Summer 1982

A Special Cat Colony

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The Palmerton Problem

Although the original and most obvious mission of the veterinary profession is the delivery of direct health care to animals, the profession has a growing list of other responsibilities. In fact, all of the health professions, veterinary medicine has the most diverse responsibilities.

One area in which veterinarians are developing important roles is environmental pollution. Veterinarians are frequently in the position to be the first to detect health problems resulting from pollution since such disorders often surface initially in animals. This point is well illustrated in the case of heavy metal toxicosis resulting from soil pollution, in the region of Palmerton, PA, located in Carbon County, in the Allentown vicinity.

About five years ago, Dr. Rennie C. Shoop (V'73), a practitioner, noted the occurrence of what he considered to be some strange metabolic problems in horses and cattle. The animals exhibited unthriftiness, fatigue, lameness, and, in some cases, spontaneous fractures. Horseowners complained that it was impossible for them to raise animals on local forage because foals developed severe lameness and unthriftiness.

As a result of Dr. Shoop's observations and soil surveys conducted by the United States Department of Agriculture (USDA), some faculty members of the School of Veterinary Medicine became involved in the problem. These included Dr. Diane Gunson, assistant professor of pathology, Dr. David Kowalczyk, assistant professor of pharmacology and toxicology, and Dr. Charles Ramberg, associate professor of nutrition. Studies by this group are still in the early stages, but have progressed far enough to indicate that there is a link between zinc and cadmium contamination of the soil with the severe lameness and other disorders observed in Palmerton.

A large zinc smelting plant is located near Palmerton, and, in 1975, a USDA study showed that soil within a ten-mile radius of the plant contained sixty to seventy-five times the normal content of cadmium. It is known that cadmium is a byproduct of the smelting operation. Further studies, in 1975 and 1977, by the U.S. Environmental Protection Agency showed significantly increased levels of cadmium in the hair and blood of children living in the area.

Recently, Dr. Gunson autopsied three horses from the Palmerton region. Two of these were foals that had been born and raised on locally-grown forage. They had a history of stiffness, severe lameness, and marked unthriftiness, with swollen and painful joints. An autopsy indicated severe osteoarthritis, with lesions similar to those observed in experimental animals that were fed high zinc diets. The joint lesions consisted of rarefaction, separation, loss of areas of cartilage, and swelling due to accumulation of synovial fluid. The foals also showed osteoporosis, and in one animal there was severe nephrocalcinosis. In another animal the bone marrow was gray and gelatinous, rather than the normal red color.

These findings are compatible with cadmium toxicosis. The dam of one of these foals had died following puncture of the lung associated with rib fractures. Although there had been no history of injury. On autopsy the mare showed nephrocalcinosis which is consistent with cadmium toxicosis. High concentrations of zinc and cadmium were found in the pancreas, liver, and kidney of these horses.

Because various heavy metals, such as lead, sulfur, zinc, and cadmium exist together as pollutants from smelting operations, it is difficult to specifically identify which are involved in producing particular clinical signs or pathological changes. The picture becomes more complicated by the fact that these heavy metals have some complex interactions in the body. For example, it is known that prolonged high intake of zinc may lead to a copper deficiency. Despite these complexities, and the obvious need for further studies, the findings in these animals point to cadmium and zinc toxicity, and, probably, a secondary copper deficiency. Copper is involved in the production of collagen crosslinks in the body. Collagen is necessary for the formation of the connective tissue, and one pathological change observed in copper deficiency is osteochondrosis. This study also illustrates the importance of considering species differences in evaluating environmental pollution. Horses and some other species, are known to store cadmium in the kidney cortex, and this could explain the nephrocalcinosis in two animals, since cadmium toxicity leads to proteinuria and the formation of calcium phosphate crystals.

Apparently cows do not store cadmium in this manner, and autopsies of cattle from the Palmerton area revealed an absence of nephrocalcinosis. Cattle also showed low levels of stored cadmium despite high levels of the metal in hay from these farms.

To further study the problem of soil pollution in the Palmerton area, Dr. Gunson and her group have acquired five pony foals which are being raised in the area on local herbage. Dr. Gunson indicates that the reduction of pollution level will be reduced. The problem is that heavy metals remain in the soil for many years and will continue to be present in herbage. One possible treatment for animals ingesting forage contaminated with cadmium and zinc would be to supplement the diet with copper. This is being tried on one Palmerton dairy farm.

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A Special Cat

The cats living and playing in bright sunny quarters on the second floor of the new veterinary hospital are unaware of their importance to medical research. These Siamese and domestic shorthaired cats provide animal models for the study of lysosomal storage diseases, a rare group of disorders affecting humans. The colony was established several years ago after a young Siamese cat, seen at the clinic, was diagnosed as having mucopolysaccharidosis (MPS), a lysosomal storage disease caused by a defect in glycosaminoglycan (GAG) metabolism.

It was the beginning of an extensive, continuous research effort by the section of medical genetics and pathology at the Veterinary School, involving the support of virtually every department here, as well as researchers in the division of medical genetics at the Mount Sinai School of Medicine, New York, N.Y.

Mark E. Haskins, V.M.D., Ph.D., assistant professor of pathology and medical genetics, is one of the investigators of MPS, its occurrence and manifestations in cats, and how this compares to the disease in humans. The research has caused him and the other investigators to delve into the function of the body, not only in terms of organs, but in terms of cells and molecules.

Dr. Haskins explained that the life of an organism depends upon a multitude of chemical reactions taking place in each cell. Cells are highly specialized chemical factories. Each, in order to fulfill its function, depends on the catalytic role of enzymes. These complex molecules form coiled, folded, three-dimensional chains. Each enzyme differs in function, its properties determined by the number and type of amino acids it contains, their sequence, and the spatial arrangement of the chain. Enzymes do not occur randomly but are specific to each cell type. The production of all enzymes is controlled by the genetic material.

Enzymes act as catalysts on specific chemical bonds: one can think of them as a key working a specific lock. Degradative enzymes break bonds in a set sequence and if one enzyme in a cell fails to work properly, the other enzymes needed to facilitate a complete chemical reaction will not function. A faulty enzyme may block the process of breaking down molecules and these, then, often are trapped within the cell.

This happens in MPS. The DNA in affected individuals has changed slightly and a faulty enzyme is produced. MPS patients lack the ability to break down GAG. The cells cope with the dysfunction by storing the GAG molecules in their lysosomes. The accumulation of material causes the cells to enlarge and this may interfere with their proper function. The error, occurring on the cellular level, has serious consequences for the organism, be it human, cat, or another species.

MPS manifests itself with varying severity, depending on the enzyme deficiency
Colony

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Colony involved. The Siamese cat was diagnosed as having MPS VI, one of the less severe forms of the syndrome. The most severe form of these diseases is Hurler syndrome, a form of MPS I, which causes mental retardation in humans and leads to death in the first decade of life. This syndrome has been identified in cats also. There are dozens of lysosomal storage diseases in humans, eleven have been identified in animals so far, six of those in cats. The development of animal models permits researchers to study the problem in depth and on a large scale. Cats reproduce quickly, and the disease can be observed as it progresses in the animal throughout its life.

The colony of cats at the Veterinary School consists of four distinct families. The original stock was Siamese; the cats in the colony now are results of crosses between afflicted cats, carriers, and healthy domestic cats. The disorder in cats, like in humans, is an autosomal recessive trait. A method has been developed to accurately identify carriers through a blood test, a test which is equally effective for carrier identification in people.

Researchers found that the enzyme aryl-sulfatase B, defective in MPS VI, differs in structure in cats from the same enzyme in people. In cats it is a dimer and in people it is a monomer. The disease in cats appears due to an inability to make the two-part dimer structure and this distinct characteristic permits partial restoration of the enzyme's function through the administration of a drug, cysteamine. This drug, by breaking the disulfide bonds, restores partial enzyme activity for short periods of time in affected cats. Work is in progress to determine the dosage needed for a long-term effect. While these findings help cats, the drug is not effective for people and the search for a solution continues.

Such a search is also under way for relief for MPS I patients, a form of the disease which affects the brain because GAG is stored in the neurons there. A second colony of cats, affected with MPS I, was established at the School after the disorder was identified in a domestic shorthaired cat. These cats show the same physical symptoms and cellular evidence as human MPS I patients, though they appear to be relatively normal in behavior. Dr. Haskins explained that it is difficult to assess mental retardation in animals.

In MPS I, the deficient enzyme is alpha-L-iduronidase. The disease occurs in three distinct clinical syndromes in humans. The most severe form is Hurler syndrome, with neuron involvement. The mildest form is the Scheie syndrome. Here the patient has corneal clouding and some bone involvement, however, retardation is not evident and these people have a relatively normal lifespan. The third syndrome is Hurler-Scheie syndrome which lies in severity between the other two. Once again, retardation may not be evident.

The Hurler syndrome, because of its severity, presents a special challenge. Dr. Haskins explained that one approach which might help such individuals would be the introduction of the normal enzyme into the body. However, there are a number of problems which must be solved first. It is difficult to obtain the enzyme, to purify it, and to prevent an immune reaction. Also, once the enzyme is injected, it is quickly taken up by the liver and very little reaches other cells. The injected enzyme, because it is a large molecule, cannot cross the blood brain barrier and thus cannot reach the affected neurons.

The ideal treatment would be genetic engineering, to repair the defective DNA, but that is not feasible at present. Another approach is the transplantation of healthy bone marrow cells which contain normal DNA.

It was this option which researchers at Penn selected. They plan to transplant healthy bone marrow into an affected cat. Before they could proceed additional research was, and is necessary. Little information about the immune system of cats existed and the compatibility testing had not been done. The cat's immune system was investigated and the team is now developing the technology and protocol to accomplish bone marrow transplants in cats. They have transplanted bone marrow into a healthy cat and are now observing it for immune reactions. Once they feel they have all the information necessary, they will attempt transplants in cats with MPS I in the hope of arresting the disorder. This work has important implications for human patients with the disease.

The two animal models are invaluable to the in-depth study of lysosomal storage diseases. Many of the findings would not have been possible without these models. The discoveries made so far were made jointly by researchers in the department of medical genetics and pathology of the Veterinary School and by Robert J. Desnick, Ph.D., M.D., of the Mount Sinai School of Medicine. Dr. Desnick studies these diseases in children. The medical genetics group here at the School, the only one of its kind affiliated with a veterinary school, is headed by Dr. Donald F. Patterson. Another member of the section, Dr. Peter F. Jezek, also oversees the screening program for metabolic diseases at Children's Hospital of Philadelphia. The group also is part of the Genetic Center at the University of Pennsylvania. The research is supported by grants from the National Institutes of Health and the March of Dimes Birth Defects Foundation.

The work with the two cat colonies was and is accomplished by utilizing the resource of many departments here at the Veterinary School and at the Mount Sinai Medical School. It is a multidisciplinary effort, reaching well beyond the boundaries of traditional veterinary medicine.