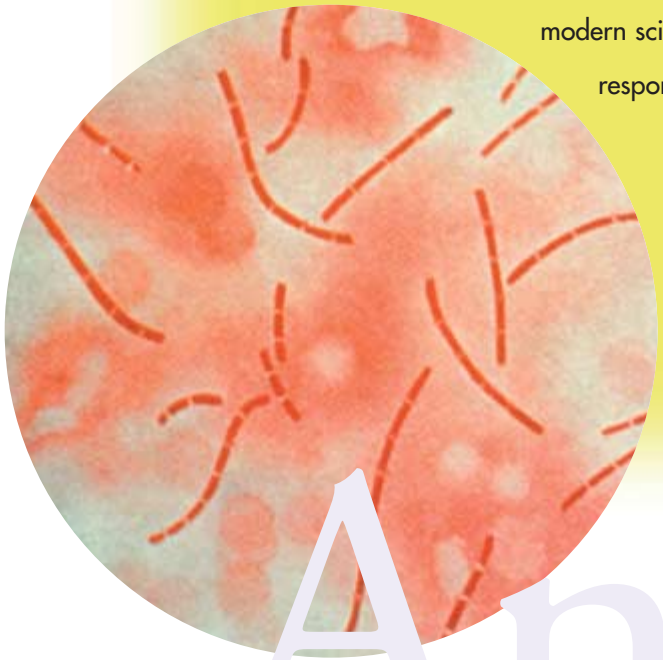
- ***AIDS (acquired immunodeficiency syndrome)—A fatal disease caused by the HIV virus. The HIV virus destroys T cells, which are the cells that fight infection. Eventually, the immune system is weakened enough that common illnesses become life threatening.***

- ***GERM—A disease-causing organism, such as a bacteria, parasite, or virus, usually single celled.***

A THEORY OF GERMS

Today, it is hard for us to fully appreciate the great revolution in medicine known as "germ theory" and the role that animal research played in its development. It seems impossible that people once believed that foul odors could create disease or that "evil spirits" could cause a person to become ill. We have also forgotten how rare it was for parents to see all of their children survive to adulthood. Still, it has been little more than a century and a half since Robert Koch made the discoveries that led Louis Pasteur to describe how small organisms called germs could invade the body and cause disease.

In the final decades of the 19th century, Koch conclusively established that a particular germ could cause a specific disease. He did this by experimentation with anthrax. Using a microscope, Koch examined the blood of cows that had died of anthrax. He observed rod-shaped bacteria and suspected they caused anthrax. When Koch infected mice with blood from anthrax-stricken cows, the mice also developed anthrax. This led Koch to list four criteria to determine that a certain germ causes a particular disease. These criteria are known as Koch's Postulates and are still used today. Integral to these criteria is Postulate #3, "The disease must be reproduced when a pure culture is inoculated into a healthy, susceptible host." Even today, with all of the advances in modern science, it would be impossible to prove that a specific germ is responsible for a disease without the use of laboratory animals.

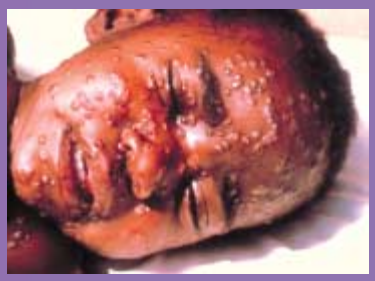


- ***ANTHRAX—A disease caused by* Bacillus anthracis *bacteria. Can cause skin lesions (cutaneous anthrax), breathing difficulties and shock (inhalation anthrax), or severe vomiting and diarrhea (gastrointestinal anthrax).***

- ***CULTURE—Micro-organisms, tissue cells, tissue, or other living matter grown in a specially prepared nutrient medium. Also refers to the cells grown, i.e., a culture of bacteria.***

overcoming disease

Until the 20th century, it was common to lose a child to disease. Smallpox, polio, diphtheria, whooping cough, tetanus, measles, and mumps maimed and killed thousands of children every year. But due to the development of vaccines, there has not been a single natural case of smallpox in the world since 1977, polio has been eradicated in the Western Hemisphere, and whooping cough, tetanus, and mumps are rarely seen in developed countries.



Smallpox causes blisters similar to chickenpox. Smallpox is easily spread through coughing or sneezing, or through contact with contaminated clothes or bed linen. Twelve and 14 days after exposure, the patient develops a fever with severe aches and pains. A rash then appears over the entire body including the palms of the hands and soles of the feet. Death occurs in 30% of patients due to a massive immune response that causes clotting of the blood and organ failure. Vaccination before exposure to smallpox prevents the illness. There is no known treatment; however, vaccination up to 5 days after the exposure may help to prevent death.

Polio is caused by a virus that enters through the mouth and is easily transmitted from person to person, particularly between children during the summer months. It causes headache, fever, and aches before entering the bloodstream and infecting the nerves controlling movement. The disease causes paralysis in the arms and/or legs (spinal polio), throat, eyes, face, heart, or lungs (bulbar polio), or both (bulbospinal polio). It can lead to suffocation and death caused by paralysis of the lung muscles. Before the invention of the "iron lung," about half of children with bulbar or bulbospinal polio died.

"In 1736 I lost one of my sons, a fine boy of four years old, by the small-pox, taken in the common way. I long regretted bitterly, and still regret that I had not given it to him by inoculation [had his son vaccinated]. This I mention for the sake of parents who omit that operation, on the supposition that they should never forgive themselves if a child died under it; my example showing that the regret may be the same either way, and that, therefore, the safer should be chosen."

Benjamin Franklin, His Autobiography: 1706-1757

VACCINE—Weakened or killed germs or part of a germ that when injected into a body stimulates antibody production and immunity against the germ but is incapable of causing a disease.

VACCINES

By infecting animals with certain microbes, Koch, Pasteur, and other researchers were able to identify the germs causing anthrax, rabies, diphtheria, and plague. These discoveries have allowed scientists to develop vaccines for animals and people made from weakened germs. The safety and effectiveness of these vaccines are also tested in laboratory animals. One of the first vaccines developed was against anthrax. Louis Pasteur weakened anthrax bacteria by heating it so that it could no longer cause illness. He then vaccinated one group of sheep with the weakened anthrax bacteria. This vaccination caused the sheep's immune system to recognize the anthrax bacteria and produce antibodies against it. He later infected the vaccinated group and a nonvaccinated group with live anthrax. The vaccinated group all survived, proving that the vaccinated animals' immune systems would recognize and fight the live anthrax and thus prevent the disease. Pasteur used animals to prove that vaccination was generally safe and would prevent disease, which in turn has saved many farm animals and people from death by anthrax.

Unfortunately, developing a vaccine is not always simple or easy. Take for instance malaria, another disease that Koch studied during the late 19th century. Malaria is one of the most ancient parasitic diseases affecting humankind, and its very name summons up a time when the origins of disease were shrouded in mystery. The Italian phrase *mala aria* (bad air) was first used to describe the supposed cause. Malaria is characterized by high fever, shivering, joint pain, headache, vomiting, and possibly convulsions and coma ending in death. Malaria remains a public health problem of staggering magnitude. There are 300 to 500 million new infections and 1.5 to 2.7 million deaths throughout the world *each year*, most of them among children.

Koch's Postulates—1. The agent must be present in every case of disease 2. The agent must be isolated from the host and grown in a laboratory dish. 3. The disease must be reproduced when a pure culture is inoculated into a heathy, susceptible host. 4. The same agent must be recovered again from the experimentally infected host.

Malaria is caused by a parasite called *Plasmodium*. This small single-cell organism invades the liver and metamorphoses so that it can burrow into red blood cells. The parasite then multiplies until the red blood cells burst, causing the host body (human or animal) to be assaulted by waves of fever as the body attempts to destroy the parasite. In some cases, the infected red blood cells become stuck in the arteries and veins of the head, leading to death. In the early 20th century, Robert Ross used Koch's Postulates to prove that bird malaria was transmitted from bird to bird by mosquitoes. The next year, a team of Italian scientists showed that human malaria was also spread by mosquitoes, paving the way for a series of simple measures to interrupt the transmission of the disease, such as the use of bed nets and insecticides. But because the malaria parasite metamorphoses as it moves from the liver to the red blood cells, it has been difficult to develop a vaccine that will stimulate the host's immune system into recognizing the two different forms of the parasite.

Even though scientists have not yet been able to develop a malaria vaccine, animal research has played an important part in developing drugs to treat malaria and helps scientists understand how to develop a vaccine for a parasite with two different forms. Dr. Nirbhay Kumar, professor in the Department of Molecular Microbiology and Immunology at the Johns Hopkins Bloomberg School of Public Health, has been studying malaria using several animal model systems including chicken and rodent models of malaria, even though these animal malaria parasites cannot infect humans. Results from the research on these animal models allow him to understand how the parasite infects liver

and blood cells and completes its transmission through an extensive development inside the mosquito vector. The major life-cycle events of this deadly human parasite are very similar if not identical among all the different animal models. Dr. Kumar points out, "The knowledge that we gain from animal malaria studies can often extrapolate to human malarias."

Dr. Kumar is using the knowledge that he has gained by studying chicken and murine malaria to develop new vaccines. He tests these new vaccines in mice and nonhuman primates to help assess whether the vaccines will stimulate the correct type of immune responses to cure people of malaria, another example of how studying animals with similar but not identical diseases is helpful.

Dr. Kumar points out that scientists must think carefully about using animals in their research. "We must be careful and judicious in our use of animals," he says. "We should use them only because there is no other way. There must be real justification for animal use." With a child dying of malaria every 20 seconds somewhere in the world, he notes, "in this case, there is a justification."

penguins!

The Baltimore Zoo is located in Druid Hill Park, a green oasis in the midst of a concrete desert. But the large colony of penguins living at the zoo must cope with a bloodthirsty adversary capable of transforming this oasis into an intensive care unit: the plasmodium-laden mosquitoes that infest the park and transmit a deadly strain of malaria.  "This is a problem in zoos throughout North America," says Dr. Thaddeus Graczyk, Associate Research Professor in the Department of Molecular Microbiology and Immunology at the Johns Hopkins Bloomberg School of Public Health. "This is a huge problem for the zoo because there is very high mortality among the newly hatched and juvenile penguins." The penguins hatch in winter and are still young and vulnerable in May or June, when the mosquitoes in Baltimore begin to bite. "We've captured a few of the mosquitoes and have seen that they all carry the parasite," says Graczyk.  But malaria is not just a problem for penguins in zoos. Malaria is also becoming a problem for wild populations, such as African penguins. African penguins are particularly vulnerable to the malaria parasite because they are a "naive" population; they have never encountered malaria before. African penguins are found on islands off the coast of South Africa, in a harsh climate where at one time there were no mosquitoes or malaria. But human development brought mosquitoes, and African penguins are now catching malaria, just like the Baltimore Zoo penguins. The penguins of the Baltimore Zoo have become an important ally in the quest to develop a malaria vaccine for African penguins and even people.  If a penguin survives the first time it becomes infected with malaria, it is much more likely to survive a second bout. By studying the Baltimore penguins, Graczyk and his colleagues have identified antibodies created by the penguins' immune systems that attack the malaria parasite and help them survive the disease. By identifying antibodies against malaria, this may help develop a malaria vaccine for penguins. Because of the similarities between malaria in penguins and humans, this development may also lead to a malaria vaccine for people.

drink the blood

EPILEPSY—Neurological disorder characterized by sudden attacks of motor or sensory malfunction with or without loss of consciousness or involuntary muscle contraction.

UNDERSTANDING EPILEPSY

In imperial Rome, epileptics were encouraged to enter the Coliseum and drink the blood of wounded gladiators. This magical "cure" was thought to be effective in banishing the seizures that caused epileptics to be feared and shunned by other citizens. Throughout the Middle Ages, epilepsy was believed to be an infectious disease, and epileptics were routinely confined to insane asylums during the 18th and 19th centuries. Even as late as 1933, epileptic inmates of U.S. mental health institutions were forcibly sterilized in an erroneous attempt to prevent them from passing their genes on to their children.

Today, there is still no cure for epilepsy. Medications can effectively control seizures in 70% of patients. Others, whose seizures are caused by abnormal electrical activity in parts of the brain that can safely be removed, undergo surgery. However, medications can have serious side effects, and brain surgery is an option in only a very small percentage of cases. This still leaves about 30% of patients whose seizures cannot be controlled by medication or surgery, highlighting the need for continuing research into the brain and epilepsy.

In the laboratory of Dr. Michael Rogawski at the National Institutes of Health (NIH), scientists are seeking to understand the mechanisms of abnormal electrical activity in the brain at the cellular and molecular level and to develop drugs that will control seizures without side effects. "Epilepsy is a chronic disease that can be a severe impediment to living a normal life," Rogawski explains, due to the difficulties caused by frequent or uncontrolled seizures and the disabilities that can be associated

NIH (National Institutes of Health)—A federal agency whose mission is to acquire new knowledge to help prevent, detect, diagnose, and treat disease and disability. NIH is the federal focal point for medical research in the United States.

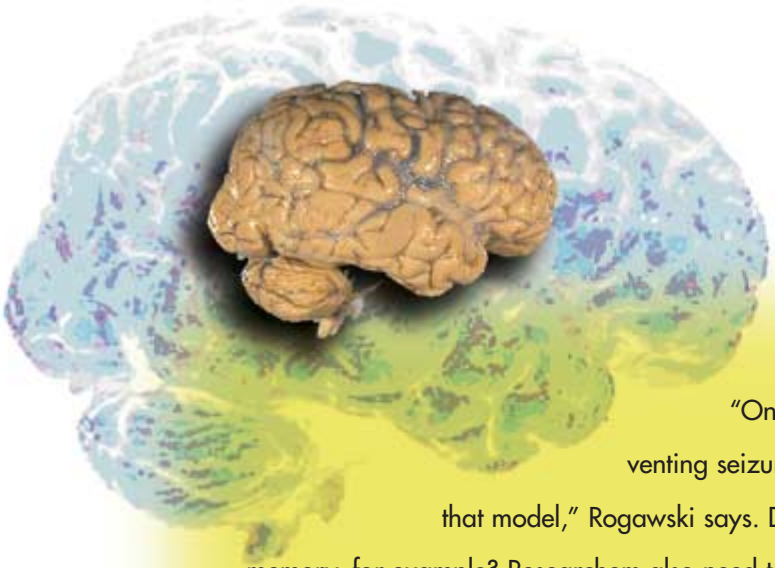
ANTICONVULSANT—A drug or procedure able to stop a seizure.

with the disease or the drugs used to treat it. Because brain activity in epileptics is normal between seizures, "it's a challenge to develop a drug that will target only the abnormal activity without interfering with normal brain functions."

The study of epilepsy in the laboratory begins in vitro. Researchers have learned to simulate a seizure in a culture of neurons, creating a "seizure in a dish." Unlike bacteria or plant cells, animal neurons when grown in a petri dish (cell model) are capable of forming simple connections that are similar to the connections made between neurons in the brain. This process makes it possible to assess the potential anticonvulsant properties of new drugs. "When trying to characterize the molecular actions of the drugs, we study them in cultured neurons," Rogawski says. Cultured rat neurons lack the complex connections between brain regions that are present in whole brains or brain slices but are still useful in the early stages of research. After a chemical compound's activity has been thoroughly studied in a cell model, the researchers use 1/2-mm-thick brain slices from young adult rats. The use of a brain slice (tissue model) allows researchers to understand how electrical activity in one region of the brain affects and interacts with another part of the brain. Researchers are able to obtain dozens of brain slices from a single animal, allowing them to perform several studies using only a single rat brain and reducing the number of animals needed for this type of research. "We can then wash potential drugs over the surface of the slice instead of injecting the whole animal," Rogawski says. If a new drug looks promising, the researchers then test the drug in animals (organism model). Without administering the drug directly to an animal model, scientists could not be certain that a drug would have therapeutic value or be safe in people. He explains that "the brain is an incredibly complex, interconnected organ. Cells or slices in a dish, while useful in the earlier stages of research, cannot completely predict the effect of a drug on an intact brain."

IN VITRO—An artificial environment outside a living organism such as a petri dish.

NEURON—A type of cell that conducts electrical impulses; also called a nerve cell; found in the brain, spinal column, and nerves.



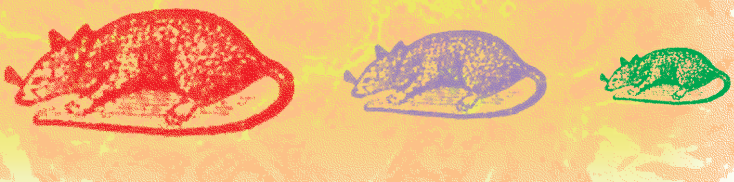
"Once a drug has been shown to be effective in preventing seizures in an animal model, we look for side effects in that model," Rogawski says. Does the drug interfere with motor coordination or memory, for example? Researchers also need to determine the dose that will prevent seizures with the lowest incidence of side effects, work that also can only be performed in whole animals.

Drugs developed in Rogawski's laboratory at NIH are now being tested in people, a potential boon to the 2.5 million Americans who have epilepsy. Although advances in cell culture and computer modeling have reduced the need for animals in research, Rogawski notes, "We still have an absolute requirement for animal models," in studying diseases like epilepsy. "The brain has billions of neurons . . . and the complexity of that system is far greater than a computer can simulate. It is absolutely essential to study the action of potential new drugs in a complete nervous system."

Rogawski's research takes advantage of the fact that epilepsy is not only a human disease. Seizures occur frequently in many purebred dogs and in baboons, as well as other species. But Rogawski and his colleagues use primarily rats and mice in their research. "They breed easily and we can control their genetics much more easily," he says.

Genetically modified rats and mice, like those used in Rogawski's research, are an important new tool for researchers. By altering a specific gene, scientists are able to breed rodents with diseases similar or identical to those in humans.

Genetically modified rats and mice are often



excellent models of human disease, which is one of the reasons that 90% of all animals used in U.S. research today are rats and mice.

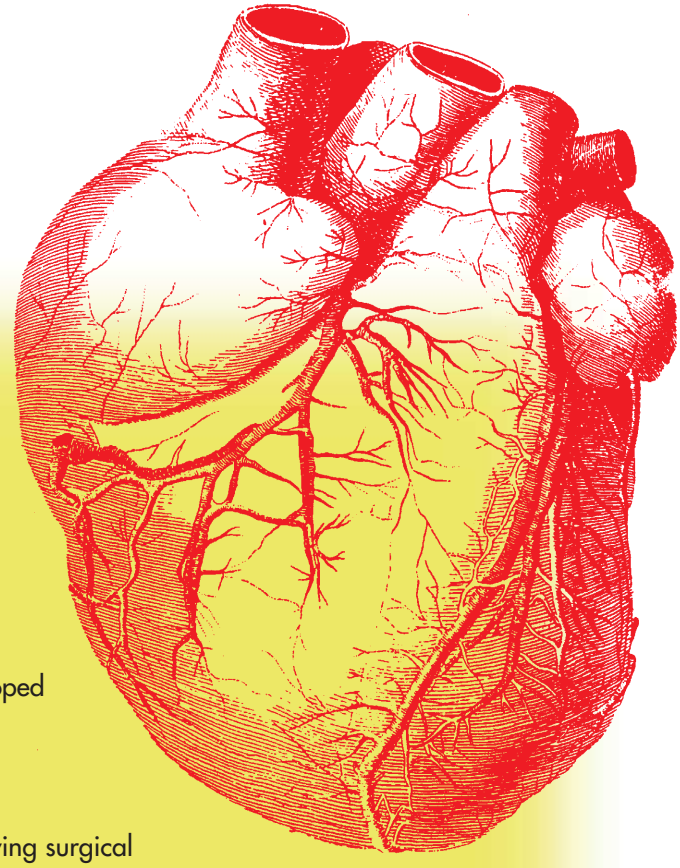
GENETICALLY MODIFIED ANIMALS

Newborn "green mouse"

Genetically modified animals (sometimes called transgenics) are developed by altering an embryo's genes, either by treatment with chemicals or by adding or removing a gene. Most genetically modified animals are mice that are developed to mimic a human disease. For example, one type of genetically modified animal has the gene for a protein called pro-opiomelanocortin (POMC) "knocked out" or made nonfunctional. POMC is converted by the body into hormones that influence pigmentation, food intake, and fat storage. People with alterations in the POMC gene become severely obese as infants and have red hair. POMC knock-out mice are severely obese and have yellow rather than brown fur, mimicking the human disease. POMC knock-out mice are being studied to understand how the body controls hunger and metabolism. They are also used to test new drugs to treat obesity.

Genetically modified animals can be useful even if they are not created to mimic a disease. Take for instance the "green mouse." Green mice have a jellyfish gene called "green fluorescent protein" inserted into their genomes. This jellyfish gene encodes a protein that glows green under ultraviolet (UV) light. Therefore, when green mice are exposed to UV light, every single cell in their body glows green. Scientists use these mice to study a wide variety of immune diseases, even though these mice are perfectly normal. By studying green mice, scientists have studied how immune cells from the mother are passed to infants through breastfeeding, how different immune cells interact, and how fetal immune cells migrate out of the womb and into the mother's organs, which may cause some autoimmune diseases.

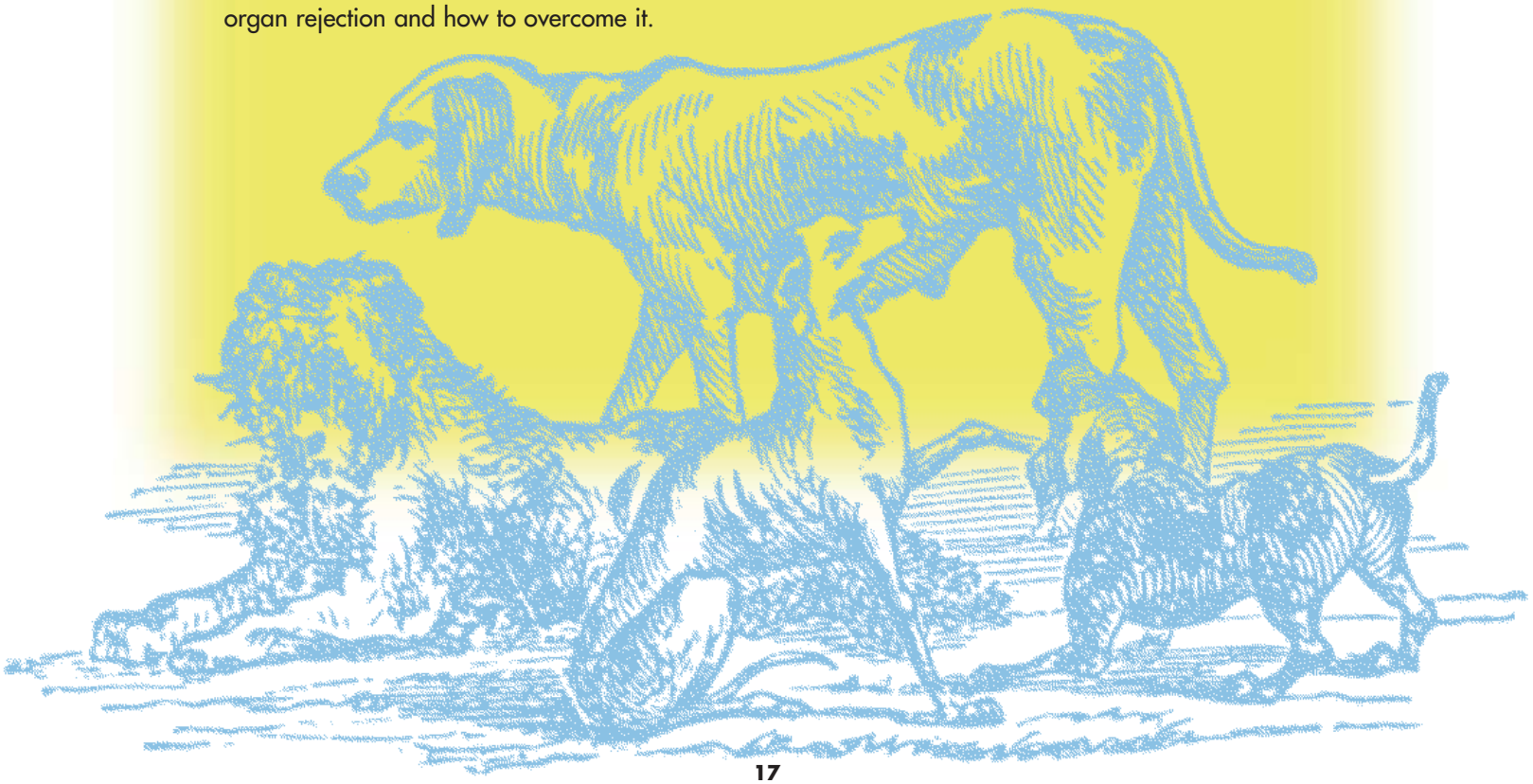
GENOME—All of the genetic material or DNA of an organism.



SURGICAL ADVANCEMENTS

Though animal research has helped to develop drugs and vaccines to control and cure many infectious diseases, many surgical procedures were and continue to be developed through the use of animal models. Organ transplantation, open heart surgery, and many other common procedures were developed using animal models.

Animal research was essential in developing many life-saving surgical procedures once thought impossible. Heart valve replacement is now a common procedure, and development of these artificial heart valves as well as the artificial hearts now being tested in people would not have been possible without animal research. Organ transplants and coronary artery bypasses require that blood vessels be sewn together. The technique of sewing blood vessels together was developed through surgeries on dogs and cats by Alexis Carrel, for which he was awarded a Nobel Prize in 1912. Research on laboratory animals also led to the understanding of organ rejection and how to overcome it.



cancer cell growth

CANCER THERAPIES

Animal studies have already contributed to the development of a drug that has been described by some as "the vanguard in a new generation of cancer drugs." Gleevec, a chemotherapy that works by inhibiting a protein that contributes to cancer cell growth, is the first effective treatment for people with chronic myeloid leukemia. Gleevec was developed using cell cultures and mouse studies. Like the research programs devoted to developing a malaria vaccine and treatments for epilepsy and heart disease, cancer research requires the use of many different models. Cell and tissue culture, whole animal models, and clinical (human) studies help scientists better understand both the cause of various diseases and better ways to prevent, treat, and possibly cure them. All of these methods were used in the development of Gleevec. In order to develop a new drug to treat a disease, it is necessary to make use of all of these models. Culture, animal, and human studies each play an important role in the struggle to understand disease and develop cures.

GLEEVEC—A drug that is highly effective in treating chronic myeloid leukemia. Although it took more than a decade of laboratory work to develop Gleevec, the drug gained FDA approval in less than 3 years. Typically, it takes 14 years to win FDA approval by proving that a new drug is safe and effect through clinical trials. Novartis, the pharmaceutical company that developed Gleevec, reports that it spent between $350 million and $500 million from 1985 to the time the drug was approved by the FDA in May 2001. On the basis of promising animal and human studies, the FDA accelerated the review process and approved Gleevec after only 32 months. There is no other safer effective treatment for people with chronic myeloid leukemia, one of the reasons why the FDA's review of Gleevec was the fastest ever recorded for an anticancer drug in the United States.

CHEMOTHERAPY—Treatment of a disease with a chemical that has a toxic effect on cancerous tissue (anticancer therapy) or on a disease-producing germ (antibiotic).

CANCER—an abnormal and uncontrolled growth of cells in any part of the body.

malaria...

People sometimes wonder why such research remains necessary. The answer is simple. Though many formerly lethal infectious diseases (such as smallpox and polio) have been controlled, people's lives are still threatened by bioterrorism, emerging diseases, (AIDS, Ebola, and West Nile), and other still uncured diseases like malaria. Malaria, for example, kills more people each year than AIDS, and the search for an effective vaccine against this ancient adversary continues. Chronic diseases like hypertension, diabetes, and depression, which are debilitating and emotionally devastating for patients and their families, comprise another important area of study. Epilepsy, a neurological condition that most often appears in late childhood or early adolescence, continues to wreak havoc on the lives of millions of Americans, and currently available medications may only partially control seizures while causing serious side effects. Finally, scientific understanding of the way that genes, environment, and behavior interact to create diseases like cancer, obesity, and drug addiction remains inadequate, as does current treatment, which often falls far short of a cure.

chronic diseases

...kills more than

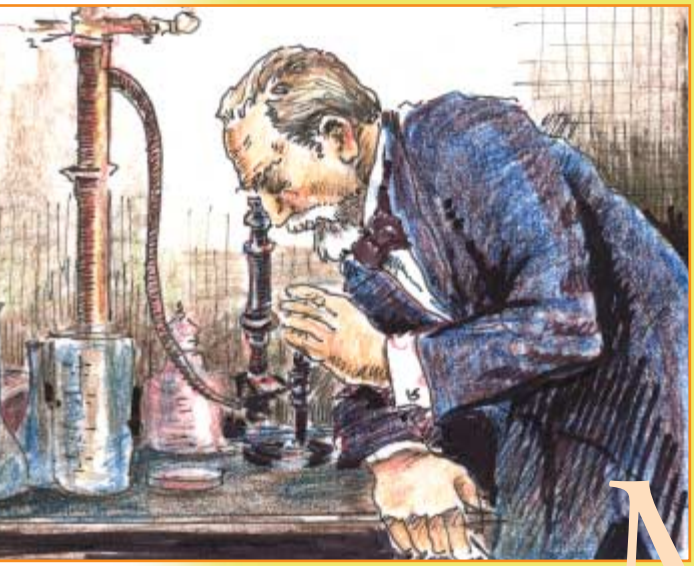
aids

HYPERTENSION—High blood pressure.

strange phenomena

THE CONCEPT OF BASIC RESEARCH

Animal research is also important in another type of research, called basic research. Basic research experiments are performed to further scientific knowledge without an obvious or immediate benefit. The goal of basic research is to understand the function of newly discovered molecules and cells, strange phenomena, or little-understood processes. In spite of the fact that there may be no obvious value when the experiments are performed, many times this new knowledge leads to breakthrough methods and treatments years or decades later. For example, chemists developed a tool called a nuclear magnetic resonance (NMR) machine to determine the structure of chemicals. When it was developed, it had no obvious applications in medicine; however, scientists eventually realized that the NMR machine could be hooked up to a computer to make a magnetic resonance imagery (MRI) machine. The MRI machine takes pictures of the bone and internal tissues of the body without the use of radioactivity. Other examples of basic research that have led to important advances in medicine are the discovery of DNA (leading to cancer treatments) and neurotransmitters (leading to antidepressants and antiseizure medications). However, there are many other instances where basic research, some of which has been done on animals, has not yet resulted in any practical benefit to humans or animals.



NMR (nuclear magnetic resonance)—a machine that measures the vibration of atoms exposed to magnetic fields. Scientists use this machine to study the physical, chemical, and biological properties of matter.

MRI machine

- *MRI (magnetic resonance imaging)—a machine that produces pictures of the bone and internal tissues of the body.*

FDA (Food and Drug Administration)—A federal agency whose mission is to promote and protect the public health by helping safe and effective products reach the market in a timely way and monitoring products for continued safety after they are in use.

SAFETY TESTING

Laboratory animals are not only crucial in understanding diseases; they are also essential in evaluating the safety of drugs, vaccines, food additives, household products, workplace chemicals, cosmetics, water and air pollutants, and many other substances. The Food and Drug Administration (FDA) oversees this process for drug, vaccine, food additive, and cosmetic safety testing. Other agencies like the Consumer Product Safety Commission, the Environmental Protection Agency, and the Occupational Safety and Health Administration regulate other types of testing.

CONSUMER PRODUCTS TESTING

In 1933, more than a dozen women were blinded and one woman died from using a permanent mascara called Lash Lure. Lash Lure contained *p*-phenylenediamine, an untested chemical. At the time, there were no regulations to ensure the safety of products. The *p*-phenylenediamine caused horrific blisters, abscesses, and ulcers on the face, eyelids, and eyes of Lash Lure users, and it led to blindness for some. In one case, the ulcers were so severe that a woman developed a bacterial infection and died.

For cosmetic products, the FDA requires that all manufacturers prove the safety of their products. This requirement applies to some makeups, perfumes, shampoos, soaps, hair sprays and dyes, and shaving cream. For many years, the only way to test the safety of products was on animals. However, during the 1980s, many alternative safety tests were developed that did not use animals, reducing the number of animals used for cosmetic testing by 90%. Though the number of animals used for cosmetic testing has been greatly reduced, there are still some products like sunscreens, antidandruff shampoos, fluoride-containing toothpastes,

ANTIBACTERIAL—a chemical that kills or inhibits the growth of bacteria.

and anti-acne creams that cannot be proven safe without the use of animal testing because they contain ingredients that cause a chemical change in the body that could potentially be harmful. Without these safety tests, it would be impossible to ensure that these products are safe for your use.

ALTERNATIVES TO ANIMAL TESTING

Alternative testing methods are developed to replace, reduce, and refine animal use and to improve the accuracy of tests for predicting human health or environmental hazards. An example of an alternative testing method is an assay that uses in vitro cell cultures to determine whether chemicals will burn or damage the skin. These alternative tests are developed by scientists in companies, universities, and government laboratories. They are then evaluated by the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM), to ensure that the alternative test can accurately determine whether a product is dangerous. ICCVAM recommendations on alternative testing methods for toxicology are used by federal agencies to update testing regulations and guidelines. The European Union has a similar organization, the European Centre for the Validation of Alternative Methods, which develops and evaluates new alternatives to animal testing.

DRUG SAFETY

A few years after the Lash Lure incident, another tragedy involving untested products occurred. A drug company in Tennessee decided to develop a liquid form of a sulfa drug (antibacterial) that would appeal to children. This drug company took a well-tested sulfa drug, mixed it with a sweet-tasting liquid that children would like, and sold it as "Elixir Sulfanilamide." Unfortunately, the drug company did not test the safety of Elixir Sulfanilamide before putting it on store shelves. The pleasant-tasting liquid in Elixir Sulfanilamide contained ethylene glycol, a sweet-tasting poison that is the main

TOXICOLOGY—The study of the poisons and their effects on living organisms.

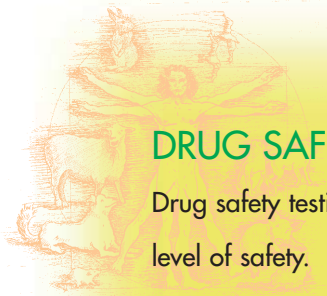
ingredient in antifreeze. Ethylene glycol poisoning causes the kidneys to fail so that toxins and fluid are not excreted from the body. Eventually, the amount of toxin build-up is so great that it overwhelms the body and causes death. Elixir Sulfanilamide killed 107 people, mostly children, before it was pulled from store shelves.

The Lash Lure and Elixir Sulfanilamide tragedies led to the passage of the Food, Drug, and Cosmetic Act of 1938. This act provided government oversight of consumer product safety and enforceable food standards and mandated that a drug company must prove to the FDA that a drug is safe before it can be sold to the public.

As the Elixir Sulfanilamide incident shows, it is important to test the safety of all drugs before they are sold to the public. Unfortunately, children around the world continue to be poisoned with ethylene-glycol-containing medicines in countries where drug testing is not as controlled as in the United States. Most recently:

Recent deaths among children due to ethylene-glycol-containing medicines:

47 died in Nigeria—1990
200 died in Bangladesh—1992
88 died in Haiti—1996
33 died in India—1998



DRUG SAFETY TESTING

Drug safety testing is a complicated process that involves many different steps to ensure the highest level of safety.

PRECLINICAL RESEARCH

The first step in developing and testing a new drug is preclinical research. Initially, scientists consult the vast amount of published information and databases to obtain as much background information as possible. If necessary, they perform studies to determine which germ, virus, chemical, or other factor causes a disease. Then the mechanisms of the disease are studied and new drugs are developed and evaluated for effectiveness and side effects using cell culture and whole animal models. Even though scientists minimize the number of animals used by testing drugs in cell culture whenever possible, it is still important to test drugs in animals. For example, the first antibacterial agent, prontosil, has no effect on bacteria in culture; but when prontosil is given to a mouse, it is broken down by the liver into the antibacterial drug sulfanilamide. Before the discovery of antibacterial agents (like prontosil and other antibiotics), many bacterial infections such as pneumonia were fatal. If prontosil had been tested only in cell culture, the use of this sulfa drug would not have been discovered.

PRECLINICAL SAFETY ASSESSMENT TESTING

Once a drug is shown to be effective in animals and to have a low incidence of side effects, it proceeds to safety assessment testing. These tests are conducted to evaluate drug safety in two different animal species, with animals receiving high doses of the new drug for 30 or 90 days. Animals are carefully monitored for side effects. After the study period, pathologists examine their organs for signs of drug toxicity. This drug safety testing in animals is carried out under guidelines mandated by

PRECLINICAL RESEARCH—medical research performed in laboratories using cell culture or animals.

PATHOLOGIST—a medical expert, usually a physician, who studies the effects of a disease or chemical on the body.

law through the FDA. It is the last safety testing performed before the drug is given to people for clinical testing.

You may wonder why two different animal species are used for testing at this stage. The reason is that no animal is exactly like a person in every way. A drug may not be toxic to rats but may be toxic to guinea pigs, and, by using two different species, the chances are greater that the toxicity of a drug will be discovered before it is ever given to a person.

This stage of safety testing usually takes about 4 years. Drug companies test for mutagenicity (ability to cause genetic changes) and carcinogenicity (ability to cause cancer). The drugs are also tested to confirm that they do not cause infertility (inability to have children) or birth defects. This stage of safety testing takes many years, because it may take a long period of time for animals to develop cancer or infertility as a result of a toxic drug.

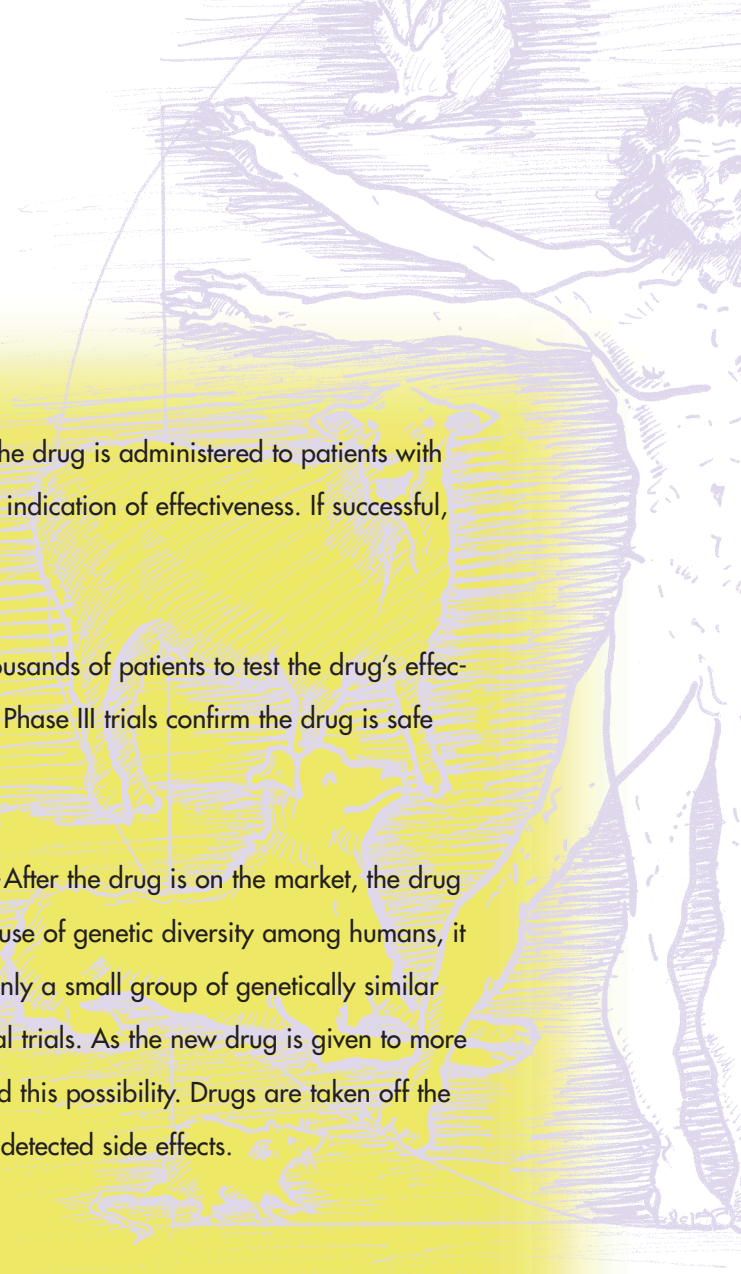
CLINICAL TRIALS

If no problems arise during preclinical testing, the drug company applies to the FDA for an Investigational New Drug Application, which authorizes the drug company to administer a new drug to people for clinical testing.

PHASE I TRIALS—A new drug is administered to a small number of normal, healthy human volunteers to study its activity and to monitor potential toxicity in people. If successful, Phase I trials lead to . . .

CLINICAL TESTING—drug testing done in humans.

FEN-PHEN—a weight-loss treatment composed of two drugs, fenfluramine and phentermine. Patients taking fen-phen were found to have a higher than normal incidence of heart valve defects.



PHASE II TRIALS—These are limited studies in which the drug is administered to patients with the disease to establish proper dosages and to give some indication of effectiveness. If successful, Phase II trials lead to...

PHASE III TRIALS—Large multicenter studies enroll thousands of patients to test the drug's effectiveness and to continue to monitor for any side effects. If Phase III trials confirm the drug is safe and effective, it is approved by the FDA.

PHASE IV (POST-MARKETING SURVEILLANCE)—After the drug is on the market, the drug maker and FDA continue to monitor for side effects. Because of genetic diversity among humans, it is possible that a new drug will cause adverse effects in only a small group of genetically similar people, which may not have been apparent during clinical trials. As the new drug is given to more and more people, careful monitoring is necessary to avoid this possibility. Drugs are taken off the market if postmarketing surveillance reveals previously undetected side effects.

Clinical testing is complex and time-consuming, averaging 14 years to complete Phase I through III testing to gain FDA approval. Sometimes, drugs will fail in clinical tests because the animal tests did not accurately predict their effects in humans. Often people wonder why it takes so long to develop a new drug and why sometimes a drug treatment (like fen-phen, which may cause heart valve damage) is not found to be dangerous until after it is sold to the public. Think about all the different possibilities that need to be explored, such as:

Does the drug cause a dangerous reaction when mixed with any other prescription or over-the-counter drug?

Is the drug safe for pregnant women, children, and the elderly and at what dosage?

Does the drug cause birth defects or subtle learning disabilities that may not be discovered until a child is in school?

Does the drug cause cancer, which may take 20 years to develop?

Is there a small number of patients who are genetically more susceptible than average to side effects?

"Cruelty Free"—What Does It Mean?

Many people look for cosmetics that are labeled "cruelty free" or "not tested on animals." But "cruelty free" does not always mean the cosmetic was not tested on animals. Because the government has not legally defined "cruelty free," it can mean many different things. While most cosmetic companies that label their products "cruelty free" use alternative safety tests that do not use animals, "cruelty free" can also mean:

- the final product was not tested on animals, but the ingredients were individually tested on animals.
- the manufacturer did not test the cosmetic on animals, but the company that supplied the ingredients did test the ingredients on animals.
- the animal testing was done by a different company.
- the animal testing was done in a foreign country.
- the animal testing was done more than 5 years ago.

If you would like to find out whether a product was tested on animals, you can contact the manufacturer and ask them to define their "cruelty free" label. You can also look for the Coalition for Consumer Information on Cosmetics logo. Products with this logo are marketed by companies that have agreed to not conduct or commission animal tests or use any ingredient that is tested on animals (www.leapingbunny.org). This pledge is backed up by independent audits to ensure neither the product or its individual ingredients is tested on animals.

REGULATION OF ANIMAL RESEARCH

UNITED STATES

While proper care of animals used in research has been an ongoing priority for the majority of the scientific community, there have been some instances of mistreatment of animals in research laboratories. As a consequence of these occurrences, as well as pressure from animal protection groups and the public, Congress enacted laws to regulate the care and use of laboratory animals. Currently there are several layers of oversight of animal research, which are outlined below.

ANIMAL WELFARE ACT

The first federal law regulating animal research was the Laboratory Animal Welfare Act passed by Congress in 1966. This law covered the transport, sale, and handling of animals and provided for licensing of animal dealers to prevent pet theft and their sale to research facilities. The original act covered dogs, cats, nonhuman primates, guinea pigs, hamsters, and rabbits. This act was passed with the help of the Animal Welfare Institute, an activist group led by Christine Stevens, which advocated more humane animal practices in laboratories. The passage of the Laboratory Animal Welfare Act was also fueled by public outrage over an exposé in *Life* magazine that graphically documented the practice of pet theft for sale to research facilities.

The Animal and Plant Health Inspection Service (APHIS) of the U.S. Department of Agriculture (USDA) enforces this act by inspecting laboratories and monitoring compliance with the act. The act, now known as the Animal

Welfare Act (AWA), has been amended four times (1970, 1976, 1985, and 1991), each time elevating the standard of animal care. The amendment of 1985 was the most extensive and had two very significant results. First, an Animal Welfare Information Center (www.nal.usda.gov/awic) was established to provide researchers with a database of alternatives to painful animal experiments. Second, each research facility in the United States using protected species must register with the USDA and establish an Institutional Animal Care and Use Committee (IACUC) to review all experimental protocols involving live, warm-blooded animals. Similar committees had already existed to monitor clinical trials. The 1985 amendment to the AWA now extended the same careful review to research on animals.

A quirk of the AWA, however, is the fact that it does not cover the most common species of laboratory animals, namely rats, mice, and birds. In passing the AWA, Congress left the definition of "animal" (that is, which species would be protected by the AWA) to the discretion of the Secretary of Agriculture, who opted not to include these species, primarily because the USDA has not had the resources to inspect all of these facilities. Despite numerous efforts by the animal protection community to change the AWA to include rats, mice, and birds, an amendment was recently passed by Congress to permanently exclude rats, mice, and birds used in research from coverage by the Animal Welfare Act. It should be noted, however, that these species are protected under Public Health Service Policy, though this oversight applies only to those research facilities that receive federal funding. There are institutions, for example some private companies and small teaching colleges, which only use rats, mice, and birds that are not subject to the AWA or Public Health Service Policy.

THE PUBLIC HEALTH SERVICE POLICY ON HUMANE CARE AND USE OF LABORATORY ANIMALS (PHS POLICY)

Another federal standard that guides the care and use of laboratory animals is the Public Health Service Policy on Humane Care and Use of Laboratory Animals (PHS Policy). PHS Policy is based on the Health Research Extension Act passed by Congress in 1985. This law applies to any research facility that receives PHS funds, which includes most universities and colleges that perform animal research. Scientists must comply with guidelines set forth in the *Guide for the Care and Use of Laboratory Animals* (the *Guide*, see below). Each research facility must maintain an IACUC and report whether they have AAALAC International accreditation (see below). While PHS Policy applies only to PHS-funded research, it is broader than the Animal Welfare Act in that all vertebrate animals (including fish and reptiles) are covered.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC)

An IACUC is established at each institution to review all proposed animal experiments. Each animal protocol must include: (1) a justification for using animals, the number of animals to be used, and the species chosen, (2) the procedures or drugs to be used to eliminate or minimize pain and discomfort, (3) a description of the methods and sources used to search for alternatives to painful procedures, and (4) a description of the search used to ensure that the experiment does not unnecessarily duplicate previous research.

An IACUC typically has at least five members, one of whom must be a Doctor of Veterinary Medicine responsible for animal care at the institution. The committee must also include at least one scientist experienced in animal research, a professional whose primary concerns are not scientific (for example, an ethicist, clergyperson, or lawyer) and a member who is not affiliated with the institution in any

way and who is meant to represent the interests of the community at large. The IACUC also inspects animal facilities twice a year to ensure that the institution is in compliance with federal regulatory policy. The Applied Research Ethics National Association (ARENA), in collaboration with the Office for Laboratory Animal Welfare at NIH, publishes guidelines to help institutions organize and support IACUCs and to help IACUCs provide effective oversight of the welfare of animals at their institution. ARENA's sister organization, Public Responsibility in Medicine and Research (PRIM&R), holds yearly meetings for IACUC members and regularly holds training programs for new IACUC members.

STATE AND LOCAL REGULATION

Individual states may regulate the care and use of animals for research even further. Massachusetts, for example, has its own laws governing the care of research animals, and the Massachusetts Department of Public Health licenses and inspects animal research facilities that house dogs or cats. Many municipalities also have laws and regulations that establish more local control over animal research occurring in their jurisdiction.

ASSOCIATION FOR ASSESSMENT AND ACCREDITATION OF LABORATORY ANIMAL CARE INTERNATIONAL (AAALAC INTERNATIONAL)

The Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC International) is a nonprofit organization founded in 1965 to promote uniform standards of animal care in U.S. laboratories.

AAALAC International monitors animal care within the United States and accredits research institutions on a voluntary basis by evaluating laboratories every 3 years to ensure scientists comply with the guidelines set forth in the *Guide*. AAALAC International is also now accrediting research and testing programs throughout the world.

THE GUIDE FOR THE CARE AND USE OF LABORATORY ANIMALS (THE GUIDE)

The *Guide*, published by the National Research Council and the Institute for Laboratory Animal Research, is not only the basis for AAALAC International accreditation (mentioned previously) but is also a central part of Public Health Service Policy on the humane care and use of laboratory animals. The *Guide*'s recommendations are enforceable based on the Health Research Extension Act passed by Congress in 1985. The *Guide* has been updated six times. Noncompliance with the policies of the *Guide* results in loss of AAALAC International accreditation and is viewed as a serious matter that jeopardizes an institution's funding by the NIH.

Table 1: Summary of Laboratory Animal Oversight

Regulation/ Regulatory or Oversight Body	Main Points
Animal Welfare Act	Protects all warm-blooded animals except rats, mice, and birds bred for research. This includes zoos, circuses, research labs, hospitals, businesses, federal agencies, dealers, breeders, etc. Each research institution that uses a covered species must have an IACUC review all animal experiment protocols. The USDA licenses research facilities and conducts annual, unannounced inspections. Violations are punished with fines, cease-and-desist orders, and license suspension or revocation.
PHS Policy	Protects all vertebrate animals (including fish, reptiles, rats, mice, and birds) used in research funded by the Public Health Service. Each research facility provides a written plan for complying with PHS Policy and the *Guide*.

Continued on next page.

Table 1: Summary of Laboratory Animal Oversight Cont.

	Main Points continued
PHS Policy	Each research institution that receives PHS funding must have the IACUC review all animal experimental protocols and inspect the facilities. No routine, unannounced inspections, but all allegations of misuse are investigated by NIH's Office of Laboratory Animal Welfare. Violations or loss of AAALAC accreditation can result in loss of PHS funding.
IACUC	A committee, organized at every research facility subject to the AWA, PHS Policy, or AAALAC accreditation, which must review and approve or deny every proposed animal protocol. Each animal protocol must include: — A justification for using animals, the number of animals to be used, and the species chosen — The procedures or drugs to be used to eliminate or minimize pain and discomfort — A description of the methods and sources used to search for alternative to painful procedures — A description of the search used to ensure that the experiment does not unnecessarily duplicate previous research Members must include: a veterinarian, a professional not involved in research (ethicist, lawyer, etc.), and a community representative (clergy, teacher, etc.). IACUC members must inspect their research facility twice a year.
AAALAC International	Nonprofit organization that accredits research facilities for compliance with the *Guide*. Accreditation is on a voluntary basis only. Announced site visits are conducted every 3 years.

EUROPEAN UNION

Prior to 1986, legislation regulating the protection of animals used in research varied among nations comprising the European Union. In 1986, the Council of the European Communities issued Council Directive 86/609/EEC. The purpose of this directive was to eliminate the disparities in laboratory animal protection laws among member nations. The directive outlines principles such as reduction in the number of animals used in research; guidelines for the adequate care of animals; elimination of unnecessary pain, suffering, distress or lasting harm; and avoidance of unnecessary duplication of experiments. While the provisions of the directive are specific, it is left to each member nation to determine how these provisions will be enacted and enforced. The directive also provided that each nation must comply with the directive by 1989 and that every 3 years each member nation must submit a report on the number of animals used in research.

UNITED KINGDOM

The major piece of legislation that regulates the use of animals in research in the United Kingdom is the Animals (Scientific Procedures) Act 1986. This act (also known as ASPA) provides for the licensing of experimental and other scientific procedures carried out on any vertebrate animal that may cause pain, suffering, distress, or lasting harm. This act covers all scientific procedures on any vertebrate animal from a simple blood draw to major surgery. While this act was passed in 1986, it continues to be amended to keep pace with changing attitudes and knowledge regarding animal care and use. In 1998, it was amended to more closely conform to Council Directive 86/609/EEC.

3Rs—Principle of reducing the number of animals used in research, refining scientific procedures to minimize pain, and replacing animal experiments with in vitro models when possible.

The ASPA regulates through licensing projects and individuals. Project licenses are issued to those responsible for directing research programs and personal licenses are issued to individuals performing specific scientific procedures such as giving an injection or taking a blood sample. These licenses are reviewed and/or renewed every 5 years. The Animals Inspectorate is responsible for assessing applications for licenses and for inspecting work in progress to ensure compliance with ASPA, and each project must undergo an in-house ethical review process that usually involves a committee much like an IACUC.

The issuance of a project license is dependent on several factors including adherence to the 3Rs (see 3Rs section), justification of cost and benefit, and training and experience. When the justification of the project is considered, several issues are further examined, such as the number of animals used, the specific product or knowledge that will be gained, and the severity of the procedures involved. Personal licenses depend mostly on sponsorship, that is, having a recognized authority vouch for an applicant's qualifications, training, experience, competence, and character. The personal license also dictates the individual's level of supervision and outlines the specific guidelines on the use of anesthetics, drugs, animal husbandry, and so forth that must be followed.

the 3Rs

CONTINUING EFFORTS TO MORE EFFICIENTLY USE LABORATORY ANIMALS)))))

Scientists continue to expand their knowledge and improve their techniques to use the fewest animals as efficiently and humanely as possible. This approach is called the "3Rs" and was created in 1954, when the Universities Federation for Animal Welfare (UFAW) hired two young scientists to produce a report on experimental methods. UFAW, founded in 1926, had already produced the first *Handbook on the Care and Management of Laboratory Animals* in 1947 when it hired William Russell, a zoologist, and Rex Burch, a microbiologist, to carry out a systematic study of the advancement of humane techniques on laboratory animals. Sir Peter Medawar, who was later to receive the Nobel Prize, supervised the project. Russell and Burch visited laboratories throughout the United Kingdom for 2 years and in 1959 published a book titled *The Principles of Humane Experimental Technique*, which introduced the concept of the 3Rs—reducing, refining, and replacing animal use.

Russell and Burch recommended *REDUCING* the number of animals used in experiments to the minimum number required to obtain statistically relevant data, *REFINING* procedures to minimize pain and distress in experimental subjects and provide for their well-being based on their behavioral needs, and *REPLACING* experiments involving whole animals with in vitro models like tissue and cell culture when possible. They based these recommendations on data acquired in the course of their study, and they predicted that implementation of the 3Rs would enhance the scientific value of experiments.

Russell and Burch stated, "We assume that experimental biologists are only too happy to treat their animals as humanely as possible." They further stated, "The central problem then is that of determining what is and what is not humane, and how humanity can be promoted without prejudice to scientific and medical aims. We must begin by examining the concept of humanity (or inhumanity) as an objective assessment of the effects of any procedure on the animal subject."

Though it took nearly 30 years for Russell and Burch's work to receive the attention it deserved, the 3Rs are now being practiced in laboratories throughout the world and have been incorporated in animal care legislation in the United States and the European Union.

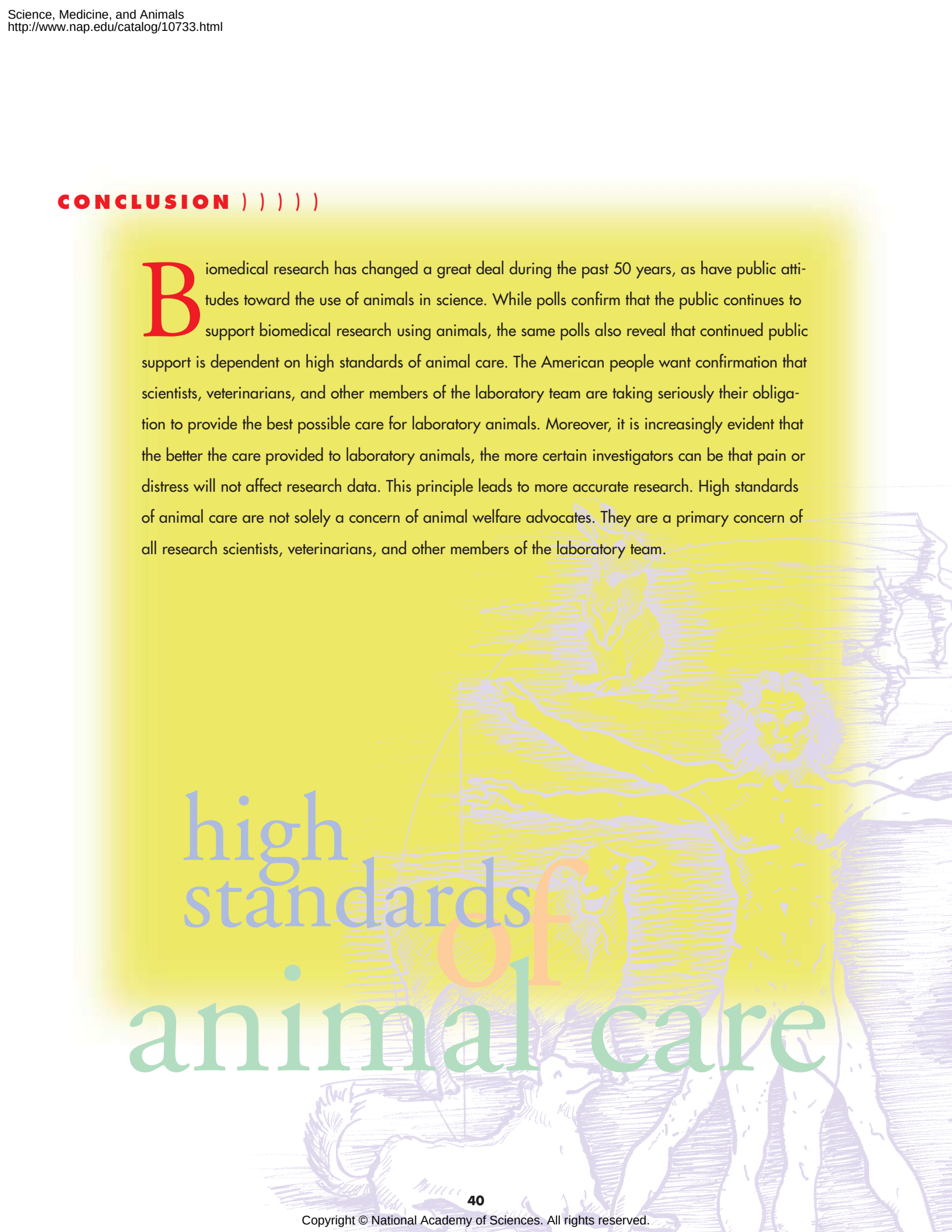
what is & what is not humane...

the 3 Rs in action

Chris McNickle worked in animal hospitals for more than 20 years before she came to the National Institutes of Health (NIH) as an animal care technician. McNickle's background in animal care helped impart not only an understanding of the ways that individual animals and different species react to illness but also "a compassion for the animal," she says. Viewing her role as that of "patient advocate," she says that her job in the laboratory is to "support the animal, watch the animal, and to try to improve the care of the animal." She strongly believes that collaboration and respect among scientists, veterinarians, and veterinary technicians results not only in higher standards of animal care but also in more effective and productive science. • McNickle points to a recent 8-month study at NIH as a model of the type of research program in which careful attention to animal well-being and teamwork among veterinarians, animal care technicians, and scientists produced the maximum scientific benefit. The human benefits of this study are great—a magnetic resonance imaging (MRI) technique that is able to diagnose a heart attack instantly. • The project was a collaborative effort from the start, she notes, and was instituted when a veterinarian, Dr. Victoria Hampshire, identified two different researchers who were both using dogs to study the flow of blood through the heart attack-damaged arteries. Dr. Hampshire got the two researchers together, and they determined that, though it was not possible to REPLACE the dog model with an in vitro culture system (it is not possible to simulate a heart attack in a laboratory dish), they could get the information they both needed from the same set of dogs and thus REDUCE the number of animals used in the studies. • McNickle points out that it is crucial to recognize that laboratory animals have many of the same responses and symptoms as people, and they need to be provided with the same level of support. Thus, a team of veterinarians and technicians REFINED previous care procedures by instituting 24-hour critical care for the dogs in the study, similar to hospital intensive care units for heart attack patients. • Human patients also benefit from close monitoring of experimental animals and round-the-clock attention to their needs, McNickle says. Many of the drugs used to care for these dogs are the same as those used in human heart attack patients. She points out that by understanding what drugs and dosages cause side effects like nausea in the dogs, doctors are better able to treat human heart attack patients. "We're better able to determine the dosage that will produce the maximum healing benefit with the least side effects," which ultimately is the goal of all animal research.

CONCLUSION

Biomedical research has changed a great deal during the past 50 years, as have public attitudes toward the use of animals in science. While polls confirm that the public continues to support biomedical research using animals, the same polls also reveal that continued public support is dependent on high standards of animal care. The American people want confirmation that scientists, veterinarians, and other members of the laboratory team are taking seriously their obligation to provide the best possible care for laboratory animals. Moreover, it is increasingly evident that the better the care provided to laboratory animals, the more certain investigators can be that pain or distress will not affect research data. This principle leads to more accurate research. High standards of animal care are not solely a concern of animal welfare advocates. They are a primary concern of all research scientists, veterinarians, and other members of the laboratory team.



RESOURCES AND WEB LINKS

Advances in Medicine through Animal Research
Americans for Medical Progress Educational Foundation, http://www.ampef.org/history.htm

Significant Events of the Last 125 Years
American Society for Microbiology, http://www.asmusa.org/mbrsrc/archive/SIGNIFICANT.htm

FDA History
US Food and Drug Administration, http://www.fda.gov/oc/history/

Science and Conscience: The Animal Experimentation Controversy
The Humane Society of the United States
National Association for Humane and Environmental Education, www.humaneteen.org

In the Name of Science: Issues in Responsible Animal Experimentation
F. Barbara Orlans
Oxford University Press, New York, 1993.

The Scalpel and The Butterfly: The War Between the Animal Research and Animal Protection
Deborah Rudacille
Farrar, Straus and Giroux, New York, 2000.

The Animal Research Controversy: Protest, Process and Public Policy. An Analysis of Strategic Issues
Andrew N. Rowan and Franklin M. Loew with Joan Weer
Tufts Center for Animals and Public Policy, N. Grafton, MA, 1995.

Of Mice, Models and Men. A Critical Analysis of Animal Research
Andrew N. Rowan
State University of New York Press, Albany, 1984.

Animal Research Is Vital to Medicine
Jack H. Botting and Adrian R. Morrison
Scientific American: http://www.sciam.com/0297issue/0297botting.html

Issues and Answers
Massachusetts Society for the Prevention of Cruelty to Animals, Center for Animal Welfare
http://labanimalwelfare.org/product_testing.html#crueltyfree

The Black Death
American University Trade and Environment Database, http://www.american.edu/TED/BUBONIC.HTM

Robert Koch, Top-Biography.com

What is Biomedical Research?
Michigan Society for Medical Research, http://www.mismr.org/educational/biomedres.html

Laboratory Animal Law
Kevin Dolan, Blackwell Science Ltd, Oxford, UK, 2000.

The Use of Animals as Models of Humans in Biomedical Research
Dr. Michael Festing

Animals and Alternatives in Testing—History, Science and Ethics
Joanne Zurlo, Deborah Rudacille and Alan M. Goldberg, Mary Ann Liebert Inc., New York, 1994

LINKS

Online Information on Animal Research

Alternatives to Animal Testing
http://sis.nlm.nih.gov/altread.htm

Altweb: Alternatives to Animal Testing on the Web
http://altweb.jhsph.edu

Americans for Medical Progress Educational Foundation
http://www.ampef.org

Firstgov for Kids
http://www.kids.gov

The Beginnings: The Laboratory and Animal Studies
http://www.fda.gov/fdac/special/newdrug/begin.html

Cosmetic Regulations
http://vm.cfsan.fda.gov/~dms/cos-toc.html

Animal Testing
http://www.fda.gov/cvm/index/consumer/con15.htm

Animal Research Facts
http://www.fbresearch.org/facts.html

Interactive Frog Dissection
http://curry.edschool.virginia.edu/go/frog/

Guide for the Care and Use of Laboratory Animals
http://www.nap.edu/readingroom/books/labrats

International Development of Animal Models
http://www.nih.gov/science/models

Johns Hopkins Center for Alternatives to Animal Testing
http://caat.jhsph.edu/

Kids 4 Research
http://www.kids4research.org

National Agricultural Library (Audiovisuals for Animal Care, Use, and Welfare)
http:/www.nalusda.gov/awic/pubs/aw200001.htm

Office of Animal Care and Use (Printable Posters)
http://oacu.od.nih.gov/posters/index.htm

Public Health Service Policy on Lab Animal Care Tutorial
http://grants.nih.gov/grants/olaw/tutorial/index.htm

Questions People Ask about Animals in Research
http://www.the-aps.org/pub_affairs/animals/index.htm

United States Office of Science and Technology Policy
http://www.ostp.gov

USDA Animal Welfare Fact Sheet
http://www.aphis.usda.gov/oa/pubs/awact.html

Why Animal Models?
http://www.ahc.umn.edu/rar/MNAALAS/Models/html

RESOURCES FOR TEACHERS AND STUDENTS
(posters, books, pamphlets, brochures, newsletters)

The ABCs of Animal Research—a colorful glossary explaining the use of animals in research and testing and the benefits animal research has produced. For middle and high schools. Contact Massachusetts Society for Medical Research at 978-251-1556 or www.msmr.org.

Animal Research: Fact vs. Myth—provides up-to-date answers to common misconceptions about animal research. Refutes the major claims of the antiresearch element of the animal rights movement. Contact the Foundation for Biomedical Research at 202-457-0654 or www.fbresearch.org.

Animal Sheets—set of four reference sheets detailing the contributions of different species to specific research advances. Set includes sheets on rodents, cats, dogs, nonhuman primates, and other animals. Contact the Foundation for Biomedical Research at 202-457-0654 or www.fbresearch.org.

Biologists Discover Amazing Things—a colorful classroom poster outlining the contributions many animal species make to biomedical advances. For middle and high schools. Contact the Federation of American Societies for Experimental Biology at 301-530-7000 or www.faseb.org.

Caring for Laboratory Animals—discusses the humane use of animals in research and explains how animals are used as research subjects and veterinary patients. Also covers legal protection of animals in research and explains the accreditation process for facilities. Contact the Foundation for Biomedical Research at 202-457-0654 or www.fbresearch.org.

Casey's Awakening—an illustrated storybook describing the role played by animals in research and testing and the care that laboratory animals receive. Accompanied by a guide of critical and creative thinking activities for teachers. For middle schools. Contact the Massachusetts Society for Medical Research at 978-251-1556 or www.msmr.org.

Exploring the Mysteries of Aging—outlines the contributions of animal research to the health of our aging population. Contact the Foundation for Biomedical Research at 202-457-0654 or www.fbresearch.org.

Friends and Partners: A Story about the Partnership of Man and Animals—an illustrated booklet describing the partnership between people and animals in the search for advances in biomedicine. Included are illustrations of animals, as well as some photographs of children who have been helped by animal research. For elementary schools. Contact the Southwest Association for Education in Biomedical Research at 520-621-3931 or www.swaebr.org.

Human and Animal Disease Fact Sheets—a series of fact sheets on human and animal disease and conditions. Fact sheets provide statistics about the disease or condition; describe the history of research on that disease; and outline some of the treatments and advances that have resulted from that research. Explains the specific role animals have played in research on these topics. For high schools and colleges. Contact the California Biomedical Research Association at 916-558-1515 or www.ca-biomed.org.

LAB Notes: Toxicology—a newsletter for teachers and students to introduce the science of toxicology and risk assessment. Includes "A Primer in Toxicology," "Poison Control Facts," "Risk Assessment," "The Use of Animals in Toxicology," "Alternatives," and more. Accompanied by classroom activities. For middle and high schools. Contact the Massachusetts Society for Medical Research at 978-251-1556 or www.msmr.org.

The Lucky Puppy—an interactive coloring storybook about animals and research. Contains coloring, drawing, and other activities. For elementary schools. Contact the North Carolina Association for Biomedical Research at 919-785-1304 or www.ncabr.org.

Overview of the Issues—a comprehensive manuscript pertaining to the use of animals in laboratory research. This manuscript is ideal for anyone interested in learning the fundamental yet important facts, figures, and statistics about the use of animals in laboratory research. Contact the Humane Society of the United States at 202-452-1100 or www.hsus.org.

People and Animals, Sharing the World—an interdisciplinary program designed to introduce and explain concepts in veterinary medicine and to explore value judgments as they relate to animals. A unique aspect of these materials is that they combine activities in social studies, science, citizenship, career education, and mathematics for an overall learning program. For elementary schools. Contact the American Veterinary Medical Association at 847-925-8070 or www.avma.org.

People and Animals: United for Health—an interactive, poster-sized health and science calendar. Topics are—Infectious Disease, Aging, Diabetes, AIDS and Feline Leukemia, Dental Health, Heart Disease, Poison Control and Product Safety, Biodiversity and the Environment, Mental Health and Substance Abuse, Body Organs and Transplantation, The Five Senses and the Brain, and Nutrition. Accompanied by the *HEADS ON! For Healthy Living* teacher's guide of critical and creative thinking activities, and teacher training workshops of the same name. For elementary schools. Contact the Massachusetts Society for Medical Research at 978-251-1556 or www.msmr.org.

People and Animals: United for Health—a curriculum resource package that serves as a background supplement on the use of animals in biomedical research, education, and testing for science curricula. Includes a 13-unit reference manual, set of 169 slides, discussion guide, and teacher's guide of critical and creative thinking activities. For middle and high schools. Contact the Massachusetts Society for Medical Research at 978-251-1556 or www.msmr.org.

Principles and Guidelines for the Use of Animals in Precollege Education—a brochure offering a framework for the humane study of animals in precollege classrooms. For middle and high schools. Contact the Institute for Laboratory Animal Research at 202-334-1264 or www.national-academies.org/ilar.

The Proud Achievements of Animal Research—focuses on the contributions of animal research to today's society and warns of the problems that would be created if animal research were stopped. Also gives a short chronological list of major medical breakthroughs utilizing animal research. Contact the Foundation for Biomedical Research at 202-457-0654 or www.fbresearch.org.

Respect for Life—a brochure on research animals and their care, their contribution to health, and the search for alternatives. Contact the National Institute of Environmental Health Sciences at 919-541-3345 or www.niehs.nih.gov

Rx for Science Literacy: The What, Where, How, and Why of Health Science Research—This 300-page K-12 teacher manual captures the complex research process and addresses the care and use of animals in the biomedical research process in an easy-to-follow, easy-to-use format. It is filled with background information, handouts, lesson plans, and activities to assist teachers of all grade levels in the classroom. This curriculum has been extensively revised and updated three times, most recently in August 2002. Additions include chapters on therapeutic cloning, bioscience careers, and transgenic animals. Endorsed by the North Carolina Department of Public Instruction. Contact the North Carolina Association for Biomedical Research at 919-785-1304 or www.ncabr.org.

Science and Conscience—Written for high school students and their teachers, *Science and Conscience* explores the facts and issues at the heart of the animal experimentation controversy. Major topics include the history of and current trends in animal experimentation, the use of animals in education, biomedical research, and product testing, and the development of laws, alternatives, and other initiatives to improve standards for animal care and scientific research alike. This full-color, 43-page booklet contains critical-thinking questions, projects, suggestions for independent study, and meaningful activities for high school classes and student clubs. It is an excellent resource for the individual student activist as well as a valuable teaching tool for high school biology instructors. Contact the National Association for Humane and Environmental Education at 202-452-1100 or www.humaneteen.org.

Science Beat—a color newsletter defining biomedical research and introducing students to the use of animals in biomedical research, including the laws and regulations that govern animal research. For middle and high schools. Contact the Massachusetts Society for Medical Research at 978-251-1556 or www.msmr.org.

Understanding the Use of Animals in Biomedical Research—excellent primer on animal research. Major points covered include the benefits to society of animal research, the various roles animals play in research, the validity of scientific research, some basic trends about the numbers of animals used, a brief overview of their care and treatment, as well as the laws and regulations that protect them. Finally, there is a section devoted to alternatives and what that really means. Contact the Foundation for Biomedical Research at 202-457-0654 or www.fbresearch.org.

The Use of Animals in Product Safety Testing—brief overview of the issue of animals in safety testing. Covers the science of toxicology and federal regulations and explains the myth of "cruelty-free" products and alternatives. Contact the Foundation for Biomedical Research at 202-457-0654 or www.fbresearch.org.

Women's Health: Developing Treatments and Cures through Animal Research—highlights the contributions of animal research to women's health. Contact the Foundation for Biomedical Research at 202-457-0654 or www.fbresearch.org.

ANIMAL RESEARCH REGULATIONS AND GUIDELINES

Animal Welfare Act, http://www.nal.usda.gov/awic/legislation/awa.htm

Health Research Extension Act of 1985,
http://grants.nih.gov/grants/olaw/references/hrea1985.htm

NetVet Veterinary Government and Law Resources, http://netvet.wustl.edu/law.htm

Public Health Service Policy on Humane Care and Use of Laboratory Animals
http://grants.nih.gov/grants/olaw/references/hrea1985.htm

USDA Animal and Plant Health Inspection Animal Care Policy Manual
http://www.aphis.usda.gov/ac/polman.html

ORGANIZATIONS DISCUSSED

Animal Welfare Information Center (AWIC), http://www.nal.usda.gov/awic

Animal Welfare Institute, www.animalwelfare.com

Applied Research Ethics National Association (ARENA), www.primr.org/arena.html

Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC International), http://www.aaalac.org

Food and Drug Administration (FDA), http://www.fda.gov

Institute for Laboratory Animal Research (ILAR), http://www.national-academies.org/ilar

Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM), http://iccvam.niens.nih.gov

National Institutes of Health (NIH), http://www.nih.gov

United States Department of Agriculture (USDA), http://www.aphis.usda.gov/ac/

OTHER ORGANIZATIONS

American Association for Laboratory Animal Science, http://www.aalas.org

American College of Laboratory Animal Medicine, http://www.aclam.org

American Society for the Prevention of Cruelty to Animals, http://www.aspca.org

American Society of Laboratory Animal Practitioners, http://www.aslap.org

American Veterinary Medical Association, http://www.avma.org

Canadian Council on Animal Care, http://www.ccac.ca

Foundation for Biomedical Research, http://www.fbresearch.org

Humane Society of the United States, http://www.hsus.org

Institutional Animal Care and Use Committee (IACUC), www.iacuc.org

National Association for Biomedical Research (NABR), http://www.nabr.org

Public Responsibility in Medicine and Research (PRIM&R), http://www.aamc.org/research/primr

Scientists Center for Animal Welfare (SCAW), http://www.scaw.com

States United for Biomedical Research, http://statesforbiomed.org

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Since 1952, the Institute for Laboratory Animal Research (ILAR) has developed guidelines and disseminated information on the scientific, technological and ethical use of animals and related biological resources in research, testing and education. ILAR promotes high quality, humane care of animals and the appropriate use of animals and alternatives. ILAR functions within the mission of the National Academies as an adviser to the federal government, the biomedical research community and the public. www.national-academies.org/ilar

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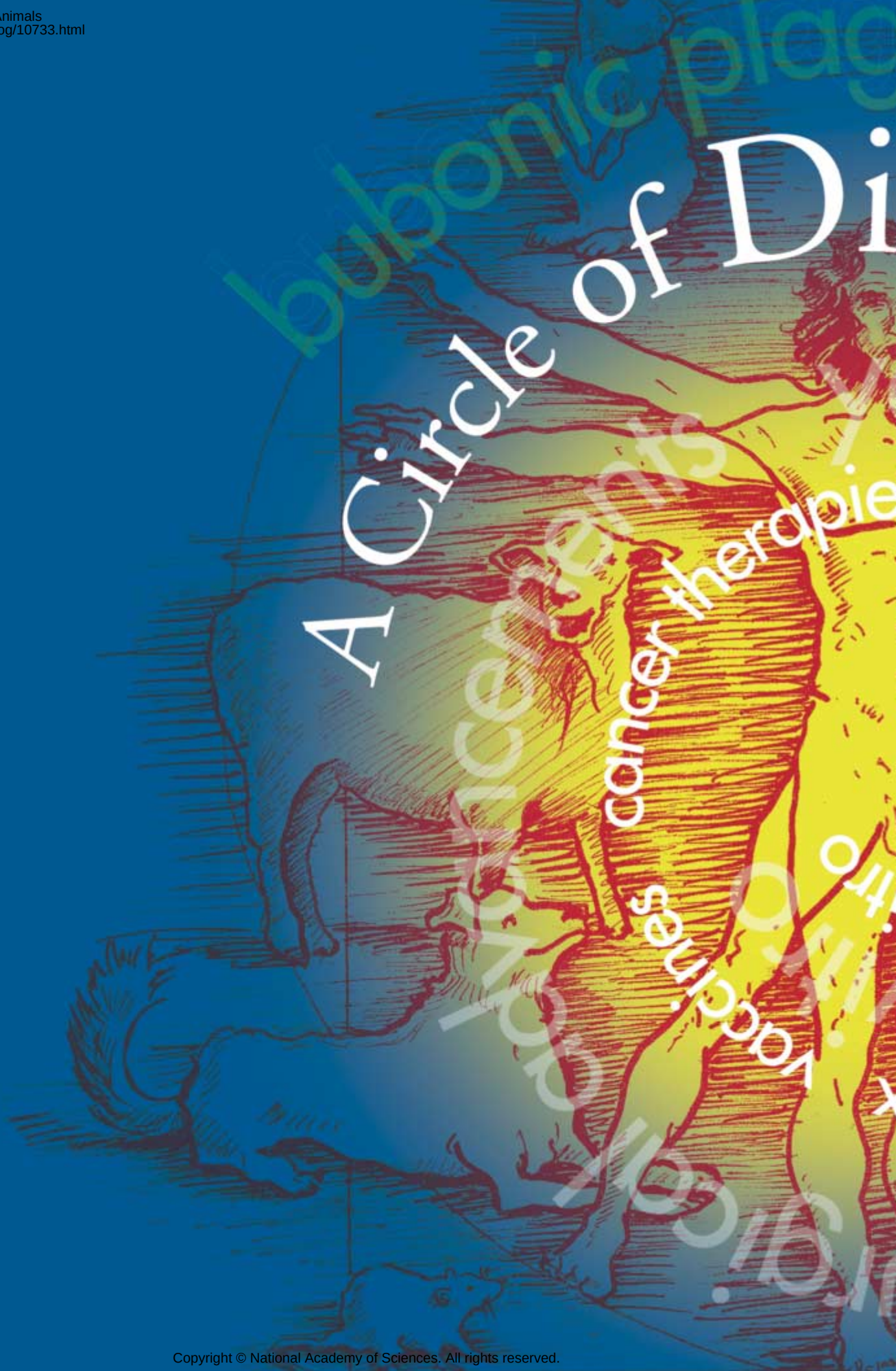

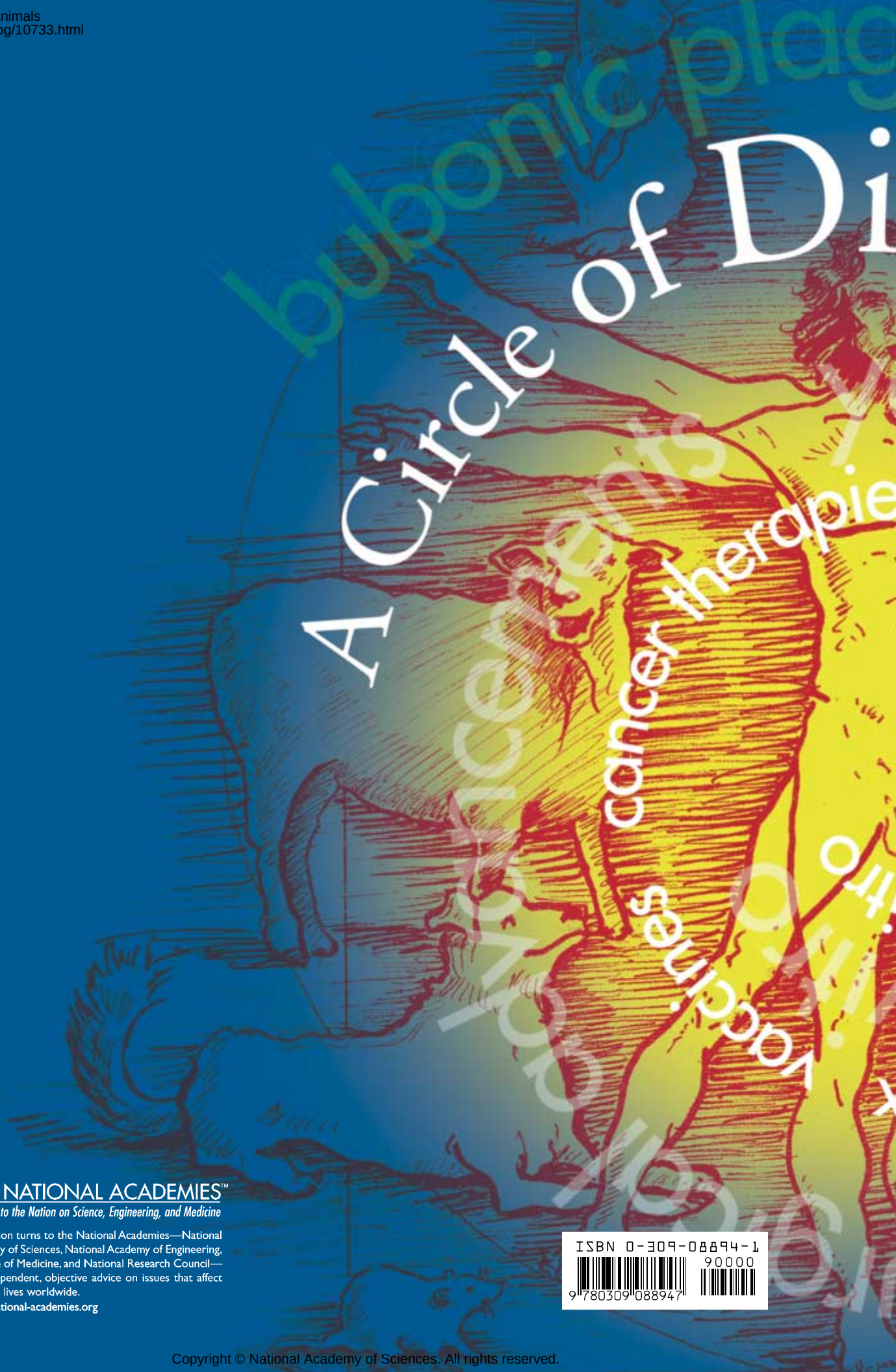

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