Glycogen Storage Disease (GSD IV) in Norwegian Forest Cats

by John Fyfe, DVM, PhD©

In November of 1994 the Norwegian Forest Cat Fanciers Association celebrated the 15th anniversary of NFC breeding in North America with a specialty show in Wilmington, DE. I was very pleased to be asked to speak to the assembled association members on the subject of genetic disease in NFC. In 1988, while an instructor in the Section of Medical Genetics at the Veterinary Hospital of the University of Pennsylvania, I was asked by the neurologist to examine two related NFC exhibiting a disease which had never been seen in cats in this country before (or elsewhere, as far as I know). Two things happened in the ensuing weeks: I became very enamored of this breed of cat, and this new disease became one of my primary research interests. I intend to describe in this Skogkatt article what we have learned in the past six years with the hope of making NFC breeders aware of the disorder and to shed some light on the research process.

A 10 month old male and a 12 month old female were brought to the hospital together. They had been raised in different households and appeared perfectly normal until about 5 months of age. Later on a third kitten from another part of the country, but sharing some of the same ancestors, was taken to another veterinary teaching hospital for diagnosis. A fourth cat was euthanized without diagnosis by a local practitioner. All of them had an identical onset and course of disease. The first signs were a fine muscular tremor and elevated body temperature. The fever did not respond to antibiotics or corticosteroid therapy, and the tremors progressed over some weeks to muscle jerks. The cats became weaker and had more difficulty walking. Three months after the onset of the first signs, they could no longer walk because of muscle atrophy, weakness and contracture of some muscles, so that some joints of the legs could no longer move. All of the affected cats needed constant nursing care, including hand feeding and being held over the litter pan. One of the cats was nursed along at home, by the owners' choice, until 13 months of age, at which time the cat died with signs suggesting sudden heart failure. The other cats were euthanized because of their debilitated condition, and complete post mortem examinations were performed.

The results of microscopic examinations of the affected cat tissues suggested that the possibility of glycogen storage disease type IV (GSD IV) caused by lack of glycogen branching enzyme (GBE). This was confirmed in the laboratory by biochemical assay of tissues which were saved frozen at the time of euthanasia. Glycogen is the storage form of glucose in cats and other mammals. Several steps are involved in the formation and utilization of glycogen for normal health,

and each of these steps of metabolism is controlled by an enzyme. Enzymes are proteins that control chemical changes in biological systems, and the production of each enzyme is controlled by a unit of genetic disease, a mutation of the gene for GBE which abolished activity of the enzyme. Further laboratory studies have strengthened this hypothesis. The affected cats have no GBE protein in liver tissue, and recent findings demonstrate a defect in GBE expression. Of great importance are findings which show that most of the affected kittens are stillborn or die within hours of birth. Initially we surveyed a few NFC catteries, and despite several carriers having been mated in these catteries, there was no history of kittens affected with the syndrome described above. To further examine this phenomenon, we established a breeding colony of cats, founded by a known carrier male of GSD IV. Among several carrier-to-carrier matings, 11 affected kittens were produced. Only one of them survived birth, and that kitten went on to have the same disease onset and progression as was seen in the privately owned cats. The affected kittens were 21% of those produced, and male and female kittens were equally represented. The results of these breeding studies were fully consistent with enzymes recessive inheritance of GSD IV and indicate that each cat which produces an affected kitten, whether sire or queen, is a carrier of GSD IV. That such a large proportion of affected kittens are stillborn explains why we recognized so few affected kittens in the catteries we surveyed initially. Among purebred catteries in general, neonatal mortality from all causes as high as 20% is not considered unusual, and stillborn kittens are usually discarded without diagnostic studies. Fortunately, GSD IV can be diagnosed in stillborn kittens by special stains of formalin-fixed tissue. Therefore, if the problem is suspected in a cattery, all stillborn kittens or kittens dying within a few hours of birth should be examined immediately by a veterinarian.

There is much concern about GSD IV among NFC breeders for several reasons. Loss of 25% of kittens, on average, in carrier to carrier matings is certainly an economic loss. More importantly, however, affected kittens which survive birth and begin kittenhood normally create a terrible emotional loss for the family which purchases them when the inevitable disease process begins. Obviously this creates bad publicity for the NFC breed, for the particular breeder, and for the purebred cat fancy in general. Witness the recent Time magazine article attacking the AKC (Dec. 12, 1994). A very important point to remember is that genetic disease occurs in all breeds of cats and dogs. There is nothing shameful about the occurrence of GSD IV in NFC. What would be shameful, however, would be to do nothing about it.

What can be done? At this time, nothing can be done to treat the affected kittens. The disease process appears to be inevitable and lethal. Responsible efforts have to be made to prevent producing affected kittens, and it is important to take a long view of the process. As with all recessive diseases, the difficulty is in positive identification of carrier cats. Whenever a carrier is bred, one half of the offspring will be carriers. As generations pass, the likelihood that carriers will

be mated together increases. When carriers are mated together, 25% of the offspring, on average, will be affected, and two thirds of the clinically normal kittens will be carriers. If carriers can be determined with accuracy, they can be prevented from contributing to the genetic burden of future generations. With accurate carrier detection, carrier cats can be neutered and sold as pets or, if necessary to preserve desirable traits, they can be bred to non-carrier cats and the offspring tested for carrier status.

We are presently working on developing a DNA-based blood test for carrier detection. My present institution, Michigan State University, has supported this effort with a ten-thousand dollar grant. The test will be designed to be performed on a few drops of blood which can be sent through regular mail either dried on filter paper or in a collection tube. We hope that such a test will cost under 50. If there is widespread participation in such a testing program, GSD IV can be eliminated from NFC in a relatively short time. If breeders do not take responsibility to eliminate carriers from breeding stock, the disease prevalence will inevitably increase.

One may ask how it is that a disorder in an uncommon cat breed, which seemingly affects few cats, attracted the attention of researchers and the commitment of funds. There is a longstanding awareness that humans and cats (and dogs, mice, rats, cows, etc., for that matter) are much more alike physiologically and genetically than they are different. For this reason, the National Institute of Health, whose mission is to investigate causes and treatments of human disease, has long provided funds for investigation of appropriate animal diseases. Animal studies were essential in the conquering of polio, smallpox, rickets, and other previously common diseases of infectious or nutritional origin that we don't think much about these days. Individual human genetic diseases are so rare that controlled studies aimed at better diagnosis and treatment are often impossible without animal studies. When a genetic disease occurs spontaneously in a family of cats, as in this case, it presents a unique opportunity to observe the disease and attempt therapeutic interventions that may later be applicable to human patients. A happy circumstance is that in so doing we learn a lot that is applicable to diagnosis and carrier detection of the animal disease and to the practice of veterinary medicine.

We are all concerned about the cost of health care these days, and sometimes people suggest that spending money to investigate rare genetic disease is a waste of resources. In truth, however, this is sometimes the best spent money. For example, over the lifetime of a single infant with an inherited metabolic disease called phenylketonuria (check your cans of diet soda), which becomes severely mentally disabled due to lack of early diagnosis, costs to the health system are many times the cost of the neonatal screening program that is in place in most states. Although GSD IV is very rare in humans, the NH hope that what we learn about the NFC disease will advance human medicine. The spinoff

benefit to NFC and all who love them will be accurate and convenient carrier detection. This will provide the opportunity and responsibility to eliminate GSD IV from NFC.