

# *The Essential Need for Animals in Medical Research*

## Introduction

Approximately 95 percent of all laboratory animals are mice and rats. Easily housed and bred, short lived (2-3 years), small, and relatively inexpensive, these rodents have become the animal model of choice for modern medical and scientific researchers. Because their physiology and genetic make-up closely resemble that of humans, rodents play an invaluable role in biomedical research. In the last decade, scientists discovered how to breed mice with genetic alterations that mimic human diseases. This capability has revolutionized medical research and dramatically increased the number of mice needed in medical science. The mouse genome contains essentially the same complement of genes found in the human genome, so studying how the genes work in mice is an effective way of discovering the role of a gene in human health and disease.

### *Man-made, genetically altered rodents*

Transgenic and knockout rodents have been created with revolutionary new technology. While transgenic mice have had a foreign gene (a piece of DNA) artificially added to their genomes, knockout mice have had a specific gene "turned off" or made useless. A great deal of promising research relies on these genetically altered mice. Transgenic rats also have been used in medical studies and found to be better models than mice for studying certain human

diseases. Genetically altered rodents have allowed scientists to observe what happens during the progression of Parkinson's disease, cancer, cystic fibrosis, heart disease, memory loss, muscular dystrophy, and spinal cord injuries. Recently, the mouse and rat genomes were sequenced. This achievement promises to significantly advance biomedicine.<sup>1</sup>

### *Naturally occurring immunodeficient mice*

SCID (severe combined immune deficiency) mice and nude (or hairless) mice are born without thymus glands and lack functioning immune systems. These mice are very important models for studying both normal and malignant human tissue. They also are needed to develop and evaluate new drugs without risking human lives.<sup>2</sup>

## Alzheimer's Disease

Scientists have evidence that a buildup of plaques containing amyloid protein deposits in the brain is a characteristic feature of Alzheimer's disease (AD), a disorder that affects patients' memories and personalities. Rats and transgenic mice bred to carry a gene that over expresses human amyloid protein have become indispensable for understanding and evaluating new drugs to prevent or delay the onset of AD. And recently, researchers have shown that vaccinating these mice with modified amyloid protein slowed the progression of the disorder. Patients are now being tested to see if the vaccine is

well tolerated and can help overcome AD.<sup>3</sup>

## Aging

Measuring physiologic changes over an entire life span would take many decades to complete in humans. However, such studies can be accomplished on "fast forward" in normal mice and rats. Research has shown that a reduced intake of calories in rodents markedly increases longevity, retards physiological deterioration, delays, and in some cases, prevents the incidence of age-associated diseases.<sup>4</sup>

## Carcinogen Testing

Scientists are evaluating several lines of knockout mice to study the mechanisms of carcinogenesis. They propose that such animals might be needed for routine testing of chemicals for carcinogenic potential. The results can be obtained more rapidly with fewer animals, and the outcome can be used effectively in chemical and drug safety assessments.<sup>5</sup>

## Cancer

During the past decade much of our knowledge of how environmental agents damage DNA and cause mutations that enhance cancer risk has come from studies with rats and mice. Scientists have produced cancer resistant mice that lack the ability to produce cyclin D1, a protein found in abnormally high amounts in human breast cancers.



They propose that cyclin D1 therapy might be highly selective in inhibiting the growth of human breast cancer cells.<sup>6</sup>

## Cystic Fibrosis

Cystic fibrosis (CF) is a childhood disease characterized by chronic lung congestion and digestive problems. CF is incurable and patients rarely live to see the age of 30. Scientists now know that CF is caused by a small defect in the gene that manufactures CTRF, a protein that regulates the passage of salts and water in and out of cells. Studies with CTRF-deficient mice have shown that the disease results from a failure to clear certain bacteria from the lung, which leads to mucus retention and subsequent lung disease. These mice have become models for developing new approaches to correct the CF defect and cure the disease.<sup>7</sup>

## Drug Addiction

Rats trained to self administer cocaine have high predictive value for human addiction because they share common triggers of relapse. In mapping the brains of adult rats that kicked the cocaine habit, researchers found that in relapse, the "high" from cocaine occurs in an area separate from where the brain retains cocaine-seeking behavior. This finding opens the possibility for developing new targets for anti-craving medication.<sup>8</sup>

## Spinal Cord Injury

Scientists are using rats to study the mechanisms underlying long-term recovery of motor skills after spinal cord injury. They found that motor function is related to the number of intact axons, the part of the nerve cell that transmits signals to motor neurons. Recent studies have demonstrated that axonal sprouting or regeneration at the injury site correlates with functional recovery and can be enhanced by the application of certain growth factors to the spinal tract. Development of these approaches to neural repair may ultimately generate new strategies for treating human spinal cord injury.<sup>9</sup>

## Heart Attack

New research has revealed that the heart muscle regenerates to some extent after a heart attack. A new strategy for treating this condition is being studied in transgenic mice. Researchers are experimenting with injecting stem cells (primitive bone marrow cells) into the periphery of the injured area to stimulate self-repair. The studies showed that the cells promoted structural and functional repair of the damaged tissue.<sup>10</sup>

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## Introduction

Less than ¼ of one percent of all laboratory animals needed in the U.S. are non-human primates. Approximately 30 different species are studied by the research community.<sup>1</sup> Many historic scientific breakthroughs, such as the discovery of the Rh factor and the development of a live polio virus vaccine were achieved through research with non-human primates. Today they are considered extremely important models in many areas of medicine because of their close relationship to humans.

## AIDS — Acquired Immune Deficiency Syndrome

Scientists face major challenges in their quest to develop a vaccine for human immunodeficiency virus (HIV), the agent that causes AIDS. Having no human model of protection to guide them, medical researchers depend heavily on monkeys for the development of promising strategies to protect people from this disease. Vaccines containing various strains of a simian immunodeficiency virus (SIV), a closely related virus that follows a disease course similar to HIV, or a hybrid human/simian immunodeficiency virus (SHIV) are being tested in macaque monkeys, and several research groups have successfully vaccinated monkeys with viral preparations that reduce viral load and halt disease progression.<sup>2</sup>

## Hepatitis B and C

Chimpanzees are uniquely susceptible to human hepatitis virus infections and serve as an important study model for this global public health problem. Research with chimpanzees has virtually eradicated hepatitis B and C infections acquired through blood transfusions, a landmark achievement in the control of viral hepatitis. Commercially available hepatitis B vaccines have prevented the development of cirrhosis and liver cancer in millions of people. Because no vaccine for hepatitis C infections is yet available, scientists continue to study the pathogenesis of this disease in chimpanzees to gain a better understanding of the infection process, to improve current treatment modalities, and to pave the way for the development of an effective vaccine.<sup>3,4</sup>

## Malaria

Researchers are beginning to overcome some of the enormous obstacles in developing a vaccine against malaria, a disease that affects millions of people annually. New-world monkeys and chimpanzees are the only species suitable for vaccine evaluation because they are susceptible to the same strains of the parasites that cause human malaria. Unlike simpler organisms, the malaria parasite has many chromosomes, thousands of genes, and a four-stage life cycle as it passes from mosquitoes to humans and back again. A number of promising vaccines

that attack the organisms at every vulnerable point in its life cycle are being tested. Some of these have successfully stimulated protective responses in animals and may soon be ready for human trials.<sup>5</sup>

## Acute Respiratory Disease

Respiratory syncytial virus (RSV) can cause life-threatening respiratory infections in infants, young children and the elderly. Since there is no effective therapy, an RSV vaccine is a high medical priority in the U.S. Researchers are designing vaccines containing live, weakened viruses that are suitable for applying with nose drops. These vaccines are being tested for their ability to protect chimpanzees, the only animal that is naturally infected by RSV and develops an illness with symptoms similar to those seen in humans.<sup>6</sup>

## Periodontal disease

Microbial infection of the tissue supporting teeth is the most common cause of bone and tooth loss in humans and may be an important risk factor for cardiovascular disease. Periodontitis is also a health problem for captive primates, making these species excellent models for studying the connection between chronic oral infections and systemic disease. Several groups of researchers have shown that immunizing monkeys with a vaccine contain-





ing a killed oral bacterium can halt infection and suppress bone loss.<sup>7</sup>

## Aging and nutrition

Scientists are currently studying the effects of long-term calorie restriction (CR) on the biology of aging in macaque monkeys. They have learned that a reduction in calories over a period of several years lowers body temperature, slows metabolism, lessens the risk of cardiovascular disease, and reduces predisposition toward diabetes. Long-term studies of CR have increased the life span of monkeys.<sup>8</sup>

## Brain biology

Because they share many features of brain biology and structure with humans, non-human primates are extremely valuable models for studying normal brain function and brain-related diseases, including mental, neurological, and addictive disorders. Many of the functional regions of the cerebral cortex that are present and identifiable in nonhuman primates have provided a precise map of the brain circuitry involved in visual and auditory perception, learning and memory deficits, and brain and spinal cord injuries.<sup>9</sup>

## Alzheimer's disease

The decline of memory and other mental functions in patients with Alzheimer's disease (AD) is associated with the loss of or damage to cholinergic nerve cells that use the chemical acetylcholine to transmit messages to other cells in the brain. Age-related reduction in the func-

tions of these nerve cells also occurs in primate species. Scientists have shown that grafting genetically modified cells to produce nerve growth factor (NGF) directly into the brains of macaque monkeys is a safe procedure that enhances the survival and function of the cholinergic nerve cells. Such studies are now being extended to humans in an attempt to slow the loss of memory in patients with AD.<sup>10</sup>

## Parkinson's disease

Parkinson's disease (PD) is a slow, progressive disease, generally found in the aged and characterized by tremors. Scientists know that the disease is associated with degeneration of brain cells that produce a chemical (neurotransmitter) called dopamine. Recently, they found a new method to deliver the gene that produces GLNF (a factor that protects brain cells) directly into the brains of monkeys. The treatment successfully prevented the progression and reversed the symptoms of PD. Clinical testing to forestall human disease is under consideration.<sup>11</sup>

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## *The Essential Need for Animals in Medical Research*

### Introduction

Dogs and cats together comprise less than ½ of one percent of all laboratory animals used in the U.S. However, their contributions to the various fields of medicine have been very significant.

Dogs played a major role in the development of surgical procedures for heart valve and artery replacement; angioplasty; reconstruction of the gastrointestinal tract, including colostomy; organ transplantation; repair of traumatic injuries; hip-joint replacement, including the testing of prosthetic devices for bone replacement; and medical devices for anesthesia.

Cats have been valuable models for understanding the function of the neuron (nerve cell), the chemical transmission of nerve impulses, and the functional organization of the brain. Neuroscientists studying cats have provided a map of the circuitry of the cerebral cortex revealing the major pathways that send signals from the eye to the brain. Their studies of the visual system have led to the prevention of amblyopia, a serious visual impairment that can cause blindness in one or both eyes and to the discovery of a treatment for strabismus, a misalignment of the eyes or “cross-eye.”<sup>1</sup>

### Diabetes

Groundbreaking work on the identification of insulin as the key hormone necessary to sustain diabetic patients was conducted with dogs. Dogs and humans share similar complications of diabetes, including blindness and circulatory failures that can result in amputation. Similar to the treatment prescribed for humans, dogs with diabetes must be given daily injection(s) of insulin to permit the utilization of glucose.

To avoid the daily, lifetime administration of insulin, medical researchers are currently studying methods for transplanting insulin-producing islet cells of the pancreas. Although allogenic islet cells (cells from same species) transplanted to diabetic patients have the potential to reverse diabetes, they must be protected from rejection by the immune system of the (diabetic) recipient. Insulin independence has been achieved in dogs following implantation of devices/capsules to preserve islet cell survival and function (insulin production). However, this technology needs further development before attempting clinical trials on humans.<sup>2</sup>

### Sleep Disorders

Narcolepsy is a neurological disorder that induces extreme daytime

sleepiness, sleep paralysis and catalepsy, characterized by sudden episodes of muscular weakness. Dogs are one of the few animals that suffer from narcolepsy. After years of research, sleep scientists have identified the gene for narcolepsy in dogs. It codes for a protein (hypocretin-1) that maintains the waking state.

Finding this gene is expected to increase our understanding of sleep and sleep disorders and provide new insights into the treatment of narcolepsy.

Similarly, researchers have demonstrated that hypocretin-1 plays an important role in both the promotion of wakefulness and the suppression of active sleep in the cat.<sup>3,4</sup>

### Cardiovascular Disease

In the past, studies with dogs have significantly advanced our understanding of atherosclerosis (narrowed or clogged arteries) and restenosis (renarrowing of coronary arteries after angioplasty). The canine aorta is a relevant model for testing the implantation of devices, such as the polyester-coated stent, designed to prevent the recurrence of arterial narrowing.<sup>5</sup>



## Blindness

Scientists have restored vision to dogs born blind with an incurable form of retinal degeneration known as retinitis pigmentosa. Dogs' eyes were injected in an area behind the retina with copies of a gene [DNA] that converts light into electrical signals. Many questions must be answered before doctors will be able to extend their studies to children.<sup>6</sup>

## AIDS — Acquired Immune Deficiency Syndrome

The feline immunodeficiency virus (FIV) provides an excellent model for AIDS vaccination studies. Like its human counterpart, HIV, the cat virus eventually suppresses the immune system's ability to protect against infections and is a leading cause of death among cats. Researchers have produced a wide variety of vaccines containing either inactivated whole viruses or purified viral proteins, which elicit antiviral responses that limit the FIV burden. The results of the studies are being analyzed to develop effective strategies for vaccines against the human virus.<sup>7</sup>

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While mice and rats are key models for research,<sup>1</sup> many other animal species also have contributed to dramatic advances in biology and medicine. A review of the medical literature affirms that studies with other animals, mainly rabbits and guinea pigs, also have made enormous contributions to understanding the cause, treatment, and prevention of many complex human diseases.

### Rabbits and guinea pigs

Research involving these species is integral to continued biomedical progress. Because the general physiology of their cells, tissues, and organs is similar to humans, these animals provide excellent models for many human diseases.

There is an urgent need to develop more efficacious vaccines or alternative vaccination regimens to achieve immunity in humans against virulent anthrax spores. Rabbits exposed to these spores develop a disease very similar to humans. A recent study has shown that rabbits immunized with a licensed vaccine preparation were protected against inhalation anthrax when challenged by aerosols containing lethal doses of spores.

Because anthrax inhalation studies cannot be conducted in humans, the rabbit model is crucial for evaluating the immune status of vaccinated humans.<sup>2</sup> Guinea pigs are also a useful model for testing the efficacy of promising anthrax vaccines.<sup>3</sup>

Rabbits have been and continue to be very important in the study of cardiovascular disease, particularly hypertension and atherosclerosis. When fed high-cholesterol diets, they develop vascular plaques similar to those in humans. Studies in rabbits have shown that lipid-lowering treatments, such as the administration of statins, act directly on plaques and decrease inflammation. The use of these compounds in humans has led to a reduction in the incidence of stroke and cardiovascular mortality.<sup>4</sup>

Guinea pigs carry the majority of their plasma cholesterol in low density lipoprotein (LDL), making them useful models for the study of cholesterol and lipoprotein metabolism.<sup>5</sup>

### Woodchucks

Although vaccines and antiviral drugs that treat acute and chronic liver disease (hepatitis, cirrhosis, cancer) caused by hepatitis B virus (HBV) are available, they are not yet fully utilized by the public. Better therapies are needed for the estimated 1.2 million chronic carriers in the U.S. Woodchucks infected with woodchuck hepatitis virus (WHV), a virus closely related to HBV, also develop severe hepatitis and are at 100% risk for cancer. For this reason, they are an ideal model for the preclinical assessment of new drugs and new strategies for human immunotherapy.<sup>6</sup>

### Pigs

The pig has become an excellent model for evaluating ways to prevent restenosis, the renarrowing of an artery following balloon angioplasty.

As a clinical alternative to dilation, heart specialists have begun implanting cardiac stents, expandable tiny mesh tubes, to prop open clogged arteries. Before starting clinical trials, the results from the porcine model demonstrated the potential therapeutic benefits of this device for the prevention and treatment of human coronary restenosis.<sup>7</sup>

The pig is also one of the best models for studying the healing process of skin wounds because the repair process is similar and the findings can easily and rapidly be applied to the human condition.<sup>8</sup>

### Sheep

Because of their anatomic similarities to humans, sheep are becoming popular as models for orthopedic research on diseases and injuries of the bones, joints, and muscles. They are frequently suitable alternatives to the use of dogs. During the last decade, sheep were used to study numerous musculoskeletal conditions, such as the repair of fractures, limb lengthening, and treatment of osteoarthritis and osteoporosis.<sup>9</sup> The sheep is also a valuable model for testing implanted mechanical valves to replace aortic valves (within the main artery of the body) and mitral valves (within the heart). Researchers have confidence that the ovine model provides data that have good predictive value for preclinical evaluation of these lifesaving devices.<sup>10</sup>



## Marine and freshwater animals (zebrafish, squid, sea snail)

Historically, fish models have played a significant role in assessing the risks associated with exposure to chemical contamination in aquatic environments.

Researchers rate zebrafish as one of the most promising animal models for studying early vertebrate development and gene function. The embryos are produced in high numbers, develop outside the mother, and most importantly, are transparent. At certain stages they are remarkably similar to human embryos, possessing all sensory systems: taste, tactile, smell, balance, vision, as well as learning. By injecting pieces of DNA into the fish embryo, scientists can create mutant fish and identify the genes and their specific roles in controlling certain processes. Because the functions of hundreds of these genes are conserved among the different vertebrate groups, the information gained from zebrafish studies can provide invaluable insights into the genetic mechanisms that control development in humans.<sup>11</sup>

The squid, octopus, and sea snail are important models for neurobiological studies. The squid has some of the largest nerve cells found in nature. By comparison, mammalian nerve cells are small and difficult to study. Researchers using the giant axon of the squid have unlocked the secrets of how human brain cells work. For example, they discovered that nerve cells use electrochemical signals to transmit messages and that learning causes physical changes in the neurons.<sup>12</sup>

Sea snails (*Aplysia*) also have large and individual neurons linked to specific behaviors that can be tracked by placing

electrodes into individual cells to measure electrical impulses conducted in the nervous system. Using this model, scientists have learned that the spaces at nerve cell endings, or synapses, adapt over time and play an important role in learning and memory.<sup>13</sup>

## Armadillo

Naturally occurring leprosy is found in wild armadillos. By studying the transmission of leprosy in this natural population, researchers will eventually learn how this ancient disease spreads among humans. Because it is still impossible to grow the leprosy bacillus in culture, armadillos are the only source of organisms for the preparation of vaccines.<sup>14</sup>

## Invertebrates (leeches)

The same leeches once used in the practice of bloodletting are being used to study memory and learning at the cellular level. The leech brain consists of 32 clumps of nerve cells along a spinal column. The simplicity of the leech's nervous system permits researchers to study the cellular basis of simple behavior. As reported recently, this animal shares with humans a binding protein that is a key component in memory.<sup>15</sup>

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