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Strides in Biomedical Research

In Nolan's lab, 90% of cases of *Toxocara canis*, roundworm, have been found to occur in puppies less than one year old, and virtually all cases where disease has resulted have been in puppies. Adult worms are found in the small intestine. In puppies less than six weeks old, larvae penetrate the intestinal wall into a blood vessel. They travel via the blood stream to the lungs. They are coughed up and then swallowed, to return to the small intestine to mature. Here, female adult worms lay about 1/2 million eggs per day which are released into the dog's feces. Direct transmission of infection to other dogs results through contact with areas contaminated with feces.

At age three months, puppies start to develop an immunity to roundworms and the larvae usually arrest in the tissues, where they do no harm. In pregnant female dogs, however, they become reactivated by the hormonal changes. They migrate to the small intestine to mature, or penetrate the placenta and settle in the puppies' livers or migrate to the mammary glands, where they are transmitted to suckling puppies.

Symptoms in puppies are coughing, vomiting worms, diarrhea and malnourishment that sometimes causes a potbelly appearance. Treatment, which prevents symptoms, should occur in the bitch prior to, and after, parturition. Puppies should be treated within the prepatent period, which is the time from initial infection in offspring to the time at which the larvae have matured and are reproducing. This is normally is 4-5 weeks after the puppies are born.

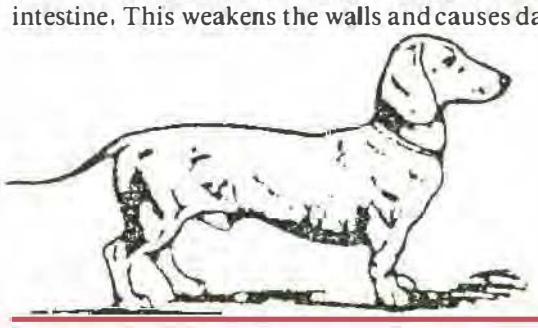
Though quite resilient, *Toxocara* eggs are subject to desiccation. Dr. Nolan recommended keeping the dog's area dry and clean. The eggs in the feces mature in approximately two weeks, so the feces should be removed immediately. Concrete runs are very effective in preventing the eggs from washing into the ground and are easy to clean.

Hookworm, *Ancylostoma caninum*, ranked second highest in frequency at VHUP last year. Normally transmitted when puppies ingest larvae with the mother's milk, it may also occur through direct contact with contaminated soil. Once ingested, larvae penetrate the intestinal walls and migrate throughout the body. In adult dogs, they either arrest in the tissues or go back to the small intestine. In females, the larvae become active late in pregnancy, and migrate to the mammary glands or, less often, the placenta.

Adult worms use their large, toothed mouths to latch onto intestinal tissue in search of blood vessels to pump. Immune systems in adult dogs combat them effectively, and any blood loss that they cause is usually insignificant. In puppies, however, the same amount of blood loss may cause anemia. Puppies' gums and eyelids should be examined for paleness. Diarrhea and tarry stools full of undigested blood are also signs of hookworm. Adult worms show up in puppies about two weeks after they have started to suckle an infected mother, and disease can be acute. According to Dr. Nolan, a puppy can be anemic one day and dead the next.

Recommended control measures are medication, which is usually effective, timely removal of feces and drying of contaminated areas to kill larvae, which hatch from their eggs in 24 hours.

Whipworm, *Trichuris vulpis*, is the most commonly seen gastrointestinal parasite. Dr. Nolan said that it is hard to diagnose because these worms lay fewer eggs. Present in 9% of the dogs tested at VHUP in 1991, whipworm is transmitted through ingestion of the eggs, which hatch in the small intestine. Adult worms embed their long, narrow frontal sections into the lining of the cecum and large intestine. This weakens the walls and causes damage, which can result in bloody diarrhea and weight loss. However, symptoms only occur when many worms are present.



The hardy whipworm eggs can survive in the environment for as long as two years, so it is important to remove the feces promptly and keep the dog's area dry. The prepatent period is three months and drugs can be administered four times per year as a prophylatic if there is no way to prevent re-infection because of a severely contaminated environment. Some drugs are effective when the worms are still in their larval stages.

Dipylidium caninum, the common tapeworm, uses suckers to attach itself to the small intestine lining, but it rarely causes tissue damage. Its segmented body, which appears ribbon-like, is comprised of proglottids, motile sections of reproductive organs which are full of eggs. Upon ripening, the millimeter-long proglottids break off and pass out with the feces. They quickly crawl out of the feces and rupture, releasing their eggs, which are eaten by larval fleas. Once mature, an infected flea bites the dog, and the dog, in biting back, ingests the larval tapeworm which is within the flea.

No disease symptoms are displayed in an infected dog. The only signs are minor intestinal distress and "scooting," whereby the dog rubs its rear along the ground to relieve irritation around the anal area caused by proglottids crawling out of the anus. Infected dogs should be treated, and fleas should be eliminated. Feces must be removed immediately, as the proglottids crawl out quickly.

The two gastrointestinal protozoans Dr. Nolan discussed are coccidia and *Giardia*. Both live in the small intestine. Coccidia are transmitted when the dog ingests cysts from feces. The cysts hatch in the small intestine, where they invade the lining of the intestine. Most veterinarians won't treat adult dogs because their immunity to coccidia is more effective than a drug.

Usually, no symptoms are evident in puppies, although minor gastrointestinal bleeding and diarrhea sometimes occur. Within two weeks after infection, the puppy's immune system is usually able to purge itself of coccidia. The cysts are very susceptible to desiccation, so it is important to keep the dog's area dry and remove the feces quickly.

Giardia are transmitted by ingestion of waterborne cysts. They hatch and replicate in the small intestine, on which they form a tight layer. They may cause malabsorption in the dog, because foods must first pass through this layer of *Giardia* to reach the intestine. Fats, least likely to be absorbed in this scenario, are usually washed out, causing the stool to appear full of mucus. Malabsorption occurs only in extreme circumstances, because older dogs usually have developed a good immunity to *Giardia*. It normally doesn't even cause much damage in puppies, who usually contract it from their mothers, although chronic diarrhea may occur. The most important control measure is to keep the dog's area dry and prevent the dog from drinking from streams and puddles. Also, timely feces removal is crucial.

Worming should be done when puppies are about two weeks old, but Dr. Nolan cautioned against overworming, which can cause other health problems.

The ectoparasites Dr. Nolan discussed were mites and fleas. Mites are of two types - those that live in the skin and cause mange and wet lesions, and those that live in the fur and frequent the skin only to eat. Mites complete their life cycle on the dog. For prevention and treatment of mites, Dr. Nolan suggested dipping the dog, and also keeping its area clean.

Fleas lay their eggs on the dog or in the environment. The eggs are very resistant to chemicals, so it is necessary either to spray with a chemical that will outlast the incubation period, anywhere from two days to two weeks, or to spray weekly. Vacuuming is somewhat effective. Adult fleas can live for up to a year in a dormant stage if no food is available, so vacant homes that were infested should be treated if they are going to be inhabited in the same year.

J.C.

Strides in Biomedical Research

Researchers Have Conquered Diseases and Discovered Better Medical Treatments Through Work With Animal Models

The use of animals in research has dramatically changed the face of human existence. Over the last century, medical advances using animal research have been made by the health organizations such as the National Institutes of Health, pharmaceutical firms and universities, to stamp out diseases such as tuberculosis, polio and diphtheria. This research has also led to improved treatment for current major killers: heart disease, cancer and diabetes.

Since the 1950s, death from heart disease has dropped by 4 percent each year; death from strokes has decreased 2 percent annually. Approximately 50 million Americans who would be at risk of death from hypertension are alive because of medical discoveries to treat their conditions. Animal research helped perfect coronary bypass surgery which has benefited an estimated 200,000 bypass patients annually.

The recent development of a mouse model for AIDS, and promising work in the development of an AIDS vaccine using primates, will help scientists make greater progress in determining the best way to treat that disease. Half a million insulin-dependent diabetics survive today because of the discovery of insulin and current diabetes research with animal models.

Dialysis extends the lives of patients in kidney failure. Kidney transplants, first done in animals, offer 7,500 patients a second chance at life each year.

Childhood diseases, such as rubella and whooping cough, have virtually disappeared due to vaccines developed through animal research. Jonas Salk developed the polio vaccine using monkeys in 1953. Now more than 30 years lates, a vaccine for chicken pox, developed using animals, is undergoing clinical trials in the United States.

Animal research has led to the discovery of penicillin and other antibiotics to treat infections. Because of these discoveries, deaths due to bacterial infection have become a rarity in the United States and many other parts of the world.

Without animal models, cancer patients would not have the options of radiation and chemotherapy. The study of treatments and cures for arthritis, cystic fibrosis, and Alzheimer's disease would be impossible. Common cataract surgery was perfected on animals, and current research to combat blindness depends on animal testing. Treatments to save burn and poison victims would not exist without the knowledge gained from animal research. In turn, this research has extended the lives of animals who are treated with vaccines, antibiotics and surgery in many of the ways that humans are aided.

Every major medical advance to cure or treat disease has been developed using research animals. These discoveries and treatments touch every human life in some way from the moment of birth.

The following is a synopsis of earlier medical breakthroughs and advances as well as ongoing biomedical research intended to improve the lives of humans and animals.

Cardiovascular Disease

Renowned open-heart surgery pioneer Dr. Michael DeBakey describes the link between animal research and heart disease in these terms: "Every major medical advance we've had in cardiovascular research from surgery to the heart-lung machine to coronary bypass, has come from research in which it was necessary to use animals."

Dr. DeBakey, chairman of the department of surgery and director of The Debakey Heart Center at Baylor College of Medicine, said neither the heart-lung machine nor other devices and surgical techniques would exist today without animal research. The heart-lung machine required over 20 years of experimental work before it was perfected for use on human beings," he said. "Even with today's technology, I would not have used a computer to develop the roller pump that made open-heart surgery possible, or the artificial artery that restored to health previously doomed patients with aneurysms. Nor could we have attempted the first successful coronary artery bypass or implanted the first temporary mechanical heart, with which we saved a patient's life two decades ago. Think of all the infants with congenital heart failure who have died. Now, 90 percent of all congenital heart cases are cured."

Most cardiovascular treatments were obtained through research on a variety of animals, including rodents, dogs, cats, rabbits, and sheep. Scientists have used dogs to develop the cardiac pacemaker and surgical techniques used in coronary artery bypass surgery and heart transplantation. Rats are the most important model for researchers studying hypertension, because certain types of rats develop hypertension spontaneously. Research with rabbits has pointed to the relationship between genetics and blood pressure, and aided researchers in the study of stress-induced cardiomyopathy and atherosclerosis.

Dr. DeBakey emphasized that current research in a permanent artificial heart requires work on calves and pigs because the animals have cardiac systems that resemble those in humans. "The truth is that there are no satisfactory insentient models at present for certain types of biomedical research and testing," Dr. DeBakey said. "A computer is not a living system and could not alone have produced the dramatic medical advances of the past decades."

Cancer

In the early 1900s, few cancer patients had any hope of long-term survival. The disease is still a major killer, with an estimated 1,375 people a day dying of cancer in the United States. But due to treatments developed through animal research and testing, about 405,000 Americans each year, or four out of 10 cancer patients, will still be alive five years after diagnosis. A decade ago many patients with cancers such as Hodgkin's disease, Ewing's sarcoma (a form of bone cancer), and lymphocytic leukemia had a poor prognosis. Today, many of those patients are cured.

Animal research led to the discoveries of most cancer treatments. Most of the first studies on chemotherapy were done with tumors in mice. Rats have played an important role in the treatment of breast cancer, due to similarities between human breast cancer and rodent mammary carcinoma. Rats have helped scientists learn more about other malignant tumors and which treatments work best. Scientists have tested on animals new therapies, such as interferon, interleukin-2 and other biologic response modifiers, which researchers hope will enhance the body's own disease-fighting systems.

According to Dr. Heiner Fiebig, who conducted research for the National Cancer Institute (NCI), animal models have played a major role in the testing of compounds to treat cancer. "Between 1955 and the mid-1970s, 40 promising compounds were identified using animal models," he said. "Animals have also had a very big impact on the use of chemotherapy." Animal research helped NCI make significant strides in the areas of leukemia, lymphoma and testicular cancer. Dr. Fiebig noted.

Diabetes

Researchers Sir Frederick Banting and Charles Best used dogs in their experiments that eventually identified insulin as an important hormone in carbohydrate metabolism. Their work led to the discovery of insulin for diabetics in 1922.

Research with rodents is helping scientists understand the causes of diabetes, and in particular, insulin-dependent (juvenile) diabetes. A group of Stanford University Medical Center made significant strides in 1988 when it engineered an antibody that cures laboratory mice of diabetes. A year-long study demonstrated that a special monoclonal antibody could block the destructive action of a T-cell lymphocyte that is believed to help trigger diabetes.

Dogs have continued to help researchers in studies of diabetes, including work on pancreatic transplants, and ocular and vascular complications associated with the disease. However, the number of dogs used in diabetes research is declining as the knowledge gained through earlier work allows researchers to use their techniques and models.

Alzheimer's Disease

Current research on Alzheimer's disease, a degenerative brain disorder affecting about 2.5 million Americans, has focused on both discovering its causes and potential treatments. Estimates show that one in 20 people over the age 65 and one in 5 people over age 85 has the disease.

Research on primates uncovered an important characteristic of the disease, which is the abundance of neuritic plaques, or clusters of nerve endings, in the cerebral cortex. A small number of elderly dogs has been studies because they often exhibit these neuritic plaques.

Researchers in California and Massachusetts have done studies with rats that may help avoid memory loss, a major effect of Alzheimer's. Researchers discovered that it is possible to keep "memory-related" cells in the brain from dying by injecting the cells with nerve growth factor.

Research for the Benefit of Animals

Animals have also benefited from medical breakthroughs. Veterinarians use many techniques and treatments to save animals, including orthopedic surgery, pacemakers, transplants and radiation therapy.

"Most drugs, diagnostic tests and surgical techniques used in veterinary medicine today come directly from research or from human medical or surgical practice that was originally based on animal research," said Dr. Franklin Loew, dean of Tufts University School of Veterinary Medicine. "The discovery process is often worked out on animals with the specific intent of being used on people, and if it is successful, veterinarians often find if economically feasible to use the same techniques on animals. Hip replacements are a good example. Over 100,000 hip replacements are done in the U.S. each year, due to research first done on dogs. Now this technique is being used on dogs."

Animal research has led to preventive treatments, including medications to kill parasites such as heartworms and hookworms that can infect pets, and vaccines to avoid rabies, feline leukemia, distemper and hepatitis. Research led to the development of a vaccine against parvovirus, a new disease that killed thousands of young dogs in the 1970s.

Approximately half of all pets over the age of 10 die from leukemia or bone, skin or breast cancer. However, new surgical techniques, radiation therapy, chemotherpay, cryosurgery and hyperthermia have helped many animals live longer.

Kidney failure, another cause of death in dogs and cats, is treatable with new micro-surgical techniques and organ transplants using the latest immunosuppressive drugs to prevent rejection.

Domestic animals, such as horses, cattle, sheep, hogs and chickens also benefit from research on breeding and nutrition. New vaccines helped protect against influenza and encephalomyelitis in horses, rinderpest in cattle, and gastroenteritis in pigs.

Biomedical research has also had a lasting effect on wildlife. Research on reproduction, nutrition, toxicology and medicine has helped save endangered species, such as the bald eagle, alligator, red wolf and Florida panther.

Significant Medical Advances Using Animal Models

Animals have played an integral role in the discovery of medical cures, treatments and vaccines. Since 1901, 57 Nobel Prizes in Physiology and Medicine have been awarded for research done with animals. The following is a sampling of some of the major medical breakthroughs that have been made using animal models.

Advances Using Animal Models

Penicillin: study of effectiveness against bacterial infection ..... mouse

Polio: ability to culture poliovirus in cells that led to vaccine ..... monkey & mouse

Cancer: study of tumors and hormonal cancer treatments ..... rat, rabbit & hen

Development of chemotherapy ..... monkey, rabbit & rodent

Tuberculosis: research that led to cure ..... cow & sheep

Insulin: discovery of insulin and study of diabetis ..... dog, rabbit, rat & mouse

C.A.T. Scan: discovery of diagnostic potential and development ..... pig

Organ Transplants: technique refinement/ rejection prevention .. mouse, rat, rabbit & dog

Aids Vaccines: development and safety testing ..... primate, rabbit & mouse

Heart Disease: study of disease/ treatments ..... rat, dog, cat, sheep & rabbit

Heart/Lung Machine: development and testing ..... dog

Cardiac Pacemaker: development and testing ..... dog

Sutures and Grafts: development/ refinement of surgical techniques ..... dog

(Sources: *JAMA, Perspectives in Biology & Medicine, Newsweek*)

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