Summary of the 2005 Tufts Genetic Conference

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The second hosting of the Tufts Canine and Feline Genetics Conference was another successful combination of scientific study and medical information imparted to the attendees. Those in attendance were split approximately 50-50 between breeders and veterinarians, and information on a variety of subjects was covered. This article will summarize the presentations from the individual speakers, and focus on the main points made by each of them concerning their particular area of expertise. For more in-depth information, please refer to the website www.vin.com/TUFTS/2005 which is open to the general public. The 2005 conference was sponsored by several organizations including: CHIC, CHF, CFA, Optigen, Nestle Purina, PennGen, OFA, Winn Feline Foundation, PennHIP, VIN, AKC, and VetGen.

The conference opened with Dr. Urs Giger, who discussed how to recognize and screen for hereditary diseases. He stated that there are over 450 hereditary diseases recognized in dogs, and greater than 180 hereditary diseases recognized in cats. Over half of these diseases have a recognized mode of inheritance, with autosomal recessive being the most common. An autosomal recessive disease will have 3 major characteristics: 1) skips generations, 2) the heterozygotes are asymptomatic carriers, and 3) the parents are usually healthy but will produce affected offspring. The goal of genetic testing is to identify diseased animals and discover animals at risk to developing disease or passing it on to offspring, ideally prior to developing signs or being bred. Genetic testing can help breeders control recessive traits in future generations, and will help identify carriers so that appropriate breedings can be planned. The best way to identify a genetic disease is through DNA testing, with the mutation specific test preferred over a linkage based test. Dr. Giger also mentioned that in his native country of Switzerland, every dog that is being bred must be tested prior to breeding. In this country, the AKC has no specific requirements and therefore it can often be difficult to determine how prevalent a disease is within the American purebred population. This can be especially difficult because of the breeding practices within the U.S. He discussed the fact that mixed breed dogs can also have genetic disease. Dr. Giger wrapped up his talk with discussion on complex modes of inheritance (polygenic traits, modifying genes, etc.) and mentioned that the sequencing of the canine genome has been completed and should be published soon.

Dr. Susan Little followed Dr. Giger with a discussion on congenital defects in kittens, many of which are also applicable to puppies. She defined a congenital defect as one which is present at birth, ranges from minor to serious, and may go unrecognized as a stillbirth or "fading" kitten. Dr. Little strongly encourages that necropsies be performed on all stillbirths and fading neonates, in the event that a genetic defect is going undetected. She mentioned that 3-5% of all humans born have congenital defects, many of which are minor but some of which cause childhood deaths. The stages of fetal development were outlined, from pre-implantation of the fertilized egg, to embryogenesis (or development of the embryo), to fetal growth. There is a critical period or stage within

development where each organ is most sensitive to disruption, and errors which occur in the early stages are usually lethal. Also noted was the fact that not all congenital defects are heritable, and those that are heritable tend to have a breed or familial predisposition. Dr. Little summarized her talk by saying that breeders can help to identify and determine heritability of congenital defects by keeping detailed records on each litter, each kitten or puppy, requesting necropsies, and sharing information.

Dr. Giger returned to the podium after Dr. Little's talk, discussing inborn errors of metabolism, which today includes essentially all biochemical disorders due to a genetically determined, specific defect in the structure and/or function of a protein or molecule. He gave several examples of defects and their clinical signs and then went on to describe the steps which are taken to screen for the defect. For example, once an abnormality is identified, laboratory tests can be conducted, biochemical pathways identified, and qualities noted such as accumulation of substrates, deficiencies, and abnormal products. Often samples such as serum, blood, urine, etc. are used in determining these pathways. Dr. Giger mentioned the importance of identifying possible errors including animal identification, sample identification, laboratory error, and parentage errors. Management of hereditary disorders includes the prevention of the production of affected animals, control of the further spread of mutant alleles, and providing therapy while addressing ethical concerns. Therapy can include surgical interventions, transplantation, gene therapy, supplementation, symptomatic therapy, and gene transfer experiments (to correct the defect).

Dr. Stephen Hannah, representing Nestle Purina, then began discussing osteoarthritis and nutrition. He went over the polygenic inheritance of osteoarthritis, and discussed an ongoing study on Labrador retrievers and nutrition. Essentially the study found that weight control and diet, along with supplements such as omega-3 fatty acids, can increase the length of time for the development of osteoarthritis in Labradors. In other words, Labradors which were nutritionally monitored and kept thin tended to develop arthritis at a much later stage in life, and may never develop clinical signs at all. Dr. Hannah went on to discuss nutritional components and supplements at length, including dietary recommendations.

The sequencing of dog and cat genomes was discussed by Dr. Kerstin Lindblad-Toh, who mentioned that the top ten diseases in dogs include cancer, epilepsy, hip dysplasia, hypothyroid, allergies, bloat, heart disease, autoimmune disease, progressive retinal atrophy, and cataracts. She discussed how the DNA sequence provides a blueprint for the disease, and makes gene mapping easier. Also explained was how to compare between genomes (i.e. human and dog, or human and mouse, etc.) and that a tool to find diseased genes includes a "mapping array." Dr. Lindblad-Toh says she prefers blood as the sample submitted for DNA analysis, because it provides better quality and quantity of DNA than cheek swabs.

Dr. Gail Smith proceeded to discuss one of the top ten diseases mentioned by Dr. Lindblad-Toh, namely canine hip dysplasia (CHD). Dr. Smith, the founder of the PennHIP method of evaluating and predicting the development of CHD, described the

importance of using hip laxity as a measurement. He described the optimum CHD screening method as that which contains an accurate phenotype, has high heritability, and has the ability to be used to apply selection pressure towards better hips. Dr. Smith stated that OFA scores can change with age and environment (lower heritability), while PennHIP is not confounded by diet or age (higher heritability). He went on to describe that OFA scores have upwards of 56% false negatives, with up to 92% of "normals" developing osteoarthritis. His conclusion from a lifespan study is that "normal" does not mean normal for life, and that the PennHIP method has a higher heritability and therefore predictability than the OFA method. He finished by stating that "tighter hips are better hips." For more detailed information on contrasting the two methods, please refer to the article on "OFA and PennHIP."

Mr. Eddie Dzuik continued the conference representing the Canine Health Information Network (CHIC). He discussed the goal of CHIC and what exactly a CHIC number means. In the past, breeders would have large kennels with hands on knowledge of the sires and dams within their bloodline. These breeders knew how their lines matured, the characteristics within their line such as temperament and trainability, and most importantly, the health of their line. It is difficult to find breeders today with the same breadth and knowledge of their breed. The facilities to house large numbers of dogs are less feasible, time management and economy play large roles. The breeder turnover rate is high, with most breeders maintaining involvement for less than 15 years. Therefore, there is more of a lack of data, less exchange of knowledge, and less ability by the individual to make informed decisions. CHIC was conceptualized by the AKC "to provide a toolset to breeders to provide data to make more informed breeding decisions to breed healthier dogs." CHIC relies upon parent club input to determine health testing requirements for each breed, so that they can be tailored to the individual breed. CHIC promotes encouraging health testing and awareness, and open exchange of information. A CHIC number is not a "stamp of approval" it only means that the testing was done for that dog and was released publicly. The number does **not** indicate normal results for the testing involved, only that it was completed and entered into the public database.

Dr. Anita Oberbauer followed the CHIC presentation with strategies for identifying and managing complex genetic disorders. Dr. Oberbauer emphasized the need for open databases and vigorous exchange of information among breeders, veterinarians, and researchers. She noted that breeders need a long term view of their objectives, rather than focusing on single generations. Among the greater than 450 genetic disorders which have been identified, approximately 70% are recessive (of those with a known mode of inheritance). Dr. Oberbauer then went on to note that complex traits, such as speed, temperament, etc. are more difficult to track and influence. In addressing complex traits first one must determine if a trait is heritable and then identify the ideal population to evaluate. Traits with higher heritability indicate a greater genetic contribution as opposed to environment, nutrition, etc. Lower heritability reflects a longer time needed to influence the trait until results are realized due to a lower genetic contribution and greater environmental component. Once it has been determined if a trait is heritable the next step is to determine the mode of inheritance – single genes versus several genes, whether there are confounding effects such as mimicry, aging related

changes, symptom sharing with other diseases, heterogeneity in disease expression, late onset of disease, etc. Polygenic traits can be particularly difficult to map when one is looking for small mutations, multiple sets of genes, modifiers, etc.

Dr. Oberbauer discussed some of the problems and suggested solutions in the study of complex disorders. First and foremost, rigorously and narrowly define the disorder, next replicate studies over different environments, lastly create ideal populations which are inbred if necessary to study the disorder. She says that genetic testing can be achieved with complex disorders but does require markers and a large number of participating individuals. One of the most significant quotes from her talk is that "there's no shame in producing a health issue – the shame is in not using that knowledge to better the breed." In order to create a better future for our canine companions we need full disclosure of traits, accurate health information, composite values so raw values needn't be published, multiple traits assessed, breeders agreeing on assigning priorities to different attributes, and more variety of sires to maintain population diversity.

Dr. Oberbauer continued her discussion the next morning on Addison's disease (AD) and epilepsy, two subjects which are very important to poodle breeders. Addison's disease appears highly heritable in poodles, particularly of the standard variety. From her research she has concluded that it is a polygenic disease, with no sex effect, no coat color effect, and has no association with hypothyroidism. AD also appears to be regulated by a single major locus, which is inherited as an autosomal recessive. There may, however, be modifying genes, which can influence the degree, onset, etc. of the disease. Epilepsy appears to be similar to AD in many ways. It is also a highly heritable disease, has no sex effect and likely no coat color effect. The age of onset is usually between 2-5 years of age and has no association with hypothyroidism. Epilepsy is polygenic and like AD appears to be regulated by a singe major locus, which is inherited as an autosomal recessive. While there are likely modifier genes involved, there is a major gene which contributes a significantly large influence on the expression of the trait that it is necessary to result in expression of the disease. It is hypothesized that both AD and epilepsy may have different genes causing the trait among different breeds. For instance, the "malin" gene has been identified in another breed as causing epilepsy, but does not appear to play a role for this disease in poodles at this point.

Going from the frying pan into the fire, Dr. Modiano followed up with information on cancer genetics, and the heritability of certain cancers. As we know with humans, some families seem particularly prone to cancer, and breast cancer has even had genes targeted to identify women at risk. In dogs, heritable cancers appear to be the causative agent in 5% or less of tumors. Pre-cancerous lesions can remain dormant for years before manifesting into clinical disease. Both human and canine genomes contain "oncogenes" which promote growth and survival of cells while tumor suppressor genes promote cell death. It only takes on hit of the oncogene to cause uncontrolled growth of cells, while two "hits" must occur to activate tumor suppressor genes. Heritable cancers manifest earlier in life, are usually multiple tumors, are theorized to be caused by a single

gene with variable penetrance, result in poor long term survival, and may be inherited as a dominant gene.

Dr. Leslie Lyons continued the conference with a discussion on feline genetic disorder and genetic testing. The main points from her talk which are applicable to dogs include the fact that while point mutations may be characterized for one breed, one must be sure the same mutation causes the same result in different breeds before offering a genetic test across breeds. She recommends that before planning any breeding one should obtain a medical history of the sire and dam, be aware of the familial medical history, analyze the relatedness of the individuals being bred, and maintain high ethics in breeding practices.

Agreeing with Dr. Lyons on these issues, Dr. Bell's talk segued into genetic counseling and breeding management of hereditary disorders. He states that "breeders and owners are looking for objective information – good or bad." It is very important that an individual interested in breeding have an in-depth understanding of breeding practices, including inbreeding, linebreeding, outbreeding, and crossbreeding. Dr. Bell discussed crossbreeding and the trend toward "designer dogs" such as the labradoodle, etc. He stated that such dogs have no better chance of being disease-free than purebred puppies, unless there is increased health testing, quality control, and background information on the crossbred population than the purebred population. At this time that is simply not the case, and crossbred dogs are priced often outrageously high simply because the public will pay. Dr. Bell stated that inbreeding and linebreeding will increase homozygosity and expose deleterious genes, while outbreeding will decrease homozygosity and prevent expression of deleterious genes. He discussed the calculation and uses of the coefficient of inbreeding (CI) and the necessity to evaluate many generations (10 or more) rather than merely perusing the first three generations with may be deceptive to the eye. Dr. Bell also discussed "popular sire syndrome" in which a stud dog is widely used and found in many pedigrees, such that genetic diversity is decreased. In such a happening, the overuse of an individual within a purebred population results in the increase of the spread of defective genes. He mentioned that the Seeing Eye organization does not use any stud dog more than 10 times, and that the European community has restrictions on the use of stud dogs.

When a breeder does come across a genetic problem within their lines, it is no longer recommended to "spay and neuter your animals and restart with someone else's animals." Instead Dr. Bell recommends that a breeder continue with his/her own lines and work away from genetic disease. A breeder's primary goal should be to maintain and enhance the quality of the breed. The secondary goal should be genetic disease control by not producing affected animals, and breeding to decrease the frequency of carriers. Recommended management strategies include determining the mode of inheritance of a genetic problem, utilizing all available genetic information, and increasing the breeding "pool" size and diversity. In the case of dominant genes, replace affected animals with an unaffected sibling or relative within the breeding program. In the case of recessive genes, breed quality carriers to genetically normal mates, replace carrier parents with genetically normal offspring, and select against carriers for breeding when a normal

relative is available. It is important not to completely cut out carriers from a breeding program, as this can have a significant limiting affect on the gene pool. If a breeder is planning on breeding an animal prior to receiving carrier test results, the appropriate choice is to breed to an animal which has tested normal (i.e. not a carrier). If genetic testing is not available for a disease, the appropriate choices include breeding high risk to low risk individuals, replace high risk with low risk individuals within a breeding population, and repeat with each generation. Relative risk breeding requires a known mode of inheritance, open health registry databases, and ***openness between breeders and owners/buyers.***

After all the discussion on managing genetic disease, Dr. George Lees discussed inherited kidney diseases in dogs and cats. Dr. Lees stated that inherited kidney disease almost always leads to chronic renal failure (CRF). Inherited kidney disease is usually a structural disorder, most often renal dysplasia or polycystic kidney disease. In the juvenile (before 3 years at age of onset) CRF usually results from renal dysplasia (RD) and primary glomerulonephritis. In the adult, CRF usually results from polycystic kidney disease and secondary glomerulonephritis. In both cases, these are progressive disorders with no specific treatment and ultimately lead to death. The clinical signs of CRF include increased drinking, increased urination, weight loss, stunted growth, decreased appetite or anorexia, vomiting, diarrhea, uremic breath, and poor hair coat. On physical exam these animals tend to be thin, dehydrated, and anemic, with uremic breath and/or oral ulceration. Laboratory tests show decreased urine concentration, azotemia, increased phosphorous, non-regenerative anemia, and may have proteinuria, glucosuria, or pyuria. Ultrasound may show abnormal looking kidneys, or a microscopic analysis of a wedge biopsy may be necessary to see structural damage. Whether it is inherited or familial, RD is not necessarily the same disorder in all breeds. The causes and pathogenesis are unknown and the underlying genetic defects are also unknown. There is no genetic test currently available.

Leaving the rather sad topic of CRF, Dr. Carmen Battaglia led a lively discussion on pedigree analysis and early neurological stimulation of puppies. He started off by saying the there is “one set of skills to breed, one set of skills to judge, and one set of skills to exhibit.” These may overlap in some areas, but each category has a specific set of skills necessary for success. Dr. Battaglia then went on to list the 8 skills he considers necessary to become a breeder: 1) know the breed standard, 2) obtain breed knowledge, 3) develop a method by which you select sires and dams, 4) evaluate pedigrees both by depth and breadth, 5) maintain a record system, 6) evaluate every litter the same way, 7) choose the best puppy, 8) manage and develop the dogs that you keep.

As a breeder you have to know what to look at and you have to know what is correct or not. Dr. Battaglia used the examples of “stick” dogs in which there is a system of measurement by breaking down the dog into main components such as head, front, rear, tail set, etc. Use whatever categories are most important for your particular breed. Then “break down” your dogs into those categories by using a color coded system to rate each part. You can then replace the names on your pedigrees with the color-coded stick dogs and analyze the inheritance of those traits you have determined are important. This

can also help you in choosing sires and dams, and seeing if a particular pairing will work or not. Once you have decided on a pair and have a litter of puppies, Dr. Battaglia also has suggestions on early neurological stimulation and ways to raise better puppies. Early neurological stimulation has been shown to lead to high achievers, improved cardiovascular performance, better tolerance to stress, and better temperaments. The website www.breedingbetterdogs.com has more information on his programs and theories.

The conference was completed by a talk by Dr. Lowell Ackerman on selected inheritable skin disorders. Leading with a discussion on sebaceous adenitis (SA) , a topic valuable to poodle breeders, Dr. Ackerman outlined current information. SA is believed to be inherited as an autosomal recessive with incomplete penetrance in standard poodles and akitas. It is an immune mediated, inflammatory process leading to the destruction of sebaceous glands in the skin, resulting in clinical signs. There are two phases of the disease process: 1) destruction of the glands by an autoimmune process and 2) an inflammatory reaction that prevents new glands from forming. These two phases can be influenced by other conditions such as atopy, food allergy, vaccination, estrus, etc. The clinical signs of SA include non-inflammatory hair loss, scaling, and odor. These generally begin to occur in young adults with variability between breeds. The diagnosis is attained by full thickness punch biopsy of the skin. Management includes corticosteroids early on in some breeds, frequent antiseborreic shampoos and emollients, high dose marine oil, and immunosuppressive drugs if necessary (cyclosporine, etc.). Some dogs spontaneously remit and others require varying degrees of ongoing treatment. Dr. Ackerman recommends not breeding affected animals and presumes that both the sire and dam of an affected animal are carriers. He went on to discuss dermatomyositis, an autosomal dominant dermatologic disease, and demodicosis, neither of which affect the poodle population as a whole in a significant manner.

Overall, the genetics conference was another resounding success. Dr. Bell did an outstanding job organizing, directing, and managing the conference, which was appreciated by the attendees, veterinarian and breeder alike. A huge amount of information was imparted, leaving the listener eager for more. Each presenter was, in general, clear and concise, with important points to make concerning their subject of expertise. There were also poster presentations, which were fun and easy to read, well presented by the authors. I believe this conference was valuable to breeders and veterinarians alike, and want to thank Dr. Bell, Tufts University, and the sponsors for their support and efforts. I look forward to attending the third installment sometime in the future.