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Medical Genetics

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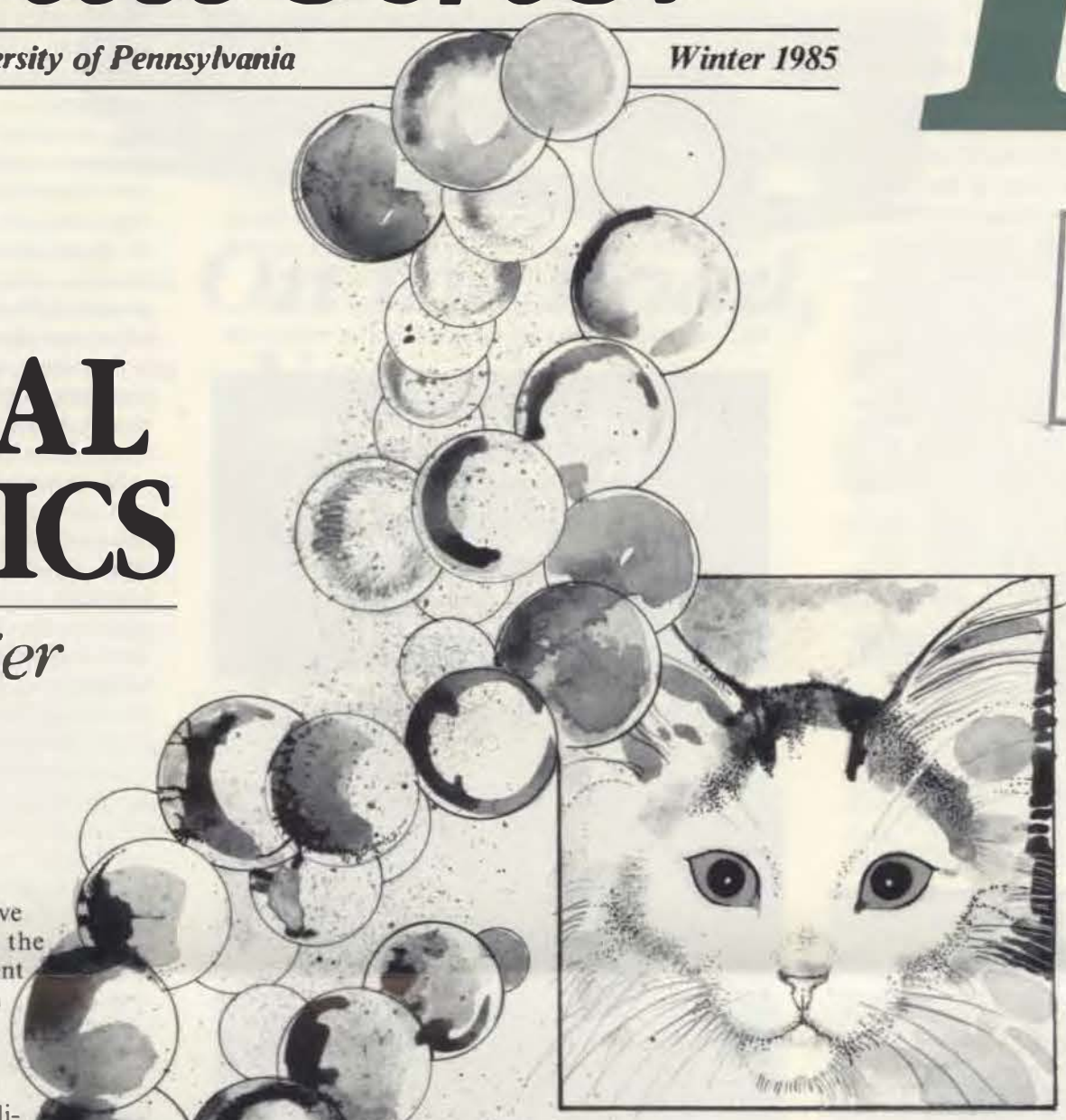
MEDICAL GENETICS

A New Frontier



Great strides have been made in the control, treatment and prevention of viral, parasitic and nutritional diseases in animals and man. Smallpox, once a threatening illness, has been eradicated; polio can be prevented through immunization, as can many of the childhood diseases. Nutrition has improved in many areas of the world and scientists are finding new ways to prevent or control parasitic disease. As communicable diseases are eradicated or prevented, researchers have focused on another group of disorders, diseases not caused by outside agents but diseases which have their origin in genetic material.

Today veterinarians increasingly deal with a large number of diseases which are wholly or partially genetic in origin. Hereditary defects of the bones and joints, the heart, eyes, and the central nervous system occupy an increasing proportion of the time of the veterinarian who deals primarily with pet animals. Evidence is accumulating that hereditary factors are responsible for the high death rate among newborn offspring of purebred dogs and cats. The high frequency of some types of cancer and degenerative diseases in older animals of certain breeds may also be due to a genetically determined increase in susceptibility to these conditions. In livestock, genetic factors have been shown to produce a large variety of defects which cause death or limit production in more subtle ways. Substantial evidence exists that the susceptibility to such diseases as leukemia and mastitis in cattle, parasitism in sheep, and leukosis in chickens is genetically determined. Close to 200 genetic diseases in animals have been identified. Of these at least 150 occur in dogs. These numbers, while appearing high, are low when compared to the number of single gene genetic defects in people where more than 2,000 have been identified.

Genetic research is highly specialized, and in 1973 the University of Pennsylvania School of Veterinary Medicine established the Section of Veterinary Medical Genetics, a formal academic subdivision devoted primarily to the identification and study of genetic diseases in domestic animals. This Section includes laboratories for the study of inborn errors of metabolism, chromosomal anomalies and congenital malformation. Since its inception the Section has been on the forefront of medicine in identifying genetic disorders in animals. Researchers cooperate closely with scientists at the University of Pennsylvania Medical School and at other institutions. The work of the Veterinary Medical Genetics Section has led to the discovery of 15 previously unknown metabolic defects in cats and dogs, and it is expected that many more disorders will be identified in the future.

A number of these diseases identified in dogs and cats are also found in humans. "These naturally occuring diseases

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provide valuable animal models for us to study," said Dr. Donald F. Patterson, Charlotte Newton Sheppard Professor of Medicine and Chief, Section of Medical Genetics. Since the 1960s, Dr. Patterson has studied congenital heart disease in dogs. The work began after an extensive survey, conducted by the Comparative Cardiovascular Studies Unit here at the School, revealed that the incidence of congenital heart diseases in dogs was 5.6/1,000. It was found that the heart diseases detected in dogs were anatomically and clinically similar to those in man. The five most common cardiovascular malformations in the dogs were, in descending order of prevalence, patent ductus arteriosis, pulmonic stenosis, discrete subaortic stenosis, persistent right aortic arch, and tetralogy of Fallot. Dr. Patterson and his colleagues discovered that specific disorders occurred in higher numbers in certain breeds. For example, there is a high frequency of tetralogy of Fallot in keeshonds. This cardiac malformation, common in humans, results in "blue babies."

Breeding colonies were established to investigate the underlying genetic basis of the five defects. Breeding studies showed that the malformations are not inherited as simple Mendelian traits. They behave as if multiple gene loci are involved, alleles which have additive effects on the growth and development of specific structures in the embryonic heart and great vessels. A cardiovascular malformation occurs when the additive genetic effect on a special developmental process exceeds a critical threshold. These studies have provided the most complete understanding of the genetics and pathogenesis of naturally occuring heart disease available in any species.

In recent years, in addition to the heart disease studies, the Medical Genetics Section has investigated inherited metabolic diseases. "Most inborn errors of metabolism involve defects in enzymes, proteins with catalytic activity," said Dr. Peter F. Jezyk, associate professor of Medicine (Medical Genetics). "In many cases there is only a partial reduction of enzyme activities, not a complete or near complete loss of activity." He explained that frequently the metabolic disorder may become evident only when the affected animal or person is ill due to infectious disease or is stressed. Then the metabolic disorder is manifested because of increased tissue breakdown and overloading of the affected metabolic pathway. Dr. Jezyk said that most inborn errors of metabolism are transmitted as simple autosomal recessive traits. He stated that it is possible that much of the high mortality seen in newborn purebred cats and dogs is due to genetic defects. "One study showed that only 8.9% of the deaths of newborn cats and dogs could be attributed to infection. But it is not feasible for breeders to have extensive diagnostic procedures performed when there are "fading" puppies or kittens; it's just too expensive. However, if large numbers of newborn animals die during the first days of life, the breeder should try to discover whether or not genetic disease is responsible."

Over the last ten years the Section of Medical Genetics has developed a metabolic screening laboratory, primarily for the dog and cat.

Reliable methods are now available to detect metabolic disorders in animals. Over the last ten years the Section of Medical Genetics has developed a metabolic screening laboratory, primarily for the dog and cat. Dr. Jezyk and his associates have determined the normal ranges for common metabolites in blood and urine and defined typical chromatographic patterns for amino acids, organic acids, carbohydrates, and glycosaminoglycans in urine. The laboratory is the only one of its kind in the world, and samples are received not only from veterinarians in this country but also from abroad. A number of years ago a program was begun where breeders and veterinarians could submit urine samples from animals on special filter paper. The samples are tested for abnormal metabolites and the breeders notified if a disorder is found. Over 15 new metabolic disorders have been identified in dogs and cats as a result of this program. Some of the most recent discoveries include methylmalonic acidemia causing hypoglycemia and growth failure in a young giant schnauzer and a lethal acrodermatitis in bull terriers. Type II tyrosinemia, associated with skin and eye problems, was identified in a German shepherd. Basset hounds with an x-linked immune deficiency have also been identified by Dr. Jezyk.

Metabolic screening plays an important role in human medicine, particularly pediatrics. "Current estimates indicate that about 20 to 30% of the patients in the nation's children's hospitals are there because of genetic disease," said Dr. Jezyk. "Many of these children have identifiable metabolic disorders." In addition to his duties at the School, Dr. Jezyk directs the Metabolic Screening Laboratory at the Children's Hospital of Philadelphia.

Several years ago, a young Siamese cat seen at the clinic was diagnosed as having mucopolysaccharidosis (MPS). This is a lysosomal storage disease caused by a defect in glycosaminoglycan (GAG) metabolism. In a healthy individual, GAG is broken down by a sequence of degradative enzymes. In individuals with MPS, one of the enzymes is defective and the degradative process is not completed. The GAG molecule which is not fully broken down is stored in the lysosomes. As this material accumulates, the lysosomes enlarge and the proper function of the cells is disrupted. MPS manifests itself with varying severity, depending on the enzyme involved. The most severe form of the disease is Hurler syndrome, which causes mental retardation in humans and leads to death during the first decade of life. This syndrome has been identified in both the cat and dog. The diseases are inherited as autosomal recessive traits. A blood test has been developed to identify carriers; it is equally effective for carrier identification in humans. "There are dozens of lysosomal storage diseases in man," said Dr. Mark Haskins, associate professor of pathology. "Each of these is rare, but when one takes them as a class of diseases, they are more common." So far 11 lysosomal storage diseases have been identified in animals.

Dr. Haskins and his colleagues are searching for a method to treat MPS in cats. A drug, cysteamine, restores partial enzyme activity for short periods of time in cats with MPS VI. Long-term studies are currently underway to evaluate this therapy in the cat. Dr. Haskins is also investigating bone marrow transplantation to correct the enzyme deficiency in cats with both MPS VI and MPS I. The researchers are also trying to clone the normal gene for the enzyme responsible for each disorder in order to use genetic engineering approaches to treatment.

Another part of the studies in the Section is the pathologic examinations of animals with birth defects. "We look at neonatal pups and kittens that die and try to determine the cause of death," Dr. Haskins said. "Recently we found

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a congenital malformation syndrome in shi tzus. The pups have abnormal heads, large livers, and malformations of the rear legs, Most are stillborn or die very early. We don't know as yet why the malformations occur or how the condition is inherited."

As diagnostic techniques become more sophisticated, the number of genetic diseases discovered will increase. Dr. Patterson pointed out that when pregnant animals are exposed to environmental agents called teratogens, the offspring may have congenital defects that resemble genetically determined abnormalities. Teratogens include radiation and certain chemicals. For example, it is known that ewes which eat the plant *veratrum* during a particular stage of pregnancy will give birth to cyclopian lambs. One of the more common forms of sexual anomalies can be due to exposure of the fetus to androgenic steroids. Sometimes it is difficult to determine whether a defect is primarily genetic in origin or is due to environmental teratogens. In these cases, research into the structure of the chromosome, the pedigrees of the affected animals, and specialized biochemical tests may provide the answer.

The researchers in the Section are also studying chromosomal abnormalities. The cytogenetics laboratory has defined the normal Giesma banding pattern of dog chromosomes, and this has aided in the identification and characterization of hereditary defects in the sexual development found in American cocker spaniels and miniature schnauzers. These and other defects in the development of the reproductive tract are being studied by Dr. Vicki Meyers-Wallen and other members of the Section of Medical Genetics.

Dr. Meyers-Wallen is investigating sex reversal in cocker spaniels and Persistent Mullerian Duct Syndrome in miniature schnauzers. A cocker spaniel with the disorder looks like an abnormal male or a female, having undescended testes or ovotestes (a combination of ovary and testes) and a vulva-like structure. The chromosome constitution of such dogs is like that of a female: 78,XX. Miniature schnauzers with Persistent Mullerian Duct Syndrome appear like normal males, though they are cryptorchid. Internally these animals have a uterus. Their chromosome constitution is 78,XY and rarely 79,XXY.

In normal development the testes of the embryo produces Mullerian inhibiting substance (MIS), which inhibits the development of a uterus or oviducts in a male fetus. It is thought that these defects are a result of MIS deficiency or refractory response to MIS by Mullerian structures (oviducts and uterus) during embryonic development.

Dr. Meyers-Wallen is studying whether the Mullerian duct persistence is associated with deficiency of MIS or whether the gene mutations responsible for these two defects in Mullerian duct regression are autosomal or

Dr. Peter F. Jezyk examines a chromatogram.

Many of the genetic diseases do not manifest themselves until the animal is over six months old.

x-linked. Sex reversal has been described in other animals and humans. So far, the miniature schnauzer is the only model described that closely resembles the Persistent Mullerian Duct Syndrome in humans. Investigation of these problems in dogs will lead to a better understanding of the disorder and may lead to methods of prevention in humans and dogs.

In 1983 the Inherited Eye Disease Studies Unit (IEDSU) was established within the Section of Medical Genetics. "This is a clinic devoted to inherited eye disorders in all animal species," said Dr. Gustavo D. Aguirre, associate professor of ophthalmology and head of the IEDSU.

The unit provides clinical examinations and genetic counseling pertaining to eye disorders. Dr. Aguirre and his colleagues have developed diagnostic methods through which dogs with inherited eye disorders can be identified early in life. "The ophthalmological manifestations of these diseases vary from breed to breed," Dr. Aguirre said. "Many do not become evident through ophthalmic examination until later in life. Often the animal has already been used for breeding." By means of an electroretinogram (ERG), the researchers at the School can detect PRA in certain breeds long before the disease can be detected by ophthalmologic exam. Thus the animals can be screened prior to becoming part of a breeding program. "Many of the eye diseases are inherited recessively," said Dr. Aguirre. "Some animals are carriers and when two such dogs are mated, some of the offspring will show the disease, some will be carriers, and some will be genetically normal." Studies have shown that PRA is not one disease but a distinct entity for each breed. The PRA studies have implications not only for dogs but also for humans. It appears that PRA is similar to retinitis pigmentosa.

In addition to the eye clinic, the Section of Medical Genetics also offers clinics in pediatrics, reproduction and genetic problems. "In our pediatric clinic we see not only young animals for routine examination but also animals with severe problems," said Dr. Jezyk. "Many of the genetic diseases do not manifest themselves until the animal is over six months old." If an animal is identified as having genetic disease, often counseling with the breeder takes place to determine where the disorder originated. "We do pedigree analysis," said Dr. Jezyk. "Often we can identify a carrier and then can advise the breeder about steps to take to eliminate the disorder from the breeding program." Recently the National Institutes of Health designated the Section of Medical Genetics as the National Referral Center for Animal Models of Human Genetic Disease.

Many of the genetic diseases found in companion animals provide valuable models for these same diseases in humans. Through their research, the members of the Section of Medical Genetics not only help to unravel the mysteries of the causes and control of genetic diseases in animals, but also find new ways, in many cases, of approaching genetic diseases in man. *H. W.*

Donation by the Kennel Club of Philadelphia

William L. Kendrick, president of the Kennel Club of Philadelphia, announced a $12,000 donation to the University of Pennsylvania School of Veterinary Medicine. "We greatly appreciate this generous donation by the Kennel Club of Philadelphia," said Dean Robert R. Marshak. "It will enable us to help relieve the financial distress of some of our students, as $6,000 will be placed in the scholarship fund to be used for student financial aid. The balance will be utilized to purchase a gastroduodenoscope and an observerscope, instruments much needed for the diagnosis and study of gastrointestinal diseases."

This gift by the Kennel Club of Philadelphia represents the largest contribution ever received by the School from an all-breed club.

GME Seminar

Granulomatous meningo-encephalitis (GME) will be the topic of a lecture series on May 25, 1986, in Washington, D.C. The lectures, part of the neurology program held under the auspices of the American College of Veterinary Internal Medicine Fourth Annual Forum, are being organized by Dr. Sheldon Steinberg, who is also chairman of the neurology meeting. "Mr. Gilbert Kahn, through the Charing Cross Research Fund, is supporting research into various aspects of GME," said Dr. Steinberg. "He has provided funds which enable us to assemble leading researchers into this disorder for the session in Washington."

The four speakers will be Dr. John T. McGrath, professor of pathology at the University of Pennsylvania School of Veterinary Medicine; Dr. Kyle G. Braund, Scott-Ritchey Laboratories, Auburn University; Dr. Robert J. Higgins, Department of Veterinary Medical Pathology, School of Veterinary Medicine, University of California, Davis; Dr. Mark Vandevelde, Institute for Comparative Neurology, University of Berne, Switzerland.

Funding for Agricultural Research

The School of Veterinary Medicine has received a grant totalling $87,750 to fund four research projects at New Bolton Center. The funded projects are as follows:

- Economic Data Envelopment Analysis of Veterinary and Nutritional Services to Dairy Herds
- Serological Identification of Swine Herds with Trichonosis by ELISA, as a Basis for Control
- Shipping Fever in Feeder Calves
- Reproductive Failure in the Pig