NOTE: This article was published in the July, 2005 Edition of Just Terrier Magazine

4/29/05
For: Terrier Magazine
Lily's Story (3,400 wds, 1 illustration)
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Lily's Story:
The push to control lens luxation in Sealyham Terriers

By George G. Packard
Director, GDC

One morning in 1997 a Sealyham Terrier named Lily hopped up on her owner's lap. It was one of those moments that dogs and their owners treasure, the prelude to a little bit of friendly nose-to-nose kibitzing. Lily was the mother of a fine two-month-old puppy, and the last thing on owner Sharon Yard's mind was lens luxation. But as soon as she looked into Lily's eyes Sharon felt a jolt of concern and apprehension.

Lens luxation is a genetic eye disease that affects a number of terrier breeds, and usually shows up in dogs between the ages of four and seven years. The fibers that hold the lens in place weaken and break and the lens literally slips, or luxates, to the bottom of the eyeball. The lens must be surgically removed in a matter of hours before increasing fluid pressure damages the retina and leaves the dog completely blind. Luxation almost always occurs in both eyes, though not always at the same time.

One of Lily's eyes wasn't right. There were deposits of a pus-like matter at the corners of the eye and something odd about the appearance of the iris. Sharon lifted Lily to the floor and went to the kitchen for a flashlight. Lily trotted after her, alerted by her owner's sudden concern. Sharon sat Lily on the table, and used the flashlight to peer into her dog's eyes, dreading what she might find.

Sure enough, she saw that the pupil was not contracting with the intense light of the flashlight, and as Lily moved her head, not at all pleased with the sudden examination, Sharon could see that the lens in one eye had a kind of wiggling movement.

Sharon had seen lens luxation before, and now had no doubt that Lily's eye was in the first stages of the disease. The lens was loose, but had not yet slipped from position. Sharon knew that she had to move quickly to save Lily's eye.

An all-too-common story

Chances are that if you breed purebred dogs Sharon's story may come all too close to home. If you haven't encountered a genetic disease in your own dogs, you probably know somebody else who has. At the very least you may have had nightmares about a problem showing up without warning in your line. There are, after all, some 300 identified canine genetic diseases, and experts estimate that almost every purebred dog is carrying a few defective genes.

Within minutes of discovering Lily's problem Sharon was on the phone to her veterinarian, who referred her immediately to a veterinary ophthalmologist. The ophthalmologist confirmed the diagnosis and put Lily right into the operating room.

Even though she was worried sick about Lily, while she waited Sharon forced herself to collect her thoughts about what this crisis meant. First, she felt devastated. She knew, of course, that she shouldn't blame herself as a breeder. She had done her best and had tried to get as much information as possible about any hint of lens luxation in the families of the dam and sire before she bred.

[PULL QUOTE]

"Suddenly Lily's pedigree seemed haunted by that hidden gene."

Sharon called up a mental picture of Lily's pedigree. If Lily was affected, then both of her parents were carriers of the defective gene. And at least one dog in each pair of grandparents would have to be a carrier, as well. (The mode of inheritance for lens luxation has not been proven, but most researchers believe that it is caused primarily by a single defective gene and that it is a recessive trait. A dog can carry one copy of a recessive gene but show no signs of the disease. With a dominant trait, a dog only needs to be carrying one copy of the defective gene to become affected.)

Sharon owned Lily's mother, whom she now knew was a carrier. (Lily's mother lived to age 14 without showing any signs of lens luxation. The fact that dozens of other confirmed carriers have also lived into old age without developing the disease is strong support for researchers' belief that lens luxation is a recessive, rather than dominant, trait.) Even if a carrier is bred with a non-carrier, several of the puppies in the litter will be also be carriers. Suddenly Lily's pedigree seemed haunted by that hidden gene.

But Sharon realized with a start that her most immediate concern was with Lily's other siblings. She would need to call the owners of Lily's brothers and sisters within the next few days, and explain that there was a strong probability that one or two more siblings could become affected. Those would be hard calls to make, and she hoped that she would find that none of the other siblings had been bred. (As it turned out, she was too late. Lily's sister had already been bred, and several affected dogs were produced in that litter).

The Sealyham Terrier is a very small breed in terms of numbers, though not in terms of spirit, as any owner will quickly attest. The breed also has the distinction of being troubled by a relatively low number of serious genetic diseases, but a late onset disease like lens luxation can be difficult to control because dogs may be bred many times before they become affected (usually from 4-7 years of age).

Sharon and other members of the American Sealyham Terrier Club (ASTC) knew that the sporadic cases of lens luxation appearing throughout the breed meant that the prevalence of carriers was probably higher than anybody realized. The club would need to move aggressively to find a way of controlling the spread of the defective gene.

Learning to Use the Tools

By 2003, after several years of hard work and with Sharon now as president, the club had put together an awareness-building campaign among breeders and owners, enrolled the breed in a DNA research study through the AKC Canine Health Foundation, and created SIGHT, the Sealyham genetic eye diseases registry.

Publicity, gene research and registries are the three basic tools that many breed clubs are now assembling in an attempt to deal with their particular genetic disease problems, but what does this really mean for the individual breeder? How do programs like these get translated into fewer affected dogs, and fewer carriers in the gene pool? The partial answer is, "Slowly and only with a huge amount of work to support the already-committed breeders and to win over the reluctant."

[PULL QUOTE]

"You can prevent autosomal recessive [single-gene] genetic diseases every time you breed if you know what genes your dogs have."

--George A. Padgett, DVM

Publicity is a tricky business in the best of times, but trying to warn people about the threat of a genetic disease without being able to offer a magic pill is an uphill slog. People, for good reason, tend to avoid bad news, especially if there doesn't seem to be much that you can do about it.

Around 2001 the ASTC began putting articles and notices in every newsletter about lens luxation and the DNA study being conducted by Dr. Gary Johnson's research group at the University of Missouri. Active club members called owners personally to encourage the donation of blood samples for the study. In 2003, with the creation of the SIGHT eye diseases registry, the club turned up the volume on publicity with mailings, brochures, a new website, one-on-one discussions with key breeders, and more articles.

Response was lukewarm to moderate. As breeder Laurie Prather wrote in an article published in the ASTC newsletter, "The Sealy Barks," in the summer of 2003, after discovering that one of her own dogs was affected,

> "…the ASTC has been issuing a lot of press about Lens Luxation. I am the first to admit that I had not taken the news seriously, simply glancing over the literature and discarding it. I frankly thought all this talk about Lens Luxation and the SIGHT Registry was much ado about nothing. I thought the eye exams would be a profound waste of time and money. Sure, the ASTC has beat the drums about Lens Luxation for awhile now, but I thought Lens Luxation was someone else's problem, and certainly would not be a problem in any of my dogs!
>
> I was skeptical about the research project, and even more skeptical about the SIGHT "open registry." Since I'd never seen it in any of my dogs, I thought the problem might not be such a big deal in the breed. But, as I look back on my discussions with others in the Club, I think the biggest factor in avoiding the tests was my fear of gossip. Would bad news be broadcast far and wide? After all, an "open registry" is open to everyone, and there is no hiding of problems. Or worse, would the news cast an aspersion on the health of my dogs and my credibility as a breeder? I was aghast at the idea of an open registry.
>
> …My husband and I talked a great deal about the implications of filing the eye exam results with the Registry, and in our discussions, we talked about pedigrees of various dogs and resulting lens luxation problems. The more we talked, the more we realized that lens luxation is a SERIOUS problem in our breed and it affects far more dogs than we ever realized. We wondered if it would become increasingly difficult, if not impossible, to breed around suspected carriers and offspring of suspected carriers. That realization casts a wide, dark shadow. I realized that it would be impossible to have a successful breeding program if we all hide our heads under the covers…"

So Laurie decided to take several of her dogs for CERF exams and to register them with SIGHT. And it was at that exam that she learned that one of her dogs, with tragic irony, was in the early stages of lens luxation.

Waiting for the gene

Even though at times it seemed that no one was listening, the ASTC publicity had indeed produced a higher level of awareness about lens luxation in the club. An Eye Health Survey mailed in the fall of 2004 produced dozens of new SIGHT registrations including several more affected dogs (two of which were from England).

In early 2005 the ASTC learned that the University of Missouri research team was planning a new gene mapping study using better data just released from the dog genome study. To be included in the new research the Sealys needed as many blood samples as possible from affected dogs and their very close relatives.

Fortunately, the constant drumming of information and the gradually increasing concern on the part of owners and breeders had prepared the way for this renewed quest for blood samples. During the early spring, the club pushed hard to find those key dogs, and to encourage their owners to provide samples. The response was strong and generous.

As of this writing (May 1) the total number of samples available to the lab had reached nearly 60, including many carriers and a dozen affecteds from the US and UK. More samples were expected to come in during May. At this point it seems possible that the Sealys will be a part of the new research study. But that is still no guarantee that the breed will soon have a gene test available for lens luxation.

Ten years ago the purebred dog community embraced gene discovery as the long-awaited savior of canine health, and blessed the arrival with huge (in terms of the dog world) amounts of money. But progress in actually finding disease genes has not been as rapid or as consistent as most people had expected. We still have fewer than three dozen gene or marker tests, and those are erratically scattered throughout the breeds. None of the tests are for the most serious and widespread polygenic problems (diseases caused by the complex interaction of many genes) like hip dysplasia or epilepsy.

There simply aren't enough researchers working on canine genes, and not enough money, with the exception of cases where there's an obvious and profitable connection between a particular human disease gene and a similar gene in dogs. The chances that any given researcher looking for a canine disease gene will succeed are quite small. At the same time, however, new methods, new technology and access to the huge amount of new data from the recently sequenced dog genome will bring research costs down and improve the probabilities for success across the board.

What is a breed club to do?

In addition to publicity and gene discovery, the third tool to which the Sealyham Terrier club, like many clubs, is now turning is the collecting and sharing of health information in an open genetic disease registry.

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> **"When there is no genetic test for carriers, the most objective tool for selection against recessive disorders is a relative-risk pedigree analysis."**
>
> Jerold S. Bell, DVM

The idea behind an open health registry is simple: When you can identify most of the dogs in your breed that are affected with the disease(s) you are concerned about, then you also know that the parents of those dogs have a high probability of being carriers. And then you can calculate carrier risk for many other dogs. With a knowledge of carrier risk, you can make informed decisions about breeding and apply selective pressure against the genetic disease.

Getting enough dogs into a registry and showing breeders how to use the data is difficult but achievable. Several breed clubs have actually used the method to make a difference in the prevalence of a targeted genetic disease within a few years, or in some cases within just a couple generations of dogs. The national kennel club in Sweden was the first to show the effectiveness of the method by achieving a significant reduction in hip dysplasia over a several year period in the late 1980s.

[SIDEBAR]

For examples and for a full explanation of methods read Dr. George Padgett's book, Control of Canine Genetic Diseases, (Howell Book House 1998).

For information on establishing breed-wide health registry programs, talk with the Orthopedic Foundation for Animals (OFA) about CHIC (Canine Health Information Center) (www.offa.org).

The Institute for Genetic Disease Control (GDC) is also a good source for information about creating and sustaining health registries. GDC pioneered the use of open registries in 1989, and is now involved in small single-disease registry projects such as the Sealyham SIGHT registry (www.gdcinstitute.org).

OK, so let's say your club — with a thrilling display of unanimity, commitment and action — has managed to put a significant number of dogs into a registry. What can you actually do with that information?

The registry can serve a number of masters from researchers to genetic counselors, but from a breeder's point of view, pedigree risk analysis should be at the top of the list.

As Jerold Bell, DVM, a veterinarian, researcher and genetics counselor says, "When there is no genetic test for carriers, the most objective tool for selection against recessive disorders is a relative-risk pedigree analysis. This information enables a breeder to assign risk factors to dogs within a pedigree and to determine the risk of producing a carrier or affected dog in the next generation. The goal of this analysis is to plan matings that have carrier risk below the average of the breeding population. This also will help to lower the carrier rate for the breed."

You may want to read that paragraph a few more times. I read dozens of Dr. Bell's articles before I met and talked with him, and even now I am always asking him to go back and explain in more detail what he just said.

So needless to say, there's quite a bit more to risk analysis than we can go into here, but let's wind this article up with a very brief introduction to the subject and to a way of graphically displaying family relationships known as the genetic pedigree.

The Genetic Pedigree

If this is your first introduction to a genetic pedigree, hang in there just a couple of minutes before you let your eyes glaze over.

I promise you it's worth it, because there's no better way to visualize the complex relationships in a line of dogs.

This particular genetic pedigree (Fig. 1) is a small one based on data in the SIGHT registry that includes ten dogs affected with lens luxation. (I have redrawn some of the relationships to disguise the actual pedigree). A large pedigree can include 100 or more dogs, and if there are multiple matings with very popular dogs involved, it can look, on first viewing, like a vast tangle of lines.

SIGHT does not have enough dogs registered yet to be able to create comprehensive pedigrees, but even at this point you can gather some very important information if you were interested in one of the dogs in this kinship group.

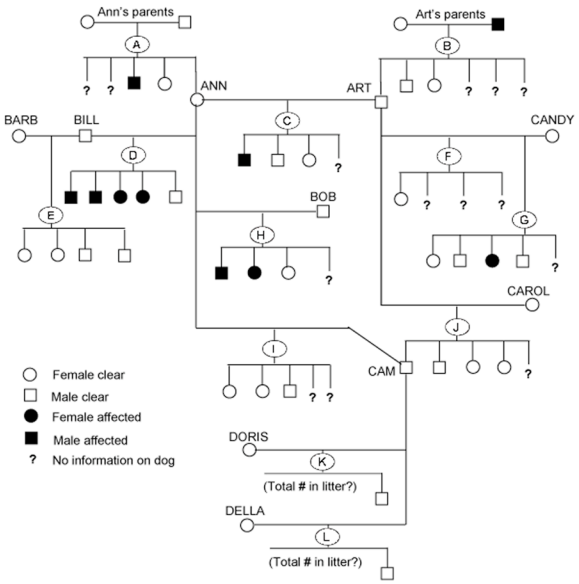

Fig. 1 Genetic pedigrees allow breeders to analyze complex relationships among related dogs and to estimate the carrier risk for any particular dog or the risk of affected dogs appearing in any litter.

First, a quick lesson in how to read the pedigree. Circles are females, squares are males. Black circles and squares are affected dogs. Parents are usually tied together with a horizontal line (although for clarity the connecting line between two mates may snake around quite a bit), and offspring are tied to the parents with a vertical line.

Because many researchers feel that lens luxation is caused by a single recessive gene, we are assuming that both parents of an affected dog must be carrying a copy of the defective gene. You can write a “c” by each parent of an affected dog.

Furthermore, one or both of the parents of a carrier must also be carrying the gene. (Contrary to what you may have heard, genes do not “skip” generations.)

As you examine this pedigree, you can put a “c?” by each parent of a carrier, because you know there is at least a 50 percent chance that it is a carrier as well. You would want to avoid breeding either of those at-risk parents to a known carrier, because there would be a significant risk that such a mating would produce an affected dog and several more carriers.

Take another look at the known carriers in the pedigree. It’s very possible that they may have been bred to other dogs who are not registered with SIGHT, and who therefore don’t show up on this pedigree. If you were interested in breeding to one of the puppies from one of these litters, you would need to roll up your sleeves and do whatever you needed to do to find out whether the carrier’s mate was a carrier herself (i.e. has she ever produced an affected puppy?)

We could spend a lot of time with this pedigree alone, but here’s just one more observation.

Bill and Ann produced Litter D. Ann and Art produced Litter C. And Art and Carol produced Litter J. Bill, Ann and Art are all carriers, because they have all produced affected dogs.

But what about Carol? We know that four puppies from Litter J are not affected. But there’s a fifth puppy in the litter that is not in the registry. If you were interested in breeding a dog with Carol you would want to do everything you could to find out if Puppy #5 was affected or not. If he isn’t affected, the chances of Carol’s being a carrier are substantially reduced.

And finally, notice that Cam, from Litter J, was bred back to Ann, a carrier. Cam’s father is Art, a known carrier, which puts Cam at significant risk for being a carrier. So what are the probabilities that any of the puppies in Litter I are carriers? (If you know the answer without any more coaching, give me a call and I can get you full time genetic counseling work on the spot.) A genetic counselor can make those calculations, and the risk analysis could be a helpful guide to you in making a breeding decision.

Did anybody say that breeding dogs was going to be easy?

Let's close with the reminder that Dr. Jerold Bell is constantly giving breeders:

"**Remember that you are selecting against defective genes, and not defective dogs.** You need to be able to preserve as many of the good traits of a particular dog as you can. So you can use the genetic pedigree to analyze the risk of whether or not a particular mating will increase or decrease the probability of producing carriers and affecteds. You may be able to preserve the traits you need from a sire, but you can select against genetic disease in his line by mating him with a dam with a very low risk for passing along the defective genes. (But you must evaluate the puppies!)."

For more information on creating and using genetic pedigrees, contact George Packard, GDC Director; Email: gdc@conknet.com

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