Canine Ophthalmology

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Dr. Simon Petersen-Jones reported results from two projects that received partial funding from the CHF: a study of ocular melanosis in Cairn Terriers, and an effort to identify the genes responsible for progressive retinal atrophy (PRA).

With end-stage ocular melanosis, a dog is blind and unable to blink, has very enlarged eyes, and suffers from glaucoma brought on by severe proliferation of pigmented cells in the front chambers of the eyes. The condition progresses slowly, but the cells eventually plug up the outflow mechanisms that enable the eyes to drain into the bloodstream. The resulting canine glaucoma is different from the human disease and is difficult to treat effectively. Dr. Petersen-Jones said the age of onset in Cairns ranges widely: while some dogs are blind at age seven, others show early signs of the disease at 13–15 years of age.

Slides of early stage ocular melanosis show the root of the iris looking like a thickened doughnut, due to the proliferation of pigmented cells. As the condition progresses, specks of pigment show up in the front chamber of the eye, before gravitating down to occlude the drainage pathways. As secondary glaucoma occurs, the eyeballs enlarge, the eyelids bulge, and the dog goes blind.

Pedigree research to date has shown that ocular melanosis is an autosomal dominant condition, but the relevant gene has not yet been identified. So far, Dr. Petersen-Jones said, his lab has been working to exclude the genes that cause similar conditions in mice.

PRA is an umbrella term for a cluster of hereditary retinal dystrophies. Dr. Petersen-Jones also reported on achromatopsia—the canine equivalent of Leber's congenital amaurosis, a disease that causes early blindness in young children. All three conditions affect the rod and cone receptors or the cells that deliver nutrition to retinal epithelial cells, causing significant loss of vision and often blindness.

PRA affects more than 100 breeds and is caused by a variety of gene mutations. It is similar to retinitis pigmentosa, a condition that affects one human in 3,500–4,000, and may be recessive, dominant, or X-linked. An eye affected by PRA is much more reflective than normal, and the blood vessels at the back of the eye are more attenuated. The condition begins with the loss of the rod photoreceptors. Dr. Petersen-Jones said a dog might react by refusing to go out at night or by showing poor night vision. As the disease progresses, the animal loses its cone-mediated daytime vision as well.

Dr. Petersen-Jones said his research has centered on Cardigan Welsh Corgis that are born without functional rods and gradually lose their cone vision. The relevant mutation affects the gene that converts light entering the eye to electrical energy, resulting in a

buildup of toxic substrates that rapidly kill the rod and cone receptors. The dogs' retinas are genetically normal, but they die without a supporting network of rods to keep them alive.

Leber's congenital amaurosis causes early blindness in three out of 100,000 children, for a total of 200,000 patients worldwide. The canine version of the condition is caused by a mutation of the *RPE65* gene that results in a protein deficiency, causing marked loss of day and night vision. Dr. Petersen-Jones said a major advantage for treatment is that the retina degenerates very slowly, in contrast to PRA, where the loss is much faster. Treatments for retinal degeneration include gene or drug therapy, transplantation using progenitor stem cells, and implantation of a "retinal chip" in an attempt to restore vision.

Theoretically, gene therapy can be used to introduce a new copy of a defective gene, or to slow down the degenerative process. Another option might be to introduce a therapeutic gene—a growth agent or neuroprotective agent—to keep the retina alive.

To introduce genes to the *RPE65* site, Dr. Petersen-Jones said researchers must inject the replacement gene into a virtual space behind the front of the retina. The treatment causes retinal detachment that clears after two or three days. However, a study several years ago showed that subretinal injection of a viral vector led to improved electroretinogram results and better retinal function in dogs. Moorfields Hospital in London, England, recently conducted the first human trials of the technique.

Dr. Petersen-Jones said further research is needed to determine how late genes can be injected to restore vision, and whether injecting the second eye will lead the body to mount an immune response that might jeopardize the vision improvements from an initial treatment. Time will tell how long the treatments last, he said, though the first dogs to receive gene therapy have retained their sight for several years.

Another treatment option for dogs is to introduce a synthetic version of the Vitamin A analog that is required for proper retinal function. The results of this therapy are not as dramatic, but some improvement in vision is still noted. Future therapeutic options could include a reservoir device to continuously inject a required drug into the retina, or an implant that gradually releases a retinal cell survival factor over a six-month period. Implants have been effective in rodents, cats, and dogs, and recently entered Phase I human trials.

Once the rod and cone receptors have died, Dr. Petersen-Jones said the only option is transplantation. However, progenitor retinal cells have shown some promise in mice, suggesting the possibility of a future treatment for advanced retinal degeneration.