AN END TO THE STORY OF THE JACOB SHEEP TAY-SACHS MUTATION

In 2010 the JSBA reported our finding a fatal congenital neurological disease in Jacob sheep, a disease nearly identical to Tay-Sachs disease in humans. Jacob sheep die at about 6-8 months; children die at about 5 years. Whether humans or Jacob sheep, it is always fatal. In response to the offer of free testing in the JSBA Newsletter and ALBC NEWS, Jacob breeders in North America submitted nearly 600 blood samples for free testing and over 150 mutation carriers were identified with about 24 flock names. The mutation is known as the G444R mutation and causes a nucleotide change and skipping of exon 11 and leads to a fatal disease called gangliosidosis. What was thought to be a rare fatal mutation in Jacob sheep is apparently present in several flocks across North America. This is the final article on Jacob sheep and the Tay-Sachs mutation and ends with the beginning of the story.

In simple terms, an affected Jacob sheep or, more importantly, a child does not have the genetic material to produce the enzyme (HexA) needed to get rid of the waste products (gangliosides) that accumulate in the central nervous system's brain cells (lysosomes). Finding this mutation in Jacob sheep, for the first time, forged a genetic link between Jacob sheep and humans and led to an opportunity to explore the possibility of using a gene therapy protocol to cure Tay-Sachs. At the same time a window on human health opened, the window on a lethal congenital disease discovered in about 1 in 5 Jacob sheep has been identified and is being closed.

In the summer of 2010, four affected Jacob sheep from St. Jude's Farm were placed in a controlled gene therapy study. Two were left untreated as controls and monitored to measure Tay-Sachs disease progression. Two Jacob sheep, St. Jude's Texas and Driver, became the first large animals to receive gene therapy as a for cure Tay-Sachs. They were treated with AAV vectors: one expressing the HexA alpha subunit and the other both alpha and beta subunits. The two untreated sheep reached an end point at six and eight months but St. Jude's Texas and St. Jude's Driver, the treated sheep, lived twice as long.

The survival time is significant inasmuch as their disease had already progressed in showing symptoms when they received the gene therapy and yet lived twice as long and behaved normally until the final week. The gene therapy investigators also observed that the AAV vector "gene repair kit" traveled through the brain and 'repaired' more lysosomes than first expected. The objective for investigators for the fall of 2011 is to prove the results can be repeated, test if the therapy can be improved and from these conclusions, plan "phase one human trials", perhaps as early as 2012. This summer, St. Jude's Farm and Painted Rock Farm contributed a larger group of affected Jacobs, all from natural breedings.

Over 150 cases of Tay-Sachs in Jacobs were traced to one ram, Turner 183K, imported from Great Britain to Nova Scotia and listed in the original AMBC (ALBC's predecessor) record. As a founder of one of the six major lines in North America, half of his offspring had the potential to be a lethal mutation carrier and, in turn, a carrier bred to a non-carrier had a 50% chance of producing another carrier. His genes and the mutation moved through the Eastern U.S. and then throughout the country and as far West as California.

Finally, we have to acknowledge the participation of the sixteen Jacob breeders who saw value in identifying the mutation carriers; some being members of the JSBA. If one purpose of an association is to register those animals that are representative of the breed and are then entered in a record to be recognized as worthy breeding stock; the future registration of Jacob sheep has the potential to exclude a considerable number of lethal, neurological mutation carriers.

The nationwide dispersion of this mutation, a 20-25% incidence, its presence in over 90% of flocks will be a challenge to rectify. Those who tested their flocks will have an advantage knowing their flock 'carrier' and 'clear' status. Breeders purchasing tested sheep can have added confidence they are not introducing the mutation to their flock. A breeder with an unidentified carrier ram and eight clear ewes can easily have 12 lambs; 6 carriers, say 3 ewes and 3 rams and 6 clear, say 3 ewes and 3 rams. All twelve could be registered but which 6 are "good" breeding stock?

The free tests have come to an end. The New York University Neurogenetics Laboratory offered free DNA mutation testing to concerned Jacob breeders for the past two years to honor an agreement between Texas A&M University and Fred and Joan Horak to identify carriers. NYU's Neurogenetics Laboratory spent nearly $120,000 providing test materials and lab manpower on behalf of Jacob breeders. There are several breeders NYU has worked with over the past two years and NYU will continue to work with them in breeding through the deleterious effects of the mutation carrier problem. At this time, NYU's Neurogenetics Laboratory will do the test for new participants at $125 per sheep. If six or more DNA specimens are submitted at the same time the cost will be $100 per test. The genetics of the carriers should not and does not need to be discarded or left behind. After all, it is tied to a known, original, imported foundation ram. A breeder can breed through and around carriers to obtain clear, normal breeding stock. Even breeding carrier to carrier can produce one of four clear offspring.

Genetics, like a good mystery story, can have a twist at the end and so it is with the end to this story. Dr. Mark Wessells and Paul Holmes read the technical paper on "Tay-Sachs Disease in Jacob Sheep" published in ***Molecular Genetics and Metabolism*** and "Pathology of GM2 Gangliosidosis in Jacob Sheep" by Brian Porter in ***Veterinary Pathology***. This summer I received an email from Mark and Paul saying "we identified two fatal cases of a lysosomal problem in Jacobs in 2008; two rams from a flock of 102 Jacobs". Like other affected lambs we observed, they reported "symptoms beginning with stiff gait to hindlimb ataxia, difficulty in rising, recumbency and impaired spatial awareness". They went on to report that in 2010, they took Jacob blood and brain tissue to Guys Hospital for testing. Based on their blood plasma analysis done in the 'human' hospital hematology lab, they concluded that the lamb's reduced Hex A and Hex B and the distended brain cells demonstrated the lambs died from a Tay-Sachs variant of gangliosidosis.

Guys Hospital is in London. Drs. Wessells and Holmes live in London and are with the Animal Health and Veterinary Laboratory Agency in England. Last week Drs. Wessells and Holmes informed British veterinarians and breeders and breed societies of this serious problem and threat to British flocks. They anticipate considerable reluctance on the part of many breeders and perhaps the Jacob Breed Society to address this genetic threat to the Jacob breed. Scientists have now discovered the Tay-Sachs threat in Turner 183K's native land and now you know the beginning of the end of the story of Jacob sheep and the Tay-Sachs mutation.

—Contributed by Fred Horak, St. Jude's Farm