Familial Kidney Disease

by Dr. Catherine Marley

Kidney disease. We all remember hearing about it, don't we. But it hasn't happened to OUR dogs. has it? So we don't worry about it. *After all, if I haven't had it in 20 years of breeding, it can't be carried in my line.* This represents the thinking of almost everyone you talk to about kidney disease, except the few who have had pups die from it, and they aren't talking at all.

The facts are frighteningly different from our perceptions. I recently contacted Dr. Ken Bovee, from the University of Pennsylvania, who had been doing research in this field for a number of years. I wanted to know if he had any advice for breeders regarding the inherited problem. His response was "Breed Labradors." He went on to say that though he had accumulated a good bit of data, including a number of test breedings, when he submitted it to the statisticians, they were unable to establish the mode of transmission.

If you think the problem will just go away, and does not concern your dogs, you may some day have a rude awakening. It is possible to breed Lhasas for over 20 years without having a single puppy sick from kidney disease, and suddenly have an entire affected litter. I know of such a case in a line which used mainly healthy older animals for breeding, and normally had large litters and very low infant mortality. (The assumption was that such breeding stock was unlikely to produce any genetic "surprises".) Renal biopsy of one healthy male from a previous litter from this bitch also revealed evidence of the typical lesion. This dog will never become ill, because his kidneys are only minimally affected. This diagnosis could only have been made by biopsy. (The bitch who produced these affected pups was herself proven, by biopsy, to be free of the lesion.)

Shortly after the first few breedings of Tibetan imports, breeders began to notice the occurrence of puppies which, at the time of weaning, urinated pale urine, drank large quantities of water, and later went on to develop clinical signs of kidney failure, ultimately dying of uremia. Over the past 40 years or so, efforts have been made to study this disease, and determine its causes. We have learned a few things. Others remain a mystery.

The actual lesion of the kidney in familial kidney dysplasia is a failure of maturation of the fetal kidney. In the dog, all pups are born with fetal kidneys, but by 8 or 10 weeks, normal puppies kidneys have differentiated further and resemble the adult kidney. In pups affected with the familial kidney disease, parts of the kidney fail to fully differentiate. On microscopic section we find areas of fetal kidney interspersed with normal kidney tissue. Sick puppies exhibit the well known signs of renal failure: failure to concentrate urine, resulting in large amounts of dilute urine, excessive water intake, vomiting, weight loss, failure to thrive. In older animals, early tooth loss, poor condition, malaise, poor appetite are additional symptoms.

However, many animals whose kidneys are affected show no sign of illness, nor are their blood or urine tests abnormal. All young mammals have at least 4 times the kidney tissue they absolutely need, so that pups who have less than 75% kidney function tissue appear normal and healthy often into advanced old age.

If familial nephrodysplasia is inherited as a simple somatic recessive gene, we can analyze the frequency of the various genotypes in the population in the following manner.

Definitions:
K = gene for normal kidneys (dominant)
k = gene for familial nephrodysplasia (recessive)
A = the frequency of the K gene
B = the frequency of the k gene

Since all the genes at each locus must add up to 100% (or 1.0), A + B = 1
therefore AK + Bk = 1
But each dog carries 2 genes at the locus concerned, so we have 3 possible genotypes,

KK = genotype of genetically clear animals
Kk = genotype of carrier animals who are biopsy negative
kk = genotype of affected animals (biopsy positive) - an unknown fraction of these appear to be perfectly healthy.

In familial kidney dysplasia, the affected state is difficult to recognize unless the animal is clinically ill. We believe that this is the case very infrequently, since over 75% of the kidney must be non-functional before the animal shows any recognizable signs of illness or abnormal test results in urine or blood. Therefore, the matings involving this allele must be very nearly random. In random matings, when a male with possible genes K and k is mated to a female with possible K and k, according to the familiar quadratic formula, the probable outcome is:
A^2 KK + 2AB Kk + B^2 kk

If the frequency of the genotype of affected animals is found to be 1%
then B^2 = 1/100 and B = 1/10

since B + A = 1, then A = 9/10

Substituting, we get: $(9/10)^2$ KK + 2(9/10 * 1/10) Kk + $(1/10)^2$ kk
or 81/100 KK + 18/100 Kk + 1/100 kk

Thus the incidence of:
the clear genotype is 81%
the carrier genotype is 18%
the affected genotype is 1%

Calculating gene frequency assumes 200 genes for 100 dogs, and would be the sum
(81 * 2)+ 18 = 180 or 90% of 200 : the frequency of the K gene = 90%
(1 * 2) + 18 = 20 or 10% of 200 : the frequency of the k gene = 10%

The implications of these numbers are ominous. Assuming a recessive mode of inheritance, if we biopsied

the kidneys of every healthy dog today, and found that 1% of them had even minimal evidence of kidney dysplasia, 18 % of the entire population are carriers. Since the obviously affected animals, (genotype kk) are probably recognized in only a small proportion of cases, the incidence of the affected state is probably greatly underestimated. The real number of affected dogs may be 10 or more times greater than the number who are discovered because they are ill from the disease. That means that if 1% of our dog population is being seen by the veterinarians because they are sick from kidney displasia, the actual incidence of the disease in clinically healthy, but biopsy positive animals, is probably closer to 10%. This would correspond to a carrier rate of about 44%.

If we had a reliable way of identifying the affected state, the kk individuals, and remove them from breeding, we could reduce the gene frequency by 50% in each generational cohort. For instance, If we started with a gene frequency of 50, that is 50% of the genes in the population were k, and 50% K and we discard all the kk individuals, theoretically we would be getting rid of one half of the k genes. The next generation would have only 25% k genes, the next generation, 12.5% and so on. by the 5th generation, the gene frequency would be down to 1%, and though it would continue growing smaller, the gene frequency would never reach 0.

An animal has to have less than 25% kidney function before routine screening blood tests show elevated levels of BUN and creatinine. As of this moment we lack a reliable means, other than surgical exploration and kidney biopsy, of identifying the great majority of affected animals. As a result, we can inadvertently use an affected individual multiple times, increasing the pathologic gene incidence in a relatively small population.

We badly need a non-invasive screening test which enables us to eliminate the affected animals which now go unrecognized. Any plan to eliminate the disease depends on knowledge of the incidence and mode of transmission. But you have to know what animal is carrying the defect before you can put any genetic information to use. The problem right now is the lack of a cheap, non-invasive method of identifying minimally affected individuals. Until you can screen animals for the defect, all the genetic information in the world won't help.

To quantify the incidence of cases, we should perform histopathology on the kidneys of all Lhasas who die or are put to sleep for whatever reason. While few people are willing to subject their seemingly healthy animals to renal biopsy, perhaps it should be considered on all the close relatives of sick animals or those animals found, on postmortem, to have the typical kidney lesion. This will enable us to have some estimate of the incidence of the kidney lesion, something completely unknown now. Once we have some idea of the incidence of the problem in a population, we have a means of evaluating possible screening techniques.

Techniques, such as radiological, ultrasound or radioisotopic are now being studied as an alternative to invasive biopsy. Abnormal kidneys may be recognizable by simple ultrasonic measurements of renal blood flow. The ultimate answer will be provided DNA research, which will be able to identify the carrier animals through the use of easily obtainable blood or skin cells . But all research on the feasibility of non-invasive diagnostic techniques depends on numbers of animals, normal and abnormal, available for testing. You hold the key to eliminating minimally affected animals from the breeding population. By ignoring the problem or pretending it doesn't exist, you contribute to the suffering and death of many Lhasas, and the distress of their breeders and owners. Only you can eliminate kidney disease. Ignoring it will not make it go away.