Animal Research Is Vital to Medicine

by Jack H. Botting and Adrian R. Morrison

Experiments using animals have played a crucial role in the development of modern medical treatments, and they will continue to be necessary as researchers seek to alleviate existing ailments and respond to the emergence of new disease. As any medical scientist will readily state, research with animals is but one of several complementary approaches. Some questions, however, can be answered only by animal research. We intend to show exactly where we regard animal research to have been essential in the past and to point to where we think it will be vital in the future. To detail all the progress that relied on animal experimentation would require many times the amount of space allotted to us. Indeed, we cannot think of an area of medical research that does not owe many of its most important advances to animal experiments.

In the mid-19th century, most debilitating diseases resulted from bacterial or viral infections, but at the time, most physicians considered these ailments to be caused by internal derangements of the body. The proof that such diseases did in fact derive from external microorganisms originated with work done by the French chemist Louis Pasteur and his contemporaries, who studied infectious diseases in domestic animals. Because of his knowledge of how contaminants caused wine and beer to spoil, Pasteur became convinced that microorganisms were also responsible for diseases such as chicken cholera and anthrax.

To test his hypothesis, Pasteur examined the contents of the guts of chickens suffering from cholera; he isolated a possible causative microbe and then grew the organism in culture. Samples of the culture given to healthy chickens and rabbits produced cholera, thus proving that Pasteur had correctly identified the offending organism. By chance, he noticed that after a time, cultures of the microorganisms lost their ability to infect. But birds given the ineffective cultures became resistant to fresh batches that were otherwise lethal to untreated birds. Physicians had previously observed that among people who survived a severe attack of certain diseases, recurrence of the disease was rare; Pasteur had found a means of producing this resistance without risk of disease. This experience suggested to him that with the administration of a weakened culture of the disease-causing bacteria, doctors might be able to induce in their patients immunity to infectious diseases.

In similar studies on rabbits and guinea pigs, Pasteur isolated the microbe that causes anthrax and then developed a vaccine against the deadly disease. With the information from animal experiments—obviously of an extent that could never have been carried out on humans—he proved not only that infectious diseases could be produced by microorganisms but also that immunization could protect against these diseases.

Pasteur's findings had a widespread effect. For example, they influenced the views of the prominent British surgeon Joseph Lister, who pioneered the use of carbolic acid to sterilize surgical instruments, sutures and wound dressings, thereby preventing infection of wounds. In 1875 Queen Victoria asked Lister to address the Royal Commission inquiry into vivisection—as the queen put it, "to make some statement in condemnation of these horrible practices." As a Quaker, Lister had spoken publicly against many cruelties of Victorian society, but despite the request of his sovereign, he was unable to condemn vivisection. His testimony to the Royal Commission stated that animal experiments had been essential to his own work on asepsis and that to restrict research with animals would prevent discoveries that would benefit humankind.

Dozens of Vaccines and Antibiotics

Following the work of Pasteur and others, scientists have established causes of and vaccines for dozens of infectious diseases, including diphtheria, tetanus, rabies, whooping cough, tuberculosis, poliomyelitis, measles, mumps and rubella. The investigation of these ailments indisputably relied heavily on animal experimentation: in most cases, researchers identified candidate microorganisms and then administered the microbes to animals to see if they contracted the illness in question.

Similar work continues to this day. Just recently, scientists developed a vaccine against *Hemophilus influenzae* type B (Hib), a major cause of meningitis, which before 1993 resulted in death or severe brain damage in more than 800 children each year in the U.S. Early versions of a vaccine produced only poor, short-lived immunity. But a new vaccine, prepared and tested in rabbits and mice, proved to be powerfully immunogenic and is now in routine use. Within two months of the vaccine's in-

troduction in the U.S. and the U.K., Hib infections fell by 70 percent.

Animal research not only produced new vaccines for the treatment of infectious disease; it also led to the development of antibacterial and antibiotic drugs. In 1935, despite aseptic precautions, trivial wounds could lead to serious infections that resulted in amputation or death. At the same time, in both Europe and the U.S., death from puerperal sepsis (a disease that mothers can contract after childbirth, usually as a result of infection by hemolytic streptococci) occurred in 200 of every 100,000 births. In addition, 60 of every 100,000 men aged 45 to 64 died from lobar pneumonia. When sulfonamide drugs became available, these figures fell dramatically: by 1960 only five out of every 100,000 mothers contracted puerperal sepsis, and only six of every 100,000 middle-aged men succumbed to lobar pneumonia. A range of other infections could also be treated with these drugs.

The story behind the introduction of sulfonamide drugs is instructive. The team investigating these compounds—Gerhard Domagk's group at Bayer Laboratories in Wuppertal-Elberfeld, Germany—insisted that all candidate compounds be screened in infected mice (using the so-called mouse protection test) rather than against bacteria grown on agar plates. Domagk's perspicacity was fortunate: the compound prontosil, for instance, proved to be extremely potent in mice, but it had no effect on bacteria in vitro—the active antibacterial substance, sulfanilamide, was formed from prontosil within the body. Scientists synthesized other, even more powerful sulfonamide drugs and used them successfully against many infections. For his work on antibacterial drugs, Domagk won the Nobel Prize in 1939.

A lack of proper animal experimentation unfortunately delayed for a decade the use of the remarkable antibiotic penicillin: Alexander Fleming, working in 1929, did not use mice to examine the efficacy of his cultures containing crude penicillin (although he did show the cultures had no toxic effects on mice and rabbits). In 1940, however, Howard W. Florey, Ernst B. Chain and others at the University of Oxford finally showed penicillin to be dramatically effective as an antibiotic via the mouse protection test.

Despite the success of vaccines and antibacterial therapy, infectious disease remains the greatest threat to human life worldwide. There is no effective vaccine against malaria or AIDS; physicians increasingly face strains of bacteria resistant to current antibacterial drugs; new infectious diseases continue to emerge. It is hard to envisage how new and better vaccines and medicines against infectious disease can be developed without experiments involving animals.

Research on animals has been vital to numerous other areas in medicine. Open-heart surgery—which saves the lives of an estimated 440,000 people every year in the U.S. alone—is now routine, thanks to 20 years of animal research by scientists such as John Gibbon of Jefferson Medical College in Philadelphia. Replacement heart valves also emerged from years of animal experimentation.

The development of treatments for kidney failure has relied on step-by-step improvement of techniques through animal experiments. Today kidney dialysis and even kidney transplants can save the lives of patients suffering from renal failure as a result of a variety of ailments, including poisoning, severe hemorrhage, hypertension or diabetes. Roughly 200,000 people require dialysis every year in the U.S.; some 11,000 receive a new kidney. Notably, a drug essential for dialysis—heparin—must be extracted from animal tissues and tested for safety on anesthetized animals.

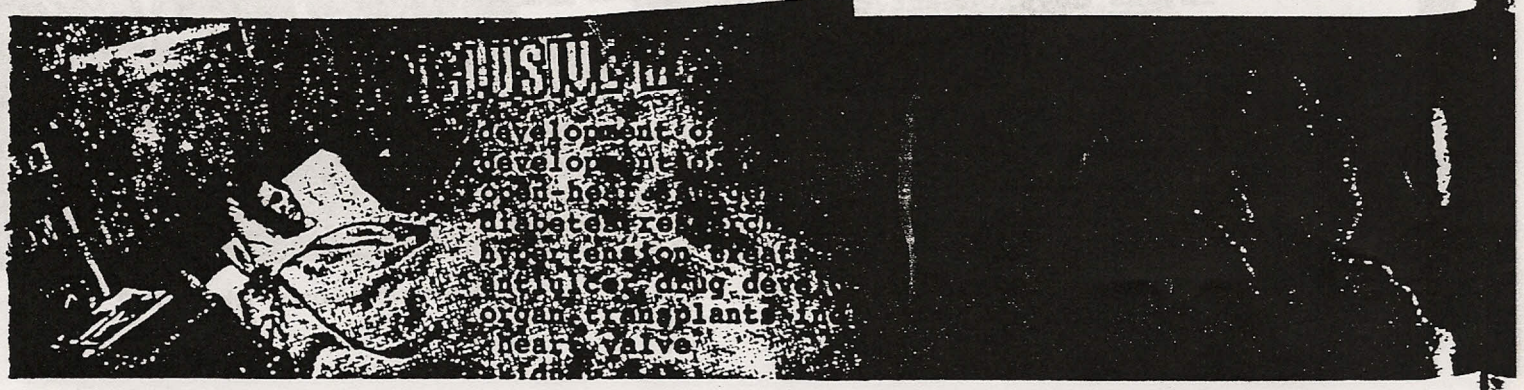
Transplantation of a kidney or any major organ presents a host of complications; animal research has been instrumental in generating solutions to these problems. Experiments on cats helped develop techniques for suturing blood vessels from the host to the donor organ so that the vessels would be strong enough to withstand arterial pressure. Investigators working with rabbits, rodents, dogs and monkeys have also determined ways to suppress the immune system to avoid rejection of the donor organ.

The list continues. Before the introduction of insulin, patients with diabetes typically died from the disease. For more than 50 years, the lifesaving hormone had to be extracted from the pancreas of cattle or pigs; these batches of insulin also had to be tested for safety and efficacy on rabbits or mice.

When we started our scientific careers, the diagnosis of malignant hypertension carried with it a prognosis of death within a year, often preceded by devastating headaches and blindness. Research on anesthetized cats in the 1950s heralded an array of progressively improved antihypertensive medicines, so that today treatment of hypertension is effective and relatively benign. Similarly, gastric ulcers often necessitated surgery with a marked risk of morbidity afterward. Now antiulcer drugs, developed from tests in rats and dogs, can control the condition and may effect a cure if administered with antibiotics to eliminate *Helicobacter pylori* infection.

Common Misconceptions

Much is made in animal-rights propaganda of alleged differences between species in their physiology or responses to drugs that supposedly render animal experiments redundant or misleading. These claims can usually be refuted by proper examination of the literature. For instance, opponents of animal research frequently cite the drug



thalidomide as an example of a medicine that was thoroughly tested on animals and showed its teratogenic effect only in humans. But this is not so. Scientists never tested thalidomide in pregnant animals until after fetal deformities were observed in humans. Once they ran these tests, researchers recognized that the drug did in fact cause fetal abnormalities in rabbits, mice, rats, hamsters and several species of monkey. Similarly, some people have claimed that penicillin would not have been used in patients had it first been administered to guinea pigs, because it is inordinately toxic to this species. Guinea pigs, however, respond to penicillin in exactly the same way as do the many patients who contract antibiotic-induced colitis when placed on long-term penicillin therapy. In both guinea pigs and humans, the cause of the colitis is infection with the bacterium *Clostridium difficile*.

In truth, there are no basic differences between the physiology of laboratory animals and humans. Both control their internal biochemistry by releasing endocrine hormones that are all essentially the same; both humans and laboratory animals send out similar chemical transmitters from nerve cells in the central and peripheral nervous systems, and both react in the same way to infection or tissue injury.

Animal models of disease are unjustly criticized by assertions that they are not identical to the conditions studied in humans. But they are not designed to be so; instead such models provide a means to study a particular procedure. Thus, cystic fibrosis in mice may not exactly mimic the human condition (which varies considerably among patients anyway), but it does provide a way to establish the optimal method of administering gene therapy to cure the disease. Opponents of animal experiments also allege that most illness can be avoided by a change of lifestyle; for example, adoption of a vegan diet that avoids all animal products. Whereas we support the promulgation of healthy practices, we do not consider that our examples could be prevented by such measures.

A Black Hole

Our opponents in this debate claim that even if animal experiments have played a part in the development of medical advances, this does not mean that they were essential. Had such techniques been outlawed, the argument goes, researchers would have been forced to be more creative and thus would have invented superior technologies. Others have suggested that there would not be a gaping black hole in place of animal research but instead more careful and respected clinical and cellular research.

In fact, there was a gaping black hole. No outstanding progress in the treatment of disease occurred until biomedical science was placed on a sound, empirical basis through experiments on animals. Early researchers, such as Pasteur and the 17th-century scientist William Harvey, who studied blood circulation in animals, were not drawn to animal experiments as an easy option. Indeed, they drew on all the techniques available at the time to answer their questions: sometimes dissection of a cadaver, sometimes observations of a patient, sometimes examination of bacteria in culture. At other times, though, they considered experimentation on animals to be necessary.

We would like to suggest an interesting exercise for those who hold the view that animal experiments, because of their irrelevance, have retarded progress: take an example of an advance dependent on animal experiments and detail how an alternative procedure could have provided the same material benefit. A suitable example would be treatment of the cardiac condition known as mitral valve insufficiency, caused by a defect in the heart's mitral valve. The production of prosthetic heart valves stemmed from years of development and testing for efficacy in dogs and calves. The artificial valve can be inserted only into a quiescent heart that has been bypassed by a heart-lung machine—an instrument that itself has been perfected after 20 years' experimentation in dogs. If, despite the benefit of 35 years of hindsight, critics of animal research cannot present a convincing scenario to show how effective treatment of mitral valve insufficiency could have developed any other way, their credibility is suspect.

Will animal experiments continue to be necessary to resolve extant medical problems? Transgenic animals with a single mutant gene have already provided a wealth of new information on the functions of proteins and their roles in disease; no doubt they will continue to do so. We also anticipate major progress in the treatment of traumatic injury to the central nervous system. The dogma that it is impossible to restore function to damaged nerve cells in the mammalian spinal cord has to be reassessed in the light of recent animal research indicating that nerve regeneration is indeed possible. It is only a matter of time before treatments begin to work. We find it difficult to envision how progress in this field—and so many others in biological and medical science—can be achieved in the future without animal experiments. ■

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