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**SHEDDING LIGHT
ON A HIDDEN
HEART DISEASE**

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ABOUT THE COVER:

Mark Oyama, DVM, with Stanley, a Doberman. Dr. Oyama, a professor of cardiology at Penn Vet, is working to ensure a heart disease, commonly found in Dobermans, is controlled as effectively as possible.



SHEDDING LIGHT ON A HIDDEN DISEASE

BY KATHERINE UNGER BAILLIE

Doberman pinschers are stately, strong and intelligent, seemingly unflappable. Yet members of this breed are more likely than any other to succumb to an insidious, inherited condition that can silently kill.

Dilated cardiomyopathy (DCM) is the second most common acquired heart disease seen in dogs, behind mitral valve disease. It's particularly prevalent in Dobermans.

"As many as 40 percent of Doberman pinschers are going to get dilated cardiomyopathy at some point in their life," said Mark Oyama, DVM, a professor of cardiology at Penn Vet. "So clearly it's a big problem for the breed."

DCM, which is typically an inherited condition in canines, also commonly strikes other large breeds such as Irish Wolfhounds and Great Danes. Fortunately for these dogs and their owners, Dr. Oyama is one of a growing number of researchers with a goal of finding better ways to screen and treat pets that have or are likely to develop DCM.

Among the challenges of this pursuit is the disease's hidden nature.

"Oftentimes a dog will be developing or have dilated cardiomyopathy and yet show no outward signs of it," said Dr. Oyama. "So you have owners who think their dog is completely normal and yet they're walking around with heart disease."

Sometimes, the first overt sign that a dog has DCM is it suddenly collapses and dies. But many dogs do display symptoms, which may include labored breathing, coughing,

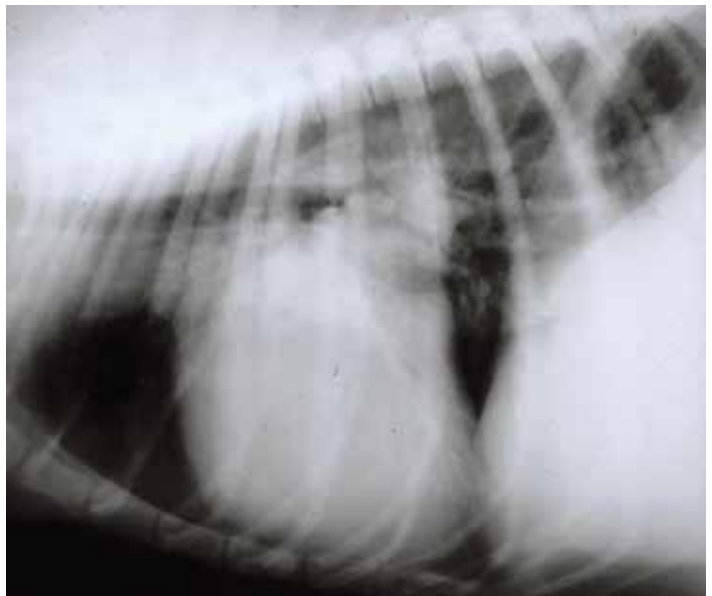
fainting, exercise intolerance, restlessness and lethargy. All of these result from the central feature of DCM, which is the weakening of the heart muscle.

While researchers don't fully understand the mechanism of disease, they do know it has to do with a malfunction in the way that heart muscle cells operate at their fundamental or cellular level. As a result of these disruptions on the molecular and cellular levels, the chambers of the heart dilate and their walls thin. The heart's pumping action weakens and fails to adequately circulate blood through the body. This, in turn, leads to congestive heart failure.

Sudden cardiac death can occur without any previous symptoms because a heart damaged by DCM may beat in an abnormal rhythm and arrest. The disease can be devastating for dog owners who would have otherwise expected to have several more years with their pet; DCM can strike Dobermans as young as two years old and most dogs die within a year of diagnosis.

TOWARD EARLY DIAGNOSIS

Currently, the gold standard for DCM diagnosis is to perform a cardiac ultrasound (echocardiogram) and to monitor the heart rhythm for 24 hours with an ambulatory electrocardiogram, known as a Holter monitor. These screenings are not inexpensive and while the expense may be justifiable for the owner of a single Doberman, it could be prohibitive for breeders who may wish to screen many dogs at once.



An X-ray of a dog's heart with DCM.

The stakes are high for early diagnosis, because veterinarians can intervene with drugs such as pimobendan, beta-blockers, diuretics and ACE inhibitors that can slow the disease's progression. Thus, much of Dr. Oyama's research on DCM has focused on developing more accurate and less expensive ways to diagnose the disease.

"One of the things that we looked at most recently is trying to find out if you could do a blood test that would help you decide if your dog has a high likelihood or a low likelihood of having cardiomyopathy," said Dr. Oyama. "That would provide a kind of middle ground between doing nothing and doing a full-blown diagnostic workup."

In a publication just out in the *Journal of Veterinary Internal Medicine*, Dr. Oyama and former Penn Vet resident Gretchen Singletary, now a veterinary specialist at Cornell University Veterinary Specialists, along with colleagues, describe a blood test that can help discern whether a dog is in the early stages of DCM. Examining 155 asymptomatic dogs, the researchers measured blood concentrations of N-terminal pro-brain natriuretic peptide, or NT-proBNP. The heart releases this peptide when it is under stress, and other researchers have used it as a marker of cardiac dysfunction in humans.

In the study, the researchers found that dogs with high levels of NT-proBNP were more likely to have DCM and had much shorter survival times than those with lower levels. This assay alone, however, did not always reliably predict a dog's likelihood of being diagnosed with DCM without an ECG. A solution to the lack of sensitivity was to pair the blood test with



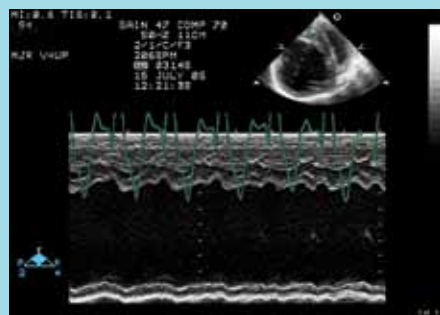
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TREATING HEART DISEASE WITH GENES

While Dr. Mark Oyama seeks better ways to determine whether or not a dog has dilated cardiomyopathy (DCM), Meg Sleeper, VMD is refining approaches to treating DCM and other heart conditions that may restore near-normal function to the heart muscle. What she finds may reach beyond the veterinary profession to improve human lives as well.

For nearly a decade, Dr. Sleeper, associate professor of cardiology, has worked with colleagues at Penn and elsewhere to develop gene therapy techniques to treat cardiac disease in dogs and cats. Gene therapy aims to correct disease-causing genetic abnormalities by using a non-pathogenic virus to “infect” specific cells in a patient with a healthy version of a gene.

One beauty of the approach is that researchers needn’t understand the exact molecular pathway that goes awry — and for DCM, scientists don’t yet have this detailed knowledge. Instead, they can zoom to the end of the pathway, correcting the ultimate problem. For DCM, that means targeting the protein pump that shuttles calcium in and out of cells. Using gene therapy that helps boost levels of calcium inside the cell, researchers can ensure the heart muscle maintains strong contractions, staving off congestive heart failure.



Cardiac ultrasound of a dog with DCM.

“With gene therapy what we’re doing is trying to get the heart muscle to produce a protein of interest,” said Dr. Sleeper. “So instead of having to give a drug every day, the muscle cells just produce the molecule, in essence becoming the drug manufacturer for us.”

Two different genes have functioned as these genetic “drugs” in Dr. Sleeper’s early trials. One, called S100A1, enhances calcium movement into heart muscle cells. The other blocks the activity of the gene phospholamban, which normally reduces movement of calcium into cells. The initial tests, conducted in about 60 dogs, look promising.

“With the studies we’ve done so far we can get about 60 to 70 percent of the heart cells to express the genes we’re introducing,” she said. “I’m hopeful that that is enough for a dog with DCM to experience a big difference in their heart function.”

This initial phase of testing has also shown that the treatment is safe in a variety of canine breeds, most of which did not have DCM. Dr. Sleeper now has grant applications submitted with the hope of experimentally treating Dobermans that do have DCM. Not only might success in these trials bode well for dogs with DCM, but also in humans with DCM and other heart conditions.

“If it turns out that we get really great results with either phospholamban or S100A1 or both, then I think that gives researchers really useful information for treating humans,” Dr. Sleeper notes.

In people, DCM can be inherited but can also develop after a heart attack or coronary disease. DCM can also be one symptom of Duchenne muscular dystrophy, which affects one out of every 3,500 boys and is caused by a mutation in the dystrophin gene. Together with Lee Sweeney, PhD, the William Maul Measey Professor and chairman of physiology at Penn Medicine, and others, Dr. Sleeper has used gene therapy to correct the problem in the muscle tissue of dogs with the disease — an important animal model for humans with muscular dystrophy.

Breakthroughs that rely on gene therapy are steadily increasing in number. Another one of Dr. Sleeper’s collaborators, Penn Vet’s Mark Haskins, VMD, PhD, has had excellent results replacing a malfunctioning enzyme in dogs with a devastating lysosomal storage disease. That treatment may soon enter clinical trials in children with the fatal condition.

Such promising results with gene therapy put Dr. Sleeper and other Penn Vet faculty at the cutting edge of medicine. “These kinds of approaches,” she said, “give us a whole different way of looking at disease.”

—BY KATHERINE UNGER BAILLIE



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the Holter monitor — a combination that resulted in a very specific and sensitive way to pre-screen dogs for disease. This two-faceted approach may offer owners a less pricey alternative to having vets perform an echocardiogram in addition to the Holter monitor to see if their dog requires further examination.

GENES FOR RISK

Another strategy for early diagnosis of DCM is to screen dogs for genes that predispose them to the condition.

“It seems realistic to think that there are breed-specific genetic abnormalities that predispose Doberman pinschers to get dilated cardiomyopathy,” said Dr. Oyama, “because the condition is so prevalent within the breed.”

But even though there are hundreds of genes that have been linked in humans with DCM, veterinary researchers have just begun to discover parallel genes in dogs.

The search for these mutations is made difficult because large populations are generally required to do genome-wide searches for abnormal genes. A breakthrough on the genetic front came earlier this year. Dr. Oyama was part of a team that reported on their discovery in a study led by Dr. Kathryn Meurs of North Carolina State University’s College of Veterinary Medicine.

Writing in the journal *Human Genetics*, Dr. Meurs’ team screened 48 healthy Dobermans and 48 Dobermans with diagnosed DCM for gene mutations that appeared prevalent in the sick dogs. In their analysis, they found one mutation that stood out in the DCM dogs. This abnormality, affecting the gene PDK4, appears to alter the metabolism of the heart, shifting it from burning fat — the heart’s preferred fuel — to sugar.

“Ultimately, this change could result in an energy-starved state,” the authors write, leading to a weakening of the heart’s contraction.

It’s clear that this one mutation is not responsible for all cases of inherited DCM in Dobermans — 18 percent of the animals with the disease in the study did not have the mutation. This fact complicates the hope for a quick genetic screening test for mutations that predisposes a dog to the disease. Such a test would be especially valuable for breeders, who would be able to use the procedure to identify individual animals to keep out of their breeding pool.

A BRIGHTER FUTURE

Despite the cruel rapidity of DCM, a dog diagnosed with the disease today is better off than it would have been 10 years ago. Researchers including Dr. Oyama continue to seek therapies that will dramatically decelerate the disease’s progression. Meanwhile, other scientists, including Margaret M. Sleeper, VMD, associate professor at Penn Vet, are aiming for treatments using gene therapy (see sidebar).

“A long time ago there simply weren’t enough people who were interested in studying cardiac diseases in dogs,” said Dr. Oyama. “Now you have a critical mass of investigators, many of whom collaborate and can look at multiple aspects of the disease.”

Together, these veterinarian-scientists may soon render DCM an eminently treatable — and one day, curable — condition. 