

The American Kennel Club Canine Health Foundation

Biennial National Parent Club Canine Health Conference

*Sponsored by Nestlé Purina PetCare Company and the
American Kennel Club*

**St. Louis, Missouri
October 21–23, 2005**

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Friday, October 21, 2005

Welcome

CHF President **Wayne Ferguson** and Executive Director **Deborah A. DiLalla** welcomed participants to the Foundation's Sixth Biennial Parent Club Conference and acknowledged the support of the Nestlé Purina PetCare Company and the American Kennel Club, as well as the members of the Orthopedic Foundation for Animals (OFA) in attendance.

Parent Clubs: Stewards of Breed Health

Larry Schwartz of the English Springer Spaniel Field Trial Association Foundation stressed that parent clubs and their breed foundations “form the backbone of disease-specific research,” working to identify and prioritize the diseases of their respective breeds. He said his own foundation had recently organized a full-day health forum, in partnership with its parent club and CHF, which featured 150 participants and technical speakers on the three top priorities emerging from the breed's health survey—temperament, epilepsy, and eyes. He also read a forthcoming article in *Dogs in Review* that will highlight his breed's recent activities and demonstrate how a breed can mobilize once it is willing to confront a health problem.

Mr. Schwartz also announced CHF's decision to introduce an annual award for club excellence in canine health, beginning in 2006. The awards committee will be on the lookout for clubs that have demonstrated leadership in research, education, or other efforts to advance the health of their breeds.

AKC Delegates' Canine Health Committee Update

Dr. William R. Newman, Chair of the AKC Delegates' Canine Health Committee, reviewed the committee's mission to gather information on the science of canine health, disseminate it to delegates, and recommend priorities for educational programs, procedures, and research. He reported that the committee's first health survey will soon be online and available to all parent clubs, and that members had also been responsible for the launch of the Canine Health Information Center (CHIC).

The committee's articles on a variety of canine health articles, including the most recent series on canine influenza, are available for Parent Clubs' use at shows and other local programs, Dr. Newman said. AKC has set up a very productive liaison structure with the American Veterinary Medical Association, introduced the AKC's *The Complete Dog Book* as a standard resource for every fourth-year veterinary student in the United States, and was instrumental in encouraging the AKC to appoint a world-recognized expert to advise it on DNA issues.

For the future, the Committee is encouraging breed clubs located within 100 miles of a veterinary school to share their knowledge and achievements with their nearby institutions, and will be launching an initiative to support greater voluntary use of DNA-certified registration.

Future research will focus on the ideal body mass index for each breed, and on the impact of cloning and stem cell research on purebred dogs.

Organization and Function of a Health Committee

Connie Vanacore, Health Committee Chair with the Irish Setter Club of America, traced her club's health projects back 40 years, to the origins of a long-term study of progressive retinal atrophy (PRA). The research "took a big leap forward" when veterinary ophthalmologists became interested in the canine genome. And at that point, the club "realized that to use the science, our members needed to understand and accept the concept of DNA testing." The test was developed in 1994.

Previously, the committee had completed its first "homegrown" health survey in 1992, to determine members' research priorities. The survey mattered, Ms. Vanacore said, because "you can have the most devastating disease in the world, but if the members won't support it there's no use continuing with it." Follow-up studies were conducted in 1997 and 2003.

The committee's philosophy is to concentrate resources on a small number of long-term studies, though members are hoping they won't have to repeat the 30 years they spent on PRA. The breed is currently involved in research on epilepsy, von Willebrand's Disease, and thyroid disease, and is participating in the cancer study at the Broad Institute at the Massachusetts Institute of Technology.

The health committee sponsors educational seminars in conjunction with its national specialty, conducts blood clinics at shows, includes a health booklet in the parent club's puppy packet, has published an extensive book of pedigrees back to 1876, and is a founding member of the Canine Health Information Center (CHIC). In 2000, the breed established an independent, tax-exempt foundation that receives all donations on behalf of the health committee. The foundation has run several successful fundraisers, including a "Gold Angel" campaign that Vanacore described as a "smash hit."

Wayne Kompare, President of the Westie Foundation of America, said the organization operates independently but has always maintained a close working relationship with its national club. He traced his emphasis on independence back to two key factors: the organization's purpose, and its constituency.

While most national breed clubs focus on competitive dog activities, the Westie Foundation's sole purpose is to raise funds. "I suspect most breeds are somewhat like Westies, in that the number of dogs that are in households of national or regional club members is relatively small," Mr. Kompare said. "Our constituency is all Westies, everywhere. I don't care if a Westie came from a puppy mill, a backyard breeder, or the most reputable breeder in the club. If that Westie has a health problem, it's our concern."

The foundation operates in three functional areas: health, fundraising, and financial/administrative. Of the six health committee members, two are veterinarians, including the committee chair, and one is a medical doctor.

The foundation has an annual budget of \$30,000 to \$40,000 and funds four to six projects per year. Mr. Kompare said the operating principle is the same one adopted by venture capitalists: out of every 10 start-up companies the sector funds, it expects that seven will fail, two will be moderate successes, and one will be a real barnburner. Over the past seven or eight years, the Westie Foundation's research has "moved the ball forward to some degree, in most cases," although the breed is still looking forward to "the really great success from one of the health projects we fund."

One frustration is the number of research projects that never come to fruition due to insufficient funding. In the past year, the Westie Foundation allocated \$28,000 to five different studies, only one of which got off the ground. To maintain momentum, the foundation has also identified a number of educational projects, over which it can assert more control. "With education, we determine how much we put into it and what it's going to be, and we ride herd on it to make sure something good comes out of it," Mr. Kompare said.

Project priorities are based on the results of a health survey every six or seven years. All 6,000 Westie owners across the U.S. are invited to participate. The results are weighted to emphasize diseases that cause death or extreme discomfort for the dog. By far the foundation's leading priority at present is atopic dermatitis.

Development & Use of Canine Health Surveys

Dr. Elsa Sell, President, BEACON for Health, said some steps are the same in conducting a successful health survey whether the survey is a first-time effort or something done on a recurring basis. "It is crucial to establish goals and design the whole plan around those goals," she said. "Do not stray from them because if you come up with a new goal somewhere in the middle, you're going to really wreak havoc with the data management system, and you will confuse your constituents who participate or are thinking about it."

Survey planners should anticipate barriers and come up with solutions before distributing the survey.

Four methods of collecting information are anonymous, confidential, open, and open registry. With open surveys, anyone interested in the breed is a potential participant. Anonymous surveys have the fewest barriers because there is some identification in all the other types.

Some surveys are quite long, which is another barrier. If a survey is 8 to 10 pages long, people look at it and throw up their hands.

Health surveys require information on all dogs, including healthy dogs.

Barriers of database management include the challenges of assembling and distributing data. After data has been collected, results must be presented in a useful form.

Data acquisition can present a barrier. If data on dogs outside the United States will be included, the database must be adjusted appropriately.

The survey form should be designed to accept either facts or opinions. Dr. Sell recommended that the survey form use correct medical terms rather than common disease names. The survey form must be user-friendly to get good participation. This can be achieved by testing the form in advance for content and usability, and making appropriate changes after the test.

Survey planners need to consider whether to process completed surveys in house or out of house. The advantage to doing it in house is that volunteers can be used, but breeders may fear data collectors will share the information collected prematurely or use it against them. Doing it out of house has the advantage of unbiased people working on the project, but they may not know anything about dogs, it is more costly, and someone must be found to do it. A possible out-of-house resource is a university interested in a research project.

The barriers to a successful survey, Dr. Sell said, exist more in people than in technology. Breeders fear that health problems in their dogs being revealed will destroy their reputations. There may be a generally held belief that a specific disease can't be genetic, especially with a breed's first big health problem. Health surveys face inadequate participation, especially participation from people with healthy dogs. Many dog owners who should participate in health surveys are not members of the Parent Club.

Club or foundation leadership is essential for successful surveys. The leadership can support the survey project by encouraging participation and publishing the results in addition to providing financial support.

Mike Wahlig, President, Poodle Club of America Foundation, said online surveys easily can become overwhelming for the person completing them. He pointed out that careful planning is vital: online surveys should not be too complex.

It is important for the survey planner to remember the objective of the survey, whether that is shock and awe, funding decisions, education, or to improve the breed. Then he should consider what will be in the final report and design the survey to get there. Other considerations include who the participants will be, who will use the data, whether to ask for facts or opinions, and whether to use common or medically correct names for diseases.

A good way to check the survey format is to ask 10 to 15 friends to look it over and make recommendations, then incorporate their suggestions. The survey planner should decide in advance how to handle additional comments written in on completed forms.

Mr. Wahlig pointed out legal considerations of data being distributed inappropriately. "You won't be sued by the guy who gives you the data, but watch out for the owner of the sire," he warned.

When a Parent Club conducts a health survey, the club, not its board of directors or its officers, owns the survey. In conducting the survey, it is creating a unilateral contract with participants. If any identifiable data is requested, the club should ask participants for releases. The Club should let participants know how the information collected will be used.

The survey should define what constitutes acceptable proof of a disease: tests or genetic markers; a consensus of opinions based on rigid protocols; a diagnosis based on consistent protocols; a diagnosis at a point in time; or hearsay.

Survey data can be submitted by a breeder, owner, co-owner, handler, or veterinarian. Permissible use of data after it is collected depends on what the survey participants were told in the first place.

Working with OFA and CHIC

The Orthopedic Foundation for Animals (OFA) was founded by owners of dogs with hip dysplasia, said **Susan LaCroix Hamil**, Director, AKC Canine Health Foundation; Director, Orthopedic Foundation for Animals. Its mission is to improve the health and well-being of companion animals regarding orthopedic genetic disease.

The OFA has funded over \$200,000 in research for AKC CHF, and contributed over \$50,000 in 2006. The OFA has a program whereby an owner, for a fee of \$10, can post a picture of their dog on the OFA website. Proceeds from this program benefit the CHF Endowment Campaign, “Double the Dollars for Dogs.”

The Canine Health Information Center (CHIC) was initiated by the AKC Delegates Health Committee in 1999 and implemented in 2001 as a collaboration between CHF and OFA. It has grown to 56 breeds in 2005. CHIC emphasizes testing; previously the emphasis was on passing the test, now it is on getting the test. It provides a source of health information for owners, breeders, and vets. CHIC collects information, puts results into a user friendly database, and recognizes dogs tested in accordance with the test protocols recommended by the breed’s Parent Club.

CHIC benefits breeders, who now have unbiased data at their disposal. Buyers can use the information, whether they are getting a dog for a pet or buying from another breeder. It also is available to the research community, which can see what project might be most beneficial, what is needed, and what already has been done. Parent Clubs want to keep the health data and make informed breeding choices. Veterinarians can use the data to determine what testing is appropriate for a specific breed and in making breeding recommendations.

“It really has far-reaching implications,” Ms. Hamil said. “But most of all, it benefits the dogs.”

CHIC's next phase is a DNA repository. A large DNA bank can be used in researching inherited diseases. This project was kicked off at the Golden Retriever National, which resulted in more than 600 samples being collected for the repository.

Selection and Funding of CHF Grants

Erika Werne, Director of Canine Research and Education, CHF, said that a Parent Club survey that is conducted every other year shows that the top five health concerns for dogs—cancer, eye disease, epilepsy, hip dysplasia, and thyroid disease—are the same every time the survey is conducted, although the order of these may change.

The request for pre-proposals is sent to 2,500 investigators worldwide. Their responses are sent to a committee that includes DVMs, MDs, CHF staff, and others to make sure the proposed research meets CHF goals. Then the CHF contacts the investigator and invites a full application, which includes investigators' CVs and can include letters of support.

The full application is sent to four experts in the proposed field of study for peer review. For example, a proposal for research on genetic renal disease would go to geneticists and renal disease experts, whose comments later would be shared anonymously with the investigators.

Ms. Werne said that more than 50 institutions in seven countries have received funding. Guidelines require that all animals participating in the research study must be cared for under CHF's Guidelines for the Care and Treatment of Animals.

Applications may be approved as grants without conditions, meaning the research includes all breeds and/or is educational. Grants with conditions may be breed specific or multi-breed. Such a grant may require 50% from Club matching. When a grant specifies matching funds, contributions match up to only the total amount approved in the grant. The board determines the level of match.

Each Parent Club's health committee liaison is responsible for general communications between CHF and the club.

Meeting the Challenge: Funding the Best Research

Ronna Dornsife, MS, CHF's Research Grants Administrator, said that ACORN grants are small grants, one year or less in duration, of up to \$12,000 and 8% indirect costs. Researchers can use these grants to test an idea, generate preliminary data, or complete a small project, either breed specific or all breed.

ACORN projects may include both clinical and laboratory studies. Large projects may be multi-institutional teams.

Ms. Dornsife said the CHF tries to find balance in the grants it gives for testing versus treatment. The ratio of grant money allocated to different diseases changes over time.

To determine if a disease is ready for further research, researchers and breed clubs should consider if the disease has been documented in more than a few dogs, if there are specific diagnostic tests or criteria for the disease, and if there already are published studies on the condition.

Some special areas in which projects might be funded include dog weight and body mass index, reproductive health, and performance or sports medicine.

Funding Breed Specific Research

Rhonda Hovan, Starlight Fund & Golden Retriever Foundation, said she has worked with fundraising on both a small and large scale.

When Ms. Hovan's top-producing Golden Retriever stud died of lymphoma, she vowed that if she ever owned another highly successful stud, she would do something about the disease. The success of her dog Star enabled her to establish the Starlight Fund. She donates stud fees to the fund, asks every breeder who uses Star as stud to contribute \$25 per pup in every litter produced, and also asks new owners of those pups to contribute \$25. When others heard about the fund via word of mouth, Ms. Hovan started receiving \$25 checks from people she never heard of. The fund has raised more than \$43,000.

Ms. Hovan's large-scale experience has been the Golden Retriever Foundation, which raised more than \$532,000 in the past year. The project began with a video and board members' hard work. It has gone from 390 donors to 1,283 donors.

Leslie Forrest, Norwegian Elkhound Association of America, represents a smaller Parent Club (about 400 members). Fundraising efforts support familial renal dysplasia research in a project that goes back to the 1970s.

A DNA bank was established in 1988 with 133 samples. The group conducted a health survey in 2000. In 2001, a study of 71 Elkhounds was published.

Research and requests for grants continue. The organization, which now has raised \$46,000 for the project, recognizes everyone who donates in its newsletter.

"We just keep asking and asking and asking," Ms. Forrest said. She emphasized that even a small club can set and meet a fund-raising goal.

Joye Neff of Berner Lovers said that her organization had raised \$86,800 to fund three grants and start a Donor Advised Fund in 2005. In the past seven years, the group has raised about \$324,500.

“Basically, I beg for money, and they send me checks,” Ms. Neff said.

People and vendors send her Berner items, and Ms. Neff sells \$1 and \$5 chance tickets for the items on her website. She collects information from the vendors that contribute and features each for one day on the site. The site also has photos from Berner events and articles.

Ms. Neff writes to thank each person who buys a ticket on her site. Each fund raiser lasts five or six weeks. A week after the drawing’s published closing date, she draws a winner and mails the prize.

The Berner Lovers also get some challenge funds for their projects. Some breeders send \$25 per puppy.

Purina Parent Club Partnership Program

Mike Allway, Manager, Breeder Services, Nestlé Purina PetCare, loves what he does. “This is a great job. I get to give money away,” he said.

The Purina Parent Club Partnership Program provides funds for canine health studies, education efforts, and rescues. Pro-Club members collect weight circles from Purina dog food and submit them to receive the funds. The Partnership works with 149 clubs, 48,000 members.

50% of funds accrued for the breed go directly to the breed’s CHF Donor Advised Fund (up to 100% if the Parent Club so chooses). The remainder can be used by the Parent Club for rescue or education programs.

Increased participation results in increased funds. To raise awareness for the program, Mr. Allway said Purina provides affiliates with advertising materials on the program. The Partnership asks clubs to talk about the program, how funds have been used, and to promote it on the club website.

AKC Museum of the Dog

Museum director **Barbara Jedda McNabb** gave participants a quick introduction to the AKC Museum of the Dog, located in an 1853 Greek revival-style home in greater St. Louis, and invited everyone to visit while they were in town. The museum houses the largest collection of canine art in the country, if not the world, including artistic masters from the 19th century to modern times and early paintings from the late 1600s on. The museum was founded in 1982, with a temporary exhibition at AKC offices in New York, and has since been supported solely through gift donations. The collection is valued at \$6.5 million, and continues to grow rapidly.

Questions and Discussion

CHF Director Susan LaCroix Hamil moderated a wide-ranging question and answer session covering the series of presentations that had just concluded.

A participant noted that her club had yet to participate in a study that had generated a dramatically positive result, and asked for strategies to keep members motivated to participate. Ms. Hamil stressed that a negative result is not a failure. “That’s a very difficult concept to sell, that just because we didn’t find what we thought we were looking for, it doesn’t mean our project was worthless.”

A participant agreed, adding that clubs can make progress without genetic tests. Some disorders in some breeds have “virtually disappeared without any of those sophisticated tests, just because people bred reasonably and responsibly and were able to work their way away from it.”

Erika Werne, CHF’s Director of Canine Research & Education, added that every piece of information contributes to the bottom line. “Honestly, I think people who care about the health of their breed are going to keep trying. You don’t stop breeding just because you get one unattractive litter, or because they’re pretty but not very bright.”

Connie Vanacore recalled that the Irish Setter Club of America spent 30 years studying PRA. “That was before they developed DNA research,” but she acknowledged that motivation is still an issue: In one recent study, the club needed 100 samples and signed up 100 dogs. “But when it came time to do the pedigrees and send the blood, we only got 50, no matter how much we nagged.”

While stressing that the genome sequence won’t solve everything, **Kerstin Lindblad-Toh**, PhD, of the Broad Institute, Massachusetts Institute of Technology, said research results can be expected to begin to take shape more quickly. “A lot of the tools and capabilities that have been a real hard task for the scientists over the last few years are now going to be easier,” she told participants. “The real bottleneck now is getting samples, and samples that are accurately characterized. The rest is easier than it used to be.”

Ms. Hamil said mapping the canine genome had been a core mission for CHF, adding that the establishment of a DNA repository will address current difficulties with sample collection.

A participant asked how to address the “fear factor” that inhibits club members from answering surveys. Another audience member suggested starting out with a breeder who is pessimistic about the process, but willing to try it out. “Just the fact that you listened to them may bring them onboard to some degree,” and they might then bring others along. Part of the problem, she said, is a limited understanding of science that prevents many dog owners from understanding the value of their participation, whether their dog is healthy or not.

Wayne Kompare said his organization had circulated its health survey to 6,000 unique westie households, only 25% of whom were national or regional club members. Several participants identified confidentiality as the key factor contributing to high response rates in their recent

health surveys, though one said the questionnaires require too much verification to permit a completely anonymous survey.

Ms. Hamil said another option is to enclose a breed insert with every AKC registration.

An audience member said successful research can lead to a different set of problems. Now that her club has a test for one of its breed's major diseases, "people don't want to test their dogs," she said. "So when you do see the big breakthrough on the horizon, you need to start working with your membership to really start getting the education out there."

A number of participants discussed strategies for involving non-AKC members in health surveys. One club found that online surveys are easily accessible to non-members and general pet owners, while another requires breeders to endorse health testing if they want to appear in the club directory. "People want to do it," one club representative said. "They want to have a genetically clear dog," if only in response to peer pressure. An attendee noted that some of that pressure comes from the Canine Health Information Center (CHIC), adding that clubs should join the program if they haven't already. Another advised against refusing advertising space to breeders who fail to test their dogs, preferring to keep them within the club circle as long as they acknowledge that the litters are untested.

Another form of peer pressure occurs within the clubs themselves, with some breeders advertising "five-star" dogs that are cleared of all potential ailments. "Talk about peer pressure!" a participant said. "When you're selling puppies at \$3,000 a shot, you know what peer pressure is. People were testing like crazy."

Participants applauded again at the suggestion that breeders in the United States should be expected to register all the puppies in a litter, as their counterparts do in other countries, rather than counting on owners to follow through. One breeder said she already registers, tests, and microchips every pup, and has worked to turn health testing into a competitive benefit within her breed.

Panelists and participants discussed acceptable response rates for health surveys, with Ms. Hamil citing rates of 35–50% or better. Mr. Kompare said his foundation's first survey achieved a 25% response, but drew from a larger pool of 2,700 dogs.

An attendee expressed concern about survey reliability, noting the data will be skewed if some breeders only report two puppies out of a litter of eight. He added that the offer of a five-star animal is misleading, since a dog testing clear of disease may be ill a week later. Ms. Hamil said it can be difficult to explain that testing is a static look at a dynamic process. "We have to remember that all we can measure is what we did on that day, and all those things are subject to change."

Meeting the Challenge: An Update on the *Double the Dollars for Dogs* Endowment Campaign

CHF Director of Development **Jeff Sossamon** described the variety of fundraising mechanisms that enable the CHF to fulfill its mission to help dogs live longer and stronger, and underscored participants' role in raising money for research. "You guys are our biggest ambassadors," he said. "Our volunteer group is our network, and everybody can play a role."

The *Double the Dollars for Dogs* endowment campaign has already raised \$475,000 toward a \$500,000 target, including \$125,000 contributed through breed clubs. Donations to the endowment are matched dollar for dollar by the AKC, and the money will be administered as a permanently restricted fund, with research funded from the interest on investments but not the principal.

Mr. Sossamon noted that everyone wins when the CHF funds health research. "Canine research is helping out tremendously all over the place," he said. "It's contributing to different species, to humans, and it's one perfect way for you to get involved and help out." He invited participants to share ideas for marketing and communications by contacting him 888-682-9696, jds@akc.org

AKC Companion Animal Recovery: Reuniting Lost Pets with Owners

Associate Director **Jason Miller** said AKC Companion Animal Recovery is the largest non-profit recovery service in the United States, with three million animals in a database that began in 1995. The organization has performed 300,000 recoveries, operating around the clock and every day of the year.

For the past 10 years, AKC CAR was the exclusive back-end recovery supplier for a microchip manufacturer, but when that contract ended in early 2005 the manufacturer began positioning itself as a direct competitor. While his organization no longer receives the manufacturer's enrollment form, Mr. Miller said owners and veterinarians can reach AKC CAR online or via a toll-free phone line: 800-252-7894.

AKC CAR also operates a support and relief fund that began with the 9/11 attacks in New York and Washington, DC, then gradually expanded to cover natural disasters. AKC volunteers were on the ground during the California wildfires and after the 2004 Florida hurricane, and are still involved with disaster recovery on the Gulf Coast.

To date, AKC CAR has received about \$1 million for relief of animals displaced by Hurricane Katrina, enabling AKC CAR to ship food and water, thousands of airline crates, medical supplies, leashes, collars, microchips, collars, fans, and generators. Mr. Miller stressed that the organization will be on the ground for the weeks and months that will be required for the region to complete its recovery, rather than dropping in for a few weeks before packing up.

Good Breed Clubs Improve Research

Karl Lark, PhD, of the University of Utah described The Georgie Project (www.georgieproject.com), named for his deceased Portuguese Water Dog, as a prototype of what a breed club and researchers can do to make progress in a difficult field.

Genetic studies need large sample sizes, and as a former soybean geneticist, Dr. Lark knew that plants have very large “litter sizes” compared to dogs and humans. “So one of the points we wanted to prove as we got into this was that in fact it can be done,” he said. “The idea is to approach genetic isolates, breeds that have dogs that are of interest, and to use free living dogs” for the research. The approach avoids the ethical, humane, and cost considerations surrounding captive dogs, and turns out to be less expensive than working with mouse colonies in laboratories.

After Georgie died in 1996 of an autoimmune disease, Dr. Lark said he was amazed to learn that Portuguese Water Dogs were ideal for genetic research. A small population of 9,000 to 10,000 dogs with excellent pedigree records, the breed had about 30 founders, of which 10 were responsible for about 90% of the present gene pool. “That makes a geneticist’s work much easier, and allows you to do quite a bit,” particularly because the population ranges from virtually unrelated individuals to dogs that are “very incestuously backcrossed.”

With 500 owners and breeders and 1,130 dogs enrolled, the project currently holds 900 DNA samples and 550 x-rays. Dogs in the database are identified by number only, making their identities “as confidential as your Visa information or your bank balance is at the bank,” and their pedigrees are checked through a DNA matrix.

The database can be used to study two types of disease, Dr. Lark explained. Simple diseases, usually recessive and controlled by one gene, include PRA and cardiomyopathy in Portuguese Water Dogs. The more complex diseases, all of which depend on multiple genes, include cancer, autoimmune disease, and osteoarthritis. Once the canine genome was sequenced, it became possible to identify the genes in the Water Dog that control its size and shape and differentiate individuals between the two classic shapes—long, thin legs and long snout, or a more powerful build comparable to a bulldog.

The ability to identify genes or gene clusters that regulate body size and shape helped explain how different dog breeds arose so quickly, he said: “There were massive clusters of genes that could move whole shape and functional differences.” Genetic research on the Water Dogs has also identified one gene for osteoarthritis and two for Addison’s disease, one that increases frequency and one that decreases it.

Future research will be much easier, now that the breed’s genetic sequence has been mapped. “Every time you get a new phenotype, a new characteristic, a new disease, you can plug it in and you already have the genetic information,” he explained. “So once that investment has been made, you have an enormously powerful tool. And you want to strike while the iron is hot, while those dogs are still there.” With that in mind, owners participating in the Georgie Project are

being asked for blood samples, and they will also be asked to participate in an autopsy program as their pets die.

“Emotionally and financially this is a tremendous venture,” he said. “But if we can autopsy as many as 300 of these 500 dogs, we will know their state of health at the time of death.” An initial series of about 15 autopsies has already identified a dog with cancer that had preclinical irritable bowel disease [editorial note: I **think** he said IBD], and a dog with Addison’s that also suffered from autoimmune polyglandular syndrome. “If we can correlate these, we may be able to get some idea for early diagnosis.”

For other breeds, Dr. Lark warned that even simple recessive diseases take time to study. More complex, cutting-edge diseases are “much more expensive, and take a much longer time to pay off. But if you don’t start now, you’ll never get there.” The Georgie Project has collected more than \$1 million over the past nine years, and was very fortunate to benefit from a \$200,000 seed grant that called for quantitative research on plants or animals.

Corporate sponsors and the National Institutes of Health are now taking an interest in the project, even though NIH decision-makers are still much more interested in mouse models. But “now that the dog genome has been sequenced, there are a lot of advantages,” he said. “The dog has a much closer genome to the human. More than 300 human genetic diseases are found in dogs. The different breeds are genetic isolates, so they’re very important and very hard to find in humans.” Even with that understanding, the NIH won’t fund a project unless a breed club has signed on.

Dr. Lark challenged the view that breeders should attempt to eliminate chromosomal aberrations once they have been isolated. “As a scientist, I tell you that if you do that, you’re throwing the baby out with the bathwater, because you have no idea what other genes may be linked,” he said. “It may be the gene for the most beautiful coat you’ve ever seen, or it may be for the shape of the dog or the behavior.” The alternative is to be sure that carrier dogs are bred with normals, rather than ruining a breed in an attempt to perfect it.

Canine Genetic Disease: Neuronal Ceroid Lipofuscinosis (NCL)

Stuart Eckmann of the Tibetan Terrier Club of America (TTCA) traced the evolution of his breed’s groundbreaking DNA bank, noting that the club had now followed 30 generations of affected dogs through the end stages of neuronal ceroid lipofuscinosis (NCL). Tracking a disease with no post-mortem test was not easy, particularly because veterinary ophthalmologists often interpreted the condition as progressive retinal atrophy. “This is not PRA,” Mr. Eckmann said. “It is a late-onset, terminal condition characterized by mobility problems and some component of dementia,” as well as blindness.

The PRA diagnosis had already been attached to many pedigrees by the time the TTCA began posting articles on NCL online. “While a practicing vet trumped whatever we said, nothing trumps the Internet. If it’s on the Internet, it must be true.” People with affected dogs began

making contact, and the sense of denial was so strong that people declined to include a speaker on NCL on the agenda for the Tibetan Terrier world congress a couple of years ago.

But when the speaker was funded through private contributions, the club began making interesting connections. The audience included parents of children with Batten's disease, and when the Tibetan owners described the abnormal head tilt associated with NCL, one of the parents recognized it as an early-stage seizure associated with Batten's. That exchange grew into a collaboration between two groups facing similar genetic problems, in which the openness of the parents' quest for a solution helped to convince the club members to embrace testing.

Both groups hope to find a genetic marker for NCL/Batten's, eventually leading to treatment. The Tibetan club has extended its DNA bank to include a tissue repository, and is archiving histopathology, clinical data, and now tissue culture to support *in vitro* analysis of potential diagnostic and treatment options.

For the parents, the dogs' shorter breeding cycles represent an opportunity to fast-forward their research and find a useful genetic marker. For the Tibetan owners, the partnership has become an invaluable dialog. "We'll tackle the same battle on different fronts, and in doing so, conquer a common enemy."

Martin Katz, PhD, of the University of Missouri presented the NCL/Batten's experience as a model for identifying the genetic base of inherited canine diseases. Although researchers have yet to identify the chromosomal abnormality responsible for NCL in Tibetans, they've found the target genes for the same condition in English Setters, Border Collies, and American Bulldogs.

The process of finding the gene for any inherited trait, including genetic disease, follows three steps. The first is to define the disease very precisely. The second is to determine the mode of inheritance. With that information, it becomes possible to identify the gene associated with the specific mutation using candidate gene analysis if candidates are known, or be looking more broadly for an association between the disorder and a specific gene.

To be diagnosed with NCL, an animal must have inherited the condition as an autosomal recessive trait, characterized by an accumulation of autofluorescent material in nervous and other tissues. The brain, retina, and other nervous tissues must be shown to degenerate as the disease progresses, leading to cognitive, motor, and behavioral changes. Premature death is the other universal diagnostic criterion.

The phenotypic markers for NCL are based largely on human research, which has identified mutations in six genes associated with Batten's disease. Although the gold standard for NCL is confirmation at autopsy, researchers needed an initial screening tool, to help breeders and owners identify dogs that might be affected. Based on the first few definitive diagnoses, Katz and his team listed a series of phenotypic behavioral markers, including nervousness, loss of coordination, upset by loud or unfamiliar sounds, bumping into objects or barriers, impaired ability to climb stairs, decreased ability to see in dim light, lost training, aggression, changes in eating habits, seizures, and onset between the ages of five and seven. Under an electron

microscope, tissue analysis confirmed massive accumulation of a yellow, autofluorescent material in the cerebellum and the retina.

With the pool of affected dogs defined, the research team compared their genetic makeup with unaffected relatives to determine whether and how the condition is inherited. With a genetic mechanism identified, the ultimate goal is a DNA test. But after screening a total of nine candidate genes, Dr. Katz and his colleagues had still not identified the relevant aberration in Tibetans.

With no more candidate genes to study, the next step is to locate the gene within the canine genome, a process that is currently under way. The late onset of the disease is a major stumbling block, making it more difficult to assemble the large number of dogs required for broader analysis.

Saturday, October 22, 2005

Welcome

Conference Co-Chair and CHF Director **Lee Arnold** acknowledged the “expertise and financial leadership” among attendees that had made the conference possible. He noted that the conference program had “brought together the best of the best,” adding that “you will truly be surprised at the cutting-edge technologies, the identification methods, the genetic tests, and all the resulting treatments that are helping our dogs to live longer and healthier lives.”

CHF President **Wayne Ferguson** noted the diversity of a participant group that included a large number of PhDs, veterinarians, and physicians. He underscored the Canine Health Foundation’s role as a catalyst for collaboration and discussion among researchers and investigators, bringing together the funds and the scientific minds that will bring about cutting-edge breakthroughs in canine health.

“This is your Foundation, dedicated to overcoming the afflictions that many of us have faced with our own dogs,” he said. CHF works with leading veterinary scientists and research organizations to determine the most efficient use of research dollars, and has developed a peer review process that has been accepted as the gold standard for canine research, so “we are directing your money wisely.” Since 1995, the Foundation has allocated more than \$14 million to a network of investigators that stretches from The Netherlands to California.

The Foundation is financially strong and fiscally sound, and reduced its overhead from 28% to 13% by moving its office to Raleigh, N.C., a decision that freed up almost \$400,000 for research. Mr. Ferguson pointed to the Foundation’s private sector alliances as another measure of its success, noting that “these major corporations don’t just throw dollars away unwisely. They’re confident in our abilities and strengths, these are relationships that we will continue to nurture and foster so we can continue to maximize your efforts.”

That same confidence extends to breed clubs and individual donors. The Foundation’s first major endowment campaign, Double the Dollars for Dogs, has already raised \$475,000 against a goal of \$500,000. “We’re doing well,” he said. “This is the state of the Foundation, and I’m very proud to stand here and give it to you.” The next 10 years will bring tremendous progress, Mr. Ferguson concluded, and “it wouldn’t happen without you.”

Steve Remspecher, Director of Marketing with the Nestlé Purina PetCare Company, commented that “it’s great to be in a room full of dog people. Yes, dog people willing to give up weekend after weekend to support their passion. Most people would call us crazy. I call us lucky, because we have the love and companionship of our canine friends.”

Mr. Remspecher attributed CHF’s success to “people with a common vision to improve and enhance the lives of our four-legged friends,” a vision that Purina shares. He added that breed club representatives attending the conference had an “enormous responsibility. You must represent the needs of your club and communicate back the information provided to you at this conference.”

Dennis Sprung, President and CEO of the American Kennel Club, noted that Parent Clubs “are the backbone of purebred dogs in America. You are the guardians of your breeds. Your passion is about your breeds and about all dogs, and you are here this weekend to learn, to share knowledge, and to educate yourselves about canine health.”

He urged each attendee “to share what you have learned with your membership, so the excellent work presented here can continue,” and acknowledged the scientists, veterinarians, club members, and breeders who make canine research a reality.

Mending Heart Failure: Stem Cells Are a Hope for the Future

“One of the most important points about this field is that it’s not a question of if cell therapy is going to move forward for cardiac and vascular repair in both animals and humans, but when,” said **Doris Taylor**, PhD, Director of the Center for Cardiovascular Repair at the University of Minnesota. Interest in stem cell treatment in human cardiac care is exploding, and similarities in risk factors suggest that lessons from human health research can be applied to canines, as well.

Atherosclerosis and ischemic heart disease appear to be uncommon in dogs, except for those with hypothyroidism or diabetes, but Dr. Taylor said it may also be unrecognized. One study of 65 dogs with confirmed atherosclerosis found that 16 died with few or no previous clinical signs, and of 29 that died suddenly in response to anesthesia, 25 had atherosclerosis.

Diabetes and heart disease are both associated with a loss of stem cells, she explained. In humans, the number of circulating endothelial progenitor cells (EPCs) decreases as the severity of diabetes increases. Similarly, Dr. Taylor’s previous research group at Duke University showed that the severity of coronary artery disease increases as EPCs decrease. Heart failure among dogs increases with age and is often associated with valvular diseases and dilated cardiomyopathy, both of which are related to decreasing EPCs.

Aging is essentially a failure of stem cells, which Dr. Taylor described as the body’s innate repair tool. “As we go through our lives, our organs and tissues are constantly repairing themselves, because we have these populations of cells in our bodies that are capable of that repair,” she explained. Research is beginning to suggest that an inflammatory response is actually a signal that a particular part of the body needs stem cells—and in that light, preclinical tests for inflammation, not cholesterol or lipids, are now seen as the best measure of heart disease.

“Our goal is to increase stem cell numbers, increase function, and increase the survival of these cells in an inflammatory or stressful environment,” she said. Over time, stem cells diminish in their numbers and effectiveness. But “if we can preserve stem cell function, we can prevent many of the diseases associated with aging.”

Dr. Taylor said stem cells have two key characteristics: They can renew themselves, and they can differentiate into a number of different tissue types. She showed a slide of a beating heart

muscle cell derived from stem cells, noting that “the first time you see beating cells in a dish, it really makes you ask the question, ‘What’s alive.’ It’s pretty phenomenal.”

Although embryonic stem cells are 10 to 15 years away from clinical use for cardiac repair, adult stem cells can be derived from muscle or bone marrow. Researchers believe the muscle-derived cells most readily produce new muscle, while marrow-derived cells are most conducive to blood vessels. With the right cues, they will respond to the environment in which they are placed, and research has also identified fat, blood, and most recently, heart tissue as sources of stem cells.

Dr. Taylor traces the progression of ischemic heart disease from inflammation secondary to a heart attack, to the death of cardiocytes, through remodeling and compensation, decompensation if the scar is large enough, and heart failure. “If there’s a large enough injury to any part of the myocardium, the rest of the heart can’t compensate, and those cells fail, literally.” Past interventions have used cells, genes, and devices. But in the future, clinicians will “try to work upstream” and prevent vascular disease by growing new vessels, working backward through a process of reverse remodeling, and “hit the home run and actually grow new cells in the heart.”

If the ultimate goal is to repair an injured heart, the challenge will be to deliver compatible cells. Dr. Taylor’s lab began testing the functional benefit of that strategy in 1989 by transplanting autologous skeletal muscle cells (myoblasts) into the hearts of rabbits, a species that is prone to heart attack. By 1998, the team had demonstrated that cells could be injected into the scarred region of a heart, leading to a thickening of the myocardial wall and improved heart function. Ten years of study also showed that dosage made a difference: the greatest improvements occurred with high doses of 100 million cells. Human clinical studies began in Europe two years later.

A key measure of clinical impact is the ability of the heart to pump blood. In normal patients, each heartbeat pumps out 50-65% of the ventricular blood. Patients with heart failure may be in the range of 24%, increasing to 32% after myoblast delivery. The procedure also helps to contract the heart muscle and shift it to a more functional oval shape. In the 300 myoblast transplantation studies that have now been completed world-wide, one-third of patients showed major improvement, one-third improved slightly, and one-third remained stable or declined. Other clinical research has confirmed the safety of transplanting bone marrow-derived stem cells, and further studies are moving forward.

In dogs, one study isolated specific populations of bone marrow cells, called multipotent adult progenitor cells (MAPC), labeled them with green fluorescent protein for future tracking, and transferred them to the damaged areas of the heart. The study showed improved cardiac output in the treated animals.

But while there is increasing evidence that stem cells can be used to treat canine heart disease, Dr. Taylor said researchers must proceed with caution. “This is a new field,” she noted. “We don’t really know what we’re doing. We think we do, but we don’t. So we have to under promise, and over deliver based on good science. If we don’t, I think we have the potential to doom what is otherwise a very promising field.”

Recently, the first negative results of cell therapy clinical trials were reported. It's good news that researchers are sharing their results, she said, but the underlying issue is that no one quite understands how these cells work. An immediate priority is to identify the cell types that are most useful for different purposes, and Dr. Taylor presented test results that linked different cell types to improvements in systolic performance, diastolic performance, and both.

The *Journal of Thoracic and Cardiovascular Surgery* recently reported a canine study in which myoblasts and bone marrow cells were transplanted two weeks after heart attacks were induced. One group of animals received 100 million myoblasts, another received 30 million bone marrow cells, and a third group received both. The combined group showed the greatest improvement, followed by the myoblast group and the bone marrow group.

In the future, Dr. Taylor said the vascular part of cardiovascular disease will be treated through a combination of stem cells and gene therapy. And one research team recently found that it could grow cardiac-like stem cells from a small piece of the heart of an adult mouse. The procedure showed a dramatic improvement in heart function, using one-tenth the dose of undifferentiated cells that would otherwise have been needed.

“The exciting thing is that I think we have the potential to create tools that we hadn't thought were possible,” including artificial heart valves and blood vessels, and eventually artificial hearts. Nine months ago, Dr. Taylor's group began studies that involve taking the cells out of a pig, rat, or mouse heart, which then serves as a matrix for creating a new artificial heart using stem cells. The procedure already works well enough that it could at least point the way to the development of a cardiac patch with intact vasculature.

The other development on the horizon is the possibility of using stem cell therapy to prevent vascular disease. In one study of animals that had already developed vascular plaque, a course of six injections at three-week intervals produced a plaque burden of 12%, compared to 30% in the control group.

Role of Chromosomes in Cancer: Diagnosis and Prognosis

Matthew Breen, PhD, of North Carolina State University noted that cancer is the most serious of the many diseases with which dogs are presented. He gave a brief overview of the stages of tumor formation and growth, noting that many dog cancers have metastasized before a primary tumor is diagnosed.

Cancer is known to be a genetic disease, and its progression is best understood at the genome level. The dog genome “is a very big place, and we also know that it's a very expensive place,” but Dr. Breen said chromosomes can be seen as a “biological filing cabinet” into which DNA is organized.

Over the past 25 years, human health studies have determined that chromosomal aberrations are hallmarks for genome instability, and have characterized about 27,000 aberrations that lead to cancers. In the last 10 to 15 years, researchers have identified the genes that drive the

development and progression of different tumors, and have linked the presence or absence of specific aberrations to particular clinical outcomes. Those outcomes depend not only on the piece of chromosome that is gained or loss, but on the relationship between those genes and the rest of the genome.

Dr. Breen described different types of chromosomal aberrations, including “reciprocal translocations,” in which genes exchange with no loss of tissue, and “imbalance aberrations,” involving a net gain or loss of DNA within a chromosome. Both types have an impact, he explained, because “genes like to live in their evolutionarily determined neighborhoods,” and the interrelationships change when they relocate. Those changes are major features of many types of cancer.

Relatively little is known about canine chromosomes and cancer, largely because the chromosomes are very difficult to work with. Dogs have 78 chromosomes, compared to 46 in humans. The chromosomes are also a lot smaller, which makes them difficult enough to work with when they’re normal, harder still to identify when they’re aberrant. A whole series of tools had to be developed to enable researchers to color code chromosomes in order to recognize the abnormalities. The technique made it possible to label the “filing cabinets” that make up the dog genome and interrogate the genome very precisely at the chromosomal level.

To look for chromosomal changes in tumors, researchers need viable cells, and Dr. Breen acknowledged the owners and breed clubs that have provided tissue for study. When the samples arrive, the malignancies are cultured in flasks. After 10 days of growth, researchers can color code specific pairs of chromosomes and check them for aberrations that correspond to specific types of cancer.

Dr. Breen said chromosomes 1, 11, 13, 14, and 31 are closely correlated with a predisposition to canine lymphoma, with different combinations related more specifically to B-cell or T-cell lymphomas. Aberrations at chromosome 13 appear to be linked with better survival rates following treatment, but the evidence is considered anecdotal for the very best of reasons—the majority of patients are still alive, and the data won’t be final until causes of death are known.

For a very long time, Dr. Breen said, clinical oncologists believed there was no such thing as a good lymphoma—if the B-cell variant was considered bad, the T-cell type was terrible. But the more recent results show that owners and researchers should never give up hope. He cited one case of a dog with an abnormality at chromosome 13 that was diagnosed with T-cell lymphoma in 2001, underwent conventional chemotherapy, and has now been in remission for nearly four years. “You could argue that the dog has been cured,” an outcome that was thought to be impossible with T-cell lymphoma.

In reply to participants’ questions, Dr. Breen said it’s difficult to know when chromosomal aberrations occur because researchers only receive tumor tissue after a lump is large enough to detect. The lumps have been getting smaller, indicating “If it turns out to be something nasty, the sooner we get that tissue, the more we can learn about what’s happening in the early days.” Researchers are also looking at tumors in dogs that relapse, to see whether the aberrations are the same the second time around.

Genetic Impact of Disease Risk: Understanding Prevention & Treatment

Jaime Modiano, VMD, PhD, University of Colorado Health Sciences Center, said that cancer is the leading cause of disease-related death in dogs as well as a leading cause of death in humans. Dogs and people have similar types of cancer with comparable histories of incidence, age of onset, location, progression, and outcome. Because pet dogs share our environment, it is possible to study both heritable risk factors and environmental factors in cancer susceptibility.

All vertebrates are prone to cancer. Cancer cells will outcompete surrounding cells. Many genes influence cancer susceptibility, and researchers must consider both genetic predisposition and environment. It is not possible to breed out a cancer gene to eliminate the disease, but it may be possible to identify risk factors in dogs and breed them out.

Many alternative therapies for cancer have been used, but such therapies should be tested for safety and success. Many therapies are derived from plants, but that does not mean herbal remedies work.

There is more cancer in dogs now than there was in the past, which some people have concluded is a result of environmental factors such as pollution or commercial products. In fact, however, there is more cancer than in the past because dogs are not dying earlier from parvovirus and other now preventable causes.

Cancer risks cannot be eliminated; cancer occurs during the process of cell division. Dr. Modiano said, “Life is the single highest risk factor for cancer.”

Researchers must design tailored therapies for canine cancer.

Non-Hodgkins Lymphoma (NHL) is among the top three dog tumors. The lifetime risk for dogs to get NHL is one in 10 to 20; for people, it is one in 50. In treating cancer in dogs, success is defined as surviving one year after treatment. That survival rate now is at 55%.

Some breeds, including Boxers, Golden Retrievers, Labradors, Scottish Terriers, Basset Hounds, Saint Bernards, and Dobermans, are at higher risk. NHL is most common in middle-aged dogs, no matter what the breed.

About 60% of dogs with cancer have B-cell lymphoma, 35% T-cell lymphoma, and the rest are unidentified. Some breeds are more prone to B-, some to T-cell tumors. As with humans, there are more T-cell cancers in younger dogs and more B-cell tumors in older dogs.

Dr. Modiano said his research had looked at related breeds as groups based on AKC groups, then as groups by genetic clusters. T-cell disease was more prevalent in older breeds and B-cell more prevalent in recent European breeds. Boxers are at greater risk for NHL than other Mastiff breeds. There are parallels among humans: Caucasians have more T-cell cancers than Asians, pointing to patterns of inheritance.

Researchers are looking closely at tumors to see if abnormalities are related. They have compared tumors in Golden Retrievers to tumors in the rest of the dog world and found deletions on chromosome 14 in all B cell tumors in the Goldens, but in few other dogs.

Matthew Breen's research team has compared the deleted section of chromosome 14 in dogs to chromosome 7 in humans to see what parts had been deleted and identify the genes to look at for cancer susceptibility. If the susceptibility in dogs becomes better understood, that information may be transferable to lymphoma in people.

Dr. Modiano said research on canine Non-Hodgkins Lymphoma is in progress. He has received conditional grant approval from CHF, pending club support.

An audience member said, "I'm in awe about what you are doing, with others, about cancer in dogs." He urged people to ask their veterinarian for chemotherapy instead of euthanasia when a dog was diagnosed with cancer. He also encouraged Dr. Modiano to think about co-factors affecting heredity.

Dr. Modiano replied, "I have a simple answer, which is that I agree."

Katrina Update

Dennis Sprung, President and CEO, American Kennel Club, said the AKC staff has been working since Hurricane Katrina to rescue displaced and abandoned dogs. This has meant weeks of working with shelters, staging centers, and breeders.

After Katrina hit, the AKC sent supplies—collars, leashes, pet food, and crates—to affected areas. It sponsored airlifts for dogs and even a few cats from Louisiana to Morristown, N.J., then airlifted the dogs back to Florida, where they were sent to Palm Beach shelters.

To fund these efforts, a disaster relief van accepted donations at dog shows, and donations were made on the AKC website. The website also had a “need help—want to help” exchange. More than 375 AKC clubs participated.

Mr. Sprung said that the AKC alerted the media to the information on the website, which resulted in links appearing on about 75 other websites and extensive newspaper coverage.

With the Katrina experience behind them, the AKC staff reached out to the area before Hurricane Rita hit to let pet owners know where to go for help.

Businesses and other organizations also contributed to the canine disaster relief efforts. Purina, for example, donated cash and food to animal shelters after both Rita and Katrina.

These two hurricanes have pointed out the need for canine disaster planning, and the AKC has begun working on a specific plan. When a disaster such as a hurricane is predicted, the AKC will send demi-containers, which are dog crates already stocked with food, water, and leashes, to a staging area before the disaster hits. There has been no coordinated effort until now, but the AKC is leading coordination for the future.

Mr. Sprung thanked the staff, clubs, and individuals who helped.

In the question and answer period, an audience member asked why assistance dogs were abandoned after Katrina and not allowed to travel with their owners. The response came from another audience member, who explained that an assistance dog takes up as much space as a person in a rescue vehicle, and priority goes to rescuing the person.

Mr. Sprung said the AKC will work with legislators and others to try to change that attitude among first responders and also will let the 75 other websites that linked to the AKC site know about it.

Another member of the audience asked how owners could get their dogs back after a disaster when the dogs had been shipped out of area. Mr. Sprung recommended owners implant an identification microchip in the dog for this purpose.

When Rita hit, a Texan said, assistance animals and pets were evacuated with the residents. Animal shelter vans met evacuation buses, took crated animals, and gave owners a receipt. The

local groups sheltered the animals and returned them to their owners when they were ready to go back home.

Panel: Canine Cancer Research Update

CHF Director **Dr. William Newman** chaired a question and answer session that focused largely on the protocols for submitting blood and tissue samples to four eminent research teams, represented on the panel by Matthew Breen, PhD of North Carolina State University, Kerstin Lindblad-Toh, PhD of the Broad Institute, Massachusetts Institute of Technology, Jaime Modiano, VMD, PhD of the University of Colorado Health Sciences Center, and Elaine Ostrander, PhD of the National Institutes of Health (NIH).

Dr. Lindblad-Toh presented a slide showing the current cancer research interests of different study teams. The panelists advised that tissue samples should be sent to Dr. Modiano or Dr. Breen, while blood samples can go to any of the four groups. Dr. Lindblad-Toh also drew attention to the formation of the Canine Comparative Oncology Genomics Consortium (CCOGC), a new body led by NIH that will soon be accepting samples for osteosarcoma, melanoma, and lymphoma.

In general, she said genetic research requires samples from affected animals and healthy older controls, with “older” defined differently for different breeds. Blood samples last for about a week, so they have to be sent quickly, based on detailed instructions that are available on the researchers’ websites. For genetic aberrations, the researchers need tumor tissues from affected dogs, normal tissues, and blood.

Dr. Ostrander encouraged participants to work with the sample coordinators listed on the slide, noting that her lab sends out cheek swab kits upon request. She stressed the importance of comparative data on older unaffected dogs, for which blood samples are needed to supplement the DNA available from a cheek swab.

All the researchers stressed that participation in their studies is confidential, unless individual breeders or owners choose to self-identify. Specific waiver provisions vary among institutions, but there is some interest in harmonizing terms and conditions to make the consent process less complex for participants. **Dr. Breen** stressed the importance of filling out the consent form in full, to ensure that samples do not stale-date while ethical and administrative conditions are met.

Each group of researchers—Drs. Lindblad-Toh and Ostrander collecting blood samples, Drs. Modiano and Breen soliciting tumor tissue—expressed a commitment to share contributions with their colleagues. The difficulty, Dr. Breen said, is that tumor samples must be delivered more quickly to ensure cell viability. For both sample types, but especially for tissue, donors should contact the labs in advance to let them know that the material is en route.

Dr. Newman asked whether the definition of older unaffected dogs was limited to relatives. Dr. Lindblad-Toh said researchers need family members for linkage studies, but look for unrelated individuals for association studies. In that case, “we typically want the controls to be unrelated at

the grandparental level, and essentially totally independent from the affected group.” Some study designs do call for comparisons between affected and unaffected siblings. Dr. Ostrander said her lab usually establishes an age cut-off of 10 years, but willingly accepts samples from younger dogs that will require verification of health status at a later date.

A couple of participants asked about research on viral or other co-factors that could serve as initiators for genetic abnormality. Dr. Modiano said a number of microbiologists and virologists are exploring the question, including some researchers looking for a canine equivalent of Epstein-Barr virus and others that identified a form of papillomavirus as the cause of equine sarcoid. He identified North Carolina State as a leading source of research on infectious co-factors, and invited participants to suggest new research questions by email.

A participant asked if the researchers would accept tumor samples from dogs that had been entered in chemotherapy. Dr. Modiano said he would accept blood for mapping studies from treated dogs, but not tissue, since the chemo alters the tumors’ genetic structure. Dr. Breen said he accepts samples from dogs that received chemotherapy three or four years previously, since their blood samples show no abnormalities. He also encouraged breed clubs to solicit the older, pre-treatment tumor samples that were collected by veterinarians and stored by pathology labs, noting that researchers can borrow the samples, take a few cells, and ship them back.

A writer covering the conference for a major consumer/pet owner magazine asked the researchers whether their interests were limited to specific breeds and cancers. The researchers agreed to provide contact information and detailed guidelines for collecting tissue and blood samples. Dr. Breen said 50% of the queries he receives already come from pet owners, rather than breed health committees.

A participant asked whether veterinarians should share samples they’ve already collected from their elderly purebred patients. Dr. Ostrander said vets should consult the breed guidelines on the researchers’ websites, then encourage the owners to provide consent and participate directly. “While you’re sending the samples in,” Dr. Newman added, “please send money to CHF.”

A participant asked for clarification of the conflicting rumors that a hip dysplasia test is right around the corner, or will never be developed. Dr. Ostrander said breed-specific tests for complex diseases will almost certainly appear over time. Dr. Lindblad-Toh said the tests won’t be 100% accurate, since clinical outcome depends on the triggers Dr. Modiano had discussed, but it will still be possible to measure an individual dog’s relative risk. Dr. Breen said researchers may not know why a particular chromosomal aberration associates with a given cancer, but will still be able to explain that cancer’s sensitivity to treatment—which is really the information that will help owners and breeders choose a course of treatment for a sick dog.

A participant asked how the panelists would deal with genetic histories of unregistered dogs whose owners hear about ongoing research through the popular media. Dr. Ostrander said mapping studies require relatedness through the great-grandparent level, and must therefore be limited to AKC-registered dogs. For future population studies to determine the frequency of a mutation in the general population, she and Dr. Lindblad-Toh agreed that pedigree will be less critical.

Dr. Newman announced that Drs. Ostrander and Modiano would be working with CHF to present a canine cancer conference in Chicago in September 2006.

Key Facts About Protein Metabolism in the Dog

Jill Cline, PhD, Nestlé Purina PetCare Research, said that protein is made up of amino acids. These long molecules are cut into small pieces in the dog's gut and ultimately absorbed through the intestinal wall. Dogs need about 20 different amino acids, about 10 of which must be provided in the diet. When a dog's diet contains inadequate protein, the body will draw on protein reserves from lean body mass (LBM).

“People used to think that feeding low protein diets to large breed puppies could help prevent skeletal problems,” Dr. Cline said. “And that's one of those urban legends that just starts hanging around with us.”

Recent research, however, supports a low energy moderate protein diet for large breed puppies. The study looked at Great Dane puppies that were fed diets with the same number of calories but with varying levels of protein. The study found a lack of growth in puppies that were fed too little protein. Large breed puppies should receive at least 25% of their calories from protein. High protein diets are not detrimental to large breed puppies.

The effects of sub-clinical protein deficiency aren't visible in a dog's musculature or coat, but the dog will have reduced resistance to toxic agents or infectious disease, reduced resistance to parasites, slower wound healing, and delayed immune problems.

Another study looked at the protein needs of large older dogs, seven years and older. Aging Pointers were fed diets with varying proportions of protein. Those fed higher protein diets had higher proportions of LBM.

“What that means is that by continuing to feed a lot of protein to older dogs you're helping them to maintain lean muscle mass,” Dr. Cline said.

As dogs age, their energy requirements decrease 20 to 25% unless they are very active older dogs. Older dogs process protein less efficiently, and may need more than younger dogs. If protein in their diet is inadequate, older dogs lose LBM.

Protein level in dogs with poor kidney function has been a cause for concern. Researchers found no decline in kidney function based on varying protein levels—diets with 10% to 40% protein had no effect on renal failure. High protein diets do not cause kidney failure in healthy dogs.

Overweight dogs historically have been put on calorie-restricted low fat diets that usually were low protein as well. Severe calorie restriction, however, leads to loss of LBM, which is the primary determinant of metabolic rate. A lower metabolic rate is counterproductive to long-term weight loss.

Researchers studied 42 overweight dogs that were put on 20%, 30%, and 39% protein diets. The total amount each dog was fed was adjusted so the dog would lose 1% of body weight a week. Researchers concluded that increasing protein was important for successful long-term weight loss. With increased LBM, the increased muscle mass burns more calories.

DNA and the AKC

The AKC created a department to work with DNA in 1997 for parentage verification and genetic identity purposes only, said **Tom Sharp**, AVP Compliance, American Kennel Club. The AKC uses DNA to verify the integrity of the registry, not for research purposes.

The AKC has two DNA programs: a compliance audit and DNA certification.

The compliance audit was introduced in 1998 with little publicity. Since then, 15 AKC inspectors have collected more than 83,000 DNA samples during routine kennel inspections throughout the United States. In the first quarter of 1998, DNA tests showed that 87% of litters had correct parentage listed. By the end of 1998, that was up to 89%, and it now is better than 95%. These results are based only on kennel inspections, not on every breeder in the United States, and may be skewed as a result.

When incorrect parentage is discovered, the AKC notifies breeders and owners. Registrations are corrected if accurate information is available or cancelled—about half are cancelled.

Sharp said that the AKC also has had voluntary DNA certification by dog owners since 1998. The owner collects a DNA sample by using a cheek swab and mails the sample and payment to the AKC. The AKC enters information on the dog and sample in its database and ships the specimen to a lab. The lab then processes the sample and returns the results to the AKC. The AKC sends the dog owner an AKC DNA certificate and adds the dog's DNA profile number to its registration record to appear on pedigrees. The AKC maintains a database to verify the parentage of DNA certified dogs.

The AKC has required DNA certification of stud dogs if fresh or frozen semen is shipped or stored since 1998. It also requires DNA certification for a dog that sires more than seven litters in a lifetime or three in one year.

DNA testing is used in a parentage evaluation program if more than one male had the potential to sire a litter. DNA profiles of the sire, dam, and pup all appear on the DNA parentage certificate.

Formerly the AKC would not register multiple sired litters. That changed in April 2000, effective with litters born since 1998. The AKC now will use DNA sampling to establish parentage and register a multiple sired litter for a \$200 registration fee and regular costs.

Conditional registration is a new program, for registered dogs when a parentage issue two or three generations ago comes to light, Sharp said. The AKC first will attempt to determine parentage for correct registration. If parentage cannot be established, then correction is not

possible, and the AKC issues conditional registration. The pedigree will list “unknown” for the sire.

Sharp said, “These dogs’ AKC number would be changed, so that there would be a Q at the beginning of the number.”

Conditionally registered dogs may not compete in conformation or field trials. After four generations, with DNA of all four generations’ dams and sires on file, the Q will be dropped from the registration number.

In another new program, the AKC is requiring DNA samples from imported breeding stock for litters to be registered.

In the future, AKC DNA samples may be available for canine health research. The AKC is working on revising the forms it uses to allow the dog owners who submit DNA samples for parentage to give consent to allow additional uses of the archived DNA. Conceptually, a standard schedule could be drawn up so that researchers could plan to use the DNA from the AKC DNA bank and build the costs into grant requests.

In the question period after the presentation, a member of the audience asked how the DNA certification requirement for imported breeding stock would affect the third generation of desert bred Salukis.

Sharp said that because the breed has an open registry, the requirement for DNA certification of imported breeding stock would not apply.

Another questioner asked about increasing the requirements for DNA certification.

Sharp said some people want DNA certification required for all breeding stock, even the first litter; some want it for all registered animals, even pets that won’t be bred.

Another audience member asked if Parent Clubs could set their own requirements for DNA certification.

Sharp said the AKC was sending a letter to all Parent Clubs on encouraging DNA certification and how to require it for all members or only for breeding stock.

New Advances in Assisted Reproduction

OFA President **Frances Smith**, DVM, PhD, DACVP, of the Smith Veterinary Clinic discussed three aspects of canine reproduction, beginning with the use of drugs to induce estrus. Previous induction regimes “were very, very ineffective, and many of them were dangerous and resulted in pyometra, rather than pregnancy,” she said. The main treatments were gonadatropins like FSH and LH, pregnant mare serum gonadotropin, and estradiol compounds like DES.

The bitch has a relatively unique reproductive cycle, characterized by a period of progesterone stimulation, or diestrus, which lasts 63 days in the pregnant animal, even longer with no pregnancy. By contrast, the greatest inroads in reproductive medicine have occurred in species that cycle more frequently—a lot is known about human reproduction, and cattle which cycle every 21 days.

Drawing on research by Margaret V. Root-Kustritz, DVM, PhD, Dr. Smith traced hormone levels at different stages in the reproductive cycle, before listing two new groups of drugs that appear effective in manipulating the cycle: dopamine agonists, and gonadatropin-releasing hormones. The first group acts by suppressing prolactin secretion, which appears to affect FSH, LH, and the way the ovary responds to them. The second can be released in minute amounts through an implanted pump to induce a safe heat, although the pump is essentially a laboratory mechanism and costly to install.

The drugs have pros and cons, Dr. Smith said. The advantage is that they can be used to manipulate the reproductive cycle, to schedule litters around national specialty events or hold off estrus for long periods of time. But there are problems, as well: None of the drugs are approved for use in dogs, and the only one that is commercially available in the United States is a compounded drug, so that users must be warned that it may not be effective or safe.

“Those are big issues,” she said. “If I were to use this on a client’s dog, I would have them sign a release saying that based on endocrine knowledge and based on my belief that this drug does contain what I think it does, we have a pretty good shot at having your bitch cycle normally, conceive, and whelp a litter.” But the drug could not be used without a release.

The treatments are also expensive, ranging from \$130.00 to \$770.00 per treatment for a 70-pound dog, not including shipping and veterinary fees. Some require 30- to 40-day courses of daily treatment, and the least expensive option, Buserilin, has a pregnancy rate of only 20%.

Deslorelin offers a 62.5% pregnancy rate with one injection, at a cost of \$250 for the single dose. Dr. Smith said she was trying it out with one of her bitches, and had recently called her clinic for an update. “What I can also tell you is that she achieved near-ovulation, she showed no external signs of heat, and the boys had not a clue that she was near ovulation. So this has been a treatment failure so far. The good news is that it did not make her ill in any way.”

Breeders can also use low-dose prostaglandin 15 minutes before collecting sperm from stud dogs that are reluctant or have low sperm counts. The drug is quite safe, but users should not ask to bring it home. Prostaglandins are a dangerous class of drugs that can be fatal to both handlers and dogs if they’re not used properly.

Embryo transfer is another exciting option. The difficulty in canines is that both the donor and the recipient must be within about a day of ovulation, but the procedure can be and has been successful. Synchronization can theoretically be used to facilitate the transfer, but the other option is to maintain larger breeding colonies with many bitches at different stages in the cycle.

For canine embryos *in vitro*, the limiting step is the maturation of non-ovulated eggs, or oocytes. The eggs can be collected at any point in the cycle, though the procedure is simplest and most straightforward when the bitch is already in estrus. In Japan, a research team at Tottori University harvested mature oocytes from bitches with pyometras. The procedure has a low success rate, but is still promising for a breeder with a spectacular bitch that must be spayed.

Canine cloning has been attempted, but Dr. Smith described one very expensive effort that was unsuccessful, as well a successful clone in South Korea that required three years, 123 embryo transfers, and enough money to take the work beyond the point where it was financially feasible.

Dr. Smith said the central question is whether breeders should adopt new techniques, just because they can. “In my reproductive practice, the biggest single reason for failed conception is still poor timing,” she said. “Most of our dogs are still very normal. We just don’t get them together at the right time.”

A participant asked about treatment options for bitches whose progesterone levels drop during pregnancy, so that their litters are lost. Dr. Smith said premature luteolysis was suspected for some time but can be proven now, thanks to the use of ultrasound. Researchers don’t know whether the problem is caused by infection or genetic issues, and the cause will have to be identified before breeders can decide whether to treat the event. Breeders who opt for treatment can use Regumate, a synthetic progestational agent designed for horses. The product carries the risk of masculinization of female fetuses, leading to “puppies who look like little girls but internally don’t have normal reproductive organs,” but the risk to the bitch is minimal.

Another attendee asked about the best timing for implanting frozen semen. Dr. Smith said the ideal is to start from the day that the progesterone reaches a level of 2, follow the levels daily, and breed four to six days later, usually on day five. But the specifics will vary from one animal to the next.

A participant warned that some reproductive problems can be 30% heritable, and that breeders should consider whether they want to pass those characteristics on to future generations. He added that falling progesterone levels may not always dictate treatment: sometimes, a bitch with low levels will abort one puppy, then carry the rest to term.

In response to another question, Dr. Smith said the sole bitch puppy in a normal-sized litter often looks very mature, but never cycles. The suspicion is that the female puppies are influenced *in utero* by placental leakage of male hormones. She said she would welcome a research grant proposal to the CHF to try to confirm this clinical observation.

A participant asked Dr. Smith whether she prefers pellets or straws for artificial insemination. Dr. Smith replied that pellets are the most biologically appropriate way to freeze sperm and offer 10% better sperm motility in good dogs, but can be more difficult to identify than straws.

Freezing ovaries to harvest the oocytes requires advance planning, and the procedure depends on a university or some other facility that is set up to conduct embryo transfers. “The boys are much more simple because of the availability of the sample,” she said, though male canine infertility is

far more common than many people appreciate. She urged breeders to collect sperm as soon as their dogs are sexually mature, and audience members who had bred older dogs agreed.

Nutritional Approach to Managing Osteoarthritis in Dogs

Steven Hannah, PhD, Head of the Molecular Biology Group at Nestlé Purina PetCare Company, stressed the value of using the tools and knowledge coming out of genetics, genomics, and molecular biology to address nutritional questions.

Any canine research should start out with the whole dog, move down to the clinical level of organs, tissues, and nutrients, and continue on to the molecular level, before translating the results back to the dog and its owner. “We have to complete that circle to get to the end of the story,” he said. Nutritionists understand that nutrients are involved in specific biologies, but advances at the molecular level have opened up the possibility of attempting to modulate that biology through nutrition.

Osteoarthritis has been studied at length, but remains a complex problem, Dr. Hannah said. The most common joint disease in canines and humans, it affects 20% of dogs, 70% in the older population. Obesity is a clear risk factor for the disease.

In osteoarthritis, the normal process of repairing and maintaining cartilage breaks down, leading to a vicious cycle that ends with bone spurs, loss of cartilage down to the bone, bone fragments in the synovial capsule, and a great deal of pain. At the molecular level, an initial insult results in a variety of inflammatory mediators, which in turn induce the enzymes that break down the cartilage. Molecular nutrition becomes a part of the picture if it can be used to shape the regulatory decisions by which protein is coded from DNA.

To assess the cellular decisions along the road to osteoarthritis, Dr. Hannah’s research team looked at all the intermediate RNA in a normal or arthritic cartilage cell. The objective was to distinguish specific cellular messages that might contribute to the disease, identify the resulting proteins, and determine how nutrition might affect the process. From their initial studies, the researchers selected about 2,000 genes or genetic messages that appeared to differ between normal and arthritic dogs, of which 300 turned out to be statistically involved.

After identifying the most promising targets and identifying the relevant biochemical pathways, the team identified two primary opportunities for nutritional intervention: managing obesity, and managing the inflammatory process. Obesity was already a known risk factor for osteoarthritis, though the research showed that it was not the only cause. But the research also demonstrated the value of Omega-3 fatty acids in controlling inflammation. It clarified the process by which the treatment replaced Omega-6 fatty acids along the COX-2 pathway and replaced production prostaglandin E2 with prostaglandin E3, which is about 100 times less inflammatory.

Many drugs are available to block the COX-2 pathway, “but I would argue that using Omega-3 fatty acids is not pharmacology, but rather nutritional biochemistry,” Dr. Hannah said. The objective is to change the flux through the pathway, rather than using a treatment like aspirin to

block it indiscriminately. “The hope would be that by using these types of approaches, a client could perhaps wean their animal off the full dose of some of these non-steroidal anti-inflammatory drugs, and perhaps use fewer steroids.”

A study of 24 osteoarthritic dogs at Colorado State University showed that the treatment reduced the enzymes that degrade cartilage, both in their active form and at earlier stages in enzyme development. In a review of 146 case studies, 88% of dog owners saw improvements after two months on the Omega-3 diet, and 40% saw major improvements. On a nine-point scale, the owners reported improvements of 3.4 for mobility after an active day, 3.0 for running and walking, and 2.2 for climbing stairs.

A participant asked whether nutrition can be used to prevent osteoarthritis from developing, or to reduce bone spurs once they occur. Dr. Hannah said the treatment could theoretically be preventive, but studies to support the theory would be difficult to conduct. He added that it's generally a good idea to address low-grade inflammation.

Asked whether there are correlations between dogs and humans in the nutritional arena, he commented that “humans are real good models for dogs, and I hope they do more human work.” But he added that human clinical studies of Omega-3 supplementation have yet to develop the underpinning biochemistry that was the subject of his work.

Dr. Hannah agreed that nutraceutical forms of Omega-3 can make a difference, but warned that supplements should not be used at the expense of a complete, balanced diet. He explained that the decision to treat Omega-3 as a veterinary product, rather than a regular diet, was partly a regulatory issue related to products that claim health benefits.

Sunday, October 23, 2005

Principles of Health Management: What Can Breed Clubs Learn from Human Health Management?

AKC Director **Charles Garvin**, MD said an interest in human or canine disease management runs the spectrum from getting an individual over an episode of acute disease to trying to eradicate the disease itself. While purebred dog owners and breeders must look out for their own animals, and clubs position themselves as the guardians of their breeds, “the AKC Board has to be concerned with the survival of the sport, and in a more global sense, with the survival of the species.”

In dealing with human health issues at the individual level, physicians go through a basic process to arrive at a diagnosis and treatment plan, Dr. Garvin said. The first step is to take a subjective history, to find out anything the patient knows about the ailment. The second is to use exams and lab tests to arrive at a more objective picture of the situation. From that point, the practitioner arrives at a diagnosis and develops a treatment plan.

The focus is different at the population level, where the initial steps involve characterizing an outbreak of infectious or chronic disease, determining the cause and modes of transmission, and developing a menu of control measures that might include immunization, treatment, and public health education. Dr. Garvin said human disease can fall into several overlapping categories, including genetic, infectious, neoplastic, toxic/ environmental, degenerative, vascular, immunologic, traumatic, and nutritional.

With the successful conclusion of the Human Genome Project in 2003, a full description of the three billion base pairs of human DNA is now freely available on the Internet, making genetic disease a key focal point for research. About 400 genes have been linked to specific ocular conditions. But only seven so far have been connected to more complex, polygenetic conditions, and the sheer number of base pairs makes ongoing research a difficult and expensive pursuit.

He said the International HapMap Project, a consortium of scientists from Canada, China, Japan, Nigeria, the United Kingdom, and the United States, was about to release a map of the 250,000 haplotypes that account for 80-90% of all clinical variations in human genetics. While the project will dramatically improve the efficiency of future genetic research, it will be important to address the ethical, legal, and societal implications of defining the specific genetic manifestations of different racial and ethnocultural groups.

Yet the HapMap has already generated results. Researchers have identified a gene that triples the risk of age-related macular degeneration, the most common cause of blindness among Americans aged 60 and over, and determined that one base pair substitution may account for up to 50% of the cases.

Similar results were presented at the CHF’s 2001 conference, when Greg Acland, PhD of Cornell University reported on the first successful attempt at canine gene therapy. Researchers had determined that the same genetic anomaly caused congenital stationary night blindness in the

Briard and Leber's congenital amaurosis in humans. After researchers injected an adeno-associated virus carrying the wild-type gene into their retinas, the Briards were restored to full, functional vision, demonstrating that canine research can yield profound results for both canines and humans.

Dr. Garvin underscored the importance of breed health surveys in setting research priorities for Parent Clubs. He encouraged participants to act as breed champions for canine health research, noting that "the one power the parent club has is peer pressure." The key question, he said, is "how to convince the breeders to test their dogs, to do the screening, and to use that information in their breeding decisions. That cultural change is the true power of the breed clubs."

He said the Dalmatian Club of America Foundation has donated more than \$140,000 to the CHF since its formation in 1995, and has \$250,000 in current assets. Its health and research committee has formed working groups on allergies, eye disorders, hearing, hypothyroidism, kidney and liver disorders, longevity, seizure disorders and epilepsy, orthopedics, and urinary stones. At the Dalmatian Club's national specialty in May, the foundation subsidized a health clinic where technicians conducted 260 bladder ultrasounds for urinary stones, drew 190 blood samples to determine normative values for Dalmatian thyroid, conducted 185 Canine Eye Registration Foundation (CERF) exams, and undertook urinalyses, bilateral hearing tests, epilepsy tests, and DNA profiles on smaller numbers of dogs. To protect confidentiality, the tests were conducted by technicians who had no connection to the Dalmatian community.

Dr. Garvin said he was particularly pleased that the clinic had added 168 Dalmatians to the CERF database in one day. But there was some concern that the tests may have overdiagnosed iris sphincter dysplasia, a relatively new disorder that was first described in Dalmatians in the 1990s. The club is re-evaluating the tests, to make sure the dogs are not incorrectly attributed.

The bladder ultrasounds, meanwhile, found that one-quarter of males and one-eighth of females had some urinary sediment, while half of males and one-eighth of females had small calculi in the range of 1.0 to 3.0 millimeters, even though all were asymptomatic for urinary stones. Research continues to determine why only some Dalmatians form stones, even though they all have high uric acid levels.

Dr. Garvin revisited the controversy over the Dalmatian-Pointer Backcross Project, an effort by Dr. Robert Schaible of the University of Indiana to introduce a "normal" uric acid gene into the Dalmatian genome. After nine generations of selecting for Dalmatian-like traits but normal uric acid levels, the dogs' appearance was considered reasonable, but the Dalmatian Club objected vehemently when the AKC Board agreed to register two of the backcrossed dogs in February 1981. Registration of any future offspring was suspended six months later, but small colonies of backcrossed dogs have continued, mainly in Indiana and California.

Dr. Garvin drew participants' attention to the *Genetic Information Nondiscrimination Act 2005*, suggesting that its provisions could benefit canines as well as humans. Its intent, he said, is to encourage the use of genetic testing for health purposes, by preventing insurance carriers or employers from discriminating based on the results. The legislation was first introduced in 1995,

and an earlier version passed the U.S. Senate by a 95-0 margin. The 2005 Act passed 98-0, and has 150 co-sponsors in the House of Representatives.

A participant asked whether the results of the CERF exams had generated a political backlash within the Dalmatian Club. Dr. Garvin said the health committee had moved quickly to address the problem, and was hoping to repeat the tests. While some club members feel strongly about addressing ISD head-on, he said there had been no objections to the actual tests.

An audience member explained that the opposition to the Dalmatian-Pointer backcross had to do with a possible genetic link between the health problem and the spotting pattern that had been selected as the breed standard. Dr. Garvin agreed, adding that Dalmatian deafness may also be linked to the pigment patterns in the piebald gene. “This situation is primarily the difference between the gross genotype-phenotype linkages on the chromosome, versus being able to narrow it down to the specific gene,” he said. By focusing down to the base pair level, “we can more effectively use a silver bullet instead of a nuclear bomb in an effort to solve the problem.”

In response to another question, he said the backcrossed dogs appear to have normal levels of uric acid, “so from a functional standpoint it does seem to be relatively effective.”

Update: Epilepsy and Canine Neurologic Disease

Dennis O’Brien, DVM, PhD of the University of Missouri said epilepsy and canine neurologic disease “strike at the essence of the animal, their mobility, personality, and ability to learn, remember, and interact with their family, and may take away life itself.” He identified movement disorders, epilepsy, storage diseases, and degenerative myelopathy as four categories of neurologic disease that may be addressed more effectively thanks to the canine genome project and other advances in molecular genetics.

Dr. O’Brien described cerebellar ataxia as a genetic disease that affects an animal’s ability to control movement. The condition affects a number of canine breeds, but research began in the early 1990s when it was identified in a kennel of English Pointers. Dr. O’Brien led a research team that found a DNA marker within a year, and the disease hasn’t been seen in the kennel since.

Buoyed by their initial success, the researchers thought it would be easy to address the same condition in Old English Sheepdogs, but “failed miserably,” Dr. O’Brien said. Now, a team from North Carolina State has undertaken a mapping study with Staffordshire Bull Terriers, and is hoping the results will help Old English Sheepdogs, as well. “We learned very early on that while there’s a lot of promise here, it wasn’t going to be as simple as we first thought it would be.”

Cerebellar ataxia is linked to Progressive Neuronal Abiotrophy-(PNA), also known as Multiple System Degeneration (MSD), in Kerry Blue Terriers and the Chinese Crested breed. The condition first appears at the age of three to four months, in the form of exaggerated movements, progressing to immobility and falls at eight to 10 months and death within two years. Working

with breeders, Dr. O'Brien and colleagues found that MSD is identical in both breeds and mapped it to a small area of canine chromosome 1. Along the way, they also found the hairlessness gene for Chinese Crested on chromosome 17.

With this type of genetic research, “the heavy lifting is in collecting the DNA, collecting the pedigrees,” Dr. O'Brien stressed. With the basic data in hand, researchers can carry the mapping process as far as they need to: with the Chinese Crested, “another trait was just another line on the spreadsheet.” After the general location of a gene has been determined, using data from the Canine Genome Project, the next step is to look at specific candidates that might relate to a particular condition. The middle third of canine chromosome 1, where MSD was isolated, corresponds to the bottom of human chromosome 6, where researchers' attention was drawn to PARK2, a cause of a hereditary form of Parkinson's disease. “This immobility, these frozen postures the dogs will adopt, their tendency to fall very readily, is very similar to Parkinson's,” he said.

PARK2 is the third-largest human gene, and its complex structure makes research very complicated. But the possibility of a connection between MSD and Parkinson's has led Dr. O'Brien's group to submit a research proposal to the National Institutes of Health, with the hope of confirming the link and developing a definitive test.

Research has also identified a genetic link between epilepsy in miniature wirehaired Dachshunds and Lafora's disease, a form of myoclonic epilepsy in humans. Dr. O'Brien said both conditions are “storage diseases,” in which the accumulation of abnormal material within brain cells leads to seizures, generalized weakness, and blindness. There has also been good progress in isolating the gene for a form of neonatal encephalopathy that may kill up to 25% of the puppies in a litter of Standard Poodles. And DNA research is under way to address a form of “Chinook seizure” in which dogs are aware of their surroundings, but experience tremors, rhythmic leg movements, and immobility.

Another storage disease, responsible for progressive weakness and loss of coordination in American Bulldogs, has been linked to the gene that causes neuronal ceroid lipofuscinosis (NCL) in sheep and mice, and a DNA test is now available. Dr. O'Brien referred to work by Martin Katz, PhD on NCL in Tibetan Terriers and its link to Batten's Disease in humans.

The presentation concluded with a segment on degenerative myelopathy, a condition that manifests at age eight or nine and progresses from poor coordination to complete paralysis and degeneration of the spinal cord. Researchers are studying the disease in German Shepherds and Corgis, but not all neurologists are convinced that the disease exists. Dr. O'Brien said the controversy demonstrated the importance of gathering solid evidence—in this case, by collecting spinal cords post-mortem that allowed pathologists to document the changes.

So far, research on degenerative myelopathy has demonstrated that negative data is valuable, too. Inflammation, excitotoxicity, oxidative stress, and methionine metabolism have all been suggested as possible causes, but while inflammation has been ruled out, there are no other answers yet. Apart from the emotional difficulties associated with post-mortem autopsies, the

late onset of the disease has made it more difficult to collect DNA and pedigree information for siblings and parents.

A participant asked whether there are any differences between degenerative myelopathy in Corgis and German Shepherds. Dr. O'Brien said the conditions have the same progression and look similar on histology, but the genetic link has not been established. A key challenge is to encourage owners to keep careful records, but "it's often easier to convince someone who's had to live with one of these dogs," he told another attendee. Actual pathology tests are important from a clinical point of view because "I don't want to assume the dog has the disease. I want to know." He stressed the value of the CHIC database in solving the problem over time.

A participant asked whether all the storage diseases are caused by abnormal accumulations of protein within cells. Dr. O'Brien said the accumulation could be protein or lipids, depending on the disease.

Another audience member asked whether obsessive circling has ever been considered as a neurological disorder. Dr. O'Brien said the habit could be a neurological symptom in some cases, but is hard to differentiate from a "dog that's happy and likes to spin."

Development of a Parent Club Health Website

Conference Co-Chair and CHF Director **Lee Arnold** stressed the importance of a Parent Club health website as a "powerful communication tool that can instantaneously transmit health information about your breed around the world." When the Chinese Shar-Pei Charitable Trust set up its health site in early 2005, he said the goal was to disseminate information and gather member feedback in a more timely way than would be possible through the breed magazine and the club's national specialty. The site has a .org designation, reflecting its focus on canine health, and serves as a fundraising tool as well as a repository for the Trust's mission statement, past and present grant information, newsletter, and financial reports.

Sue Godek, President of the American German Shepherd Dog Charitable Foundation, said her organization moved from a page on its Parent Club website to a stand-alone site to ensure that it had enough space for donor information, financial reports, health surveys, and other material. She gave a detailed review of the mechanics and technical details behind website design, illustration, typography, use of frames, phrasing of metatags, protection of website addresses, and testing on different browsers.

"After you've done all this work," she urged attendees, "please don't forget to back up your site."

Joyce Campbell, DVM, Chair of the American Boxer Club's Health and Research Committee, said access to the club's health site is password-protected and controlled by the site's three webmistresses. In addition to a membership list, the site includes articles on key health issues and links to other sites of interest.

CHF Director Dr. Duane Butherus highlighted the CHF website as a resource for smaller clubs that haven't set up their own independent charitable foundations. The site contains detailed information and resources on problems like cancer that affect all breeds, as well as more specific content that can be searched by breed or health condition.

While websites can be used to administer online health surveys, Dr. Butherus acknowledged how difficult it is to convince parent club members that the surveys are truly blind. The alternative is to post downloadable survey forms online, rather than trying to distribute paper copies at national specialties.

A participant asked how to select a designer for a new website. Mr. Arnold said a professional web designer had volunteered as webmaster for his club's site. Ms. Godek said a local college student might design a site as a class project, in exchange for a small honorarium. But an audience member warned that someone will have to maintain the site once it's been developed. "An out of date website is worse than no website at all," she said.

The panelists agreed that a separate health website is a good way to generate interest, and donations, from owners who are not members of their breed clubs.

An attendee said she had used her personal website to distribute a puppy buyers' checklist, to increase understanding of her breed's health issues. She said breeders have been supportive, and the checklist has been particularly useful in helping buyers distinguish legitimate breeders from puppy mills.

Canine Endocrinology Update

Thomas Graves, DVM, PhD of the Department of Veterinary Clinical Medicine, University of Illinois, gave an overview of canine diabetes and hypothyroidism. He noted that diabetes is becoming a more serious problem in dogs, and is already a major issue in human medicine: diabetes-related deaths are increasing exponentially, and the condition will lead to more than 50,000 amputations and 50,000 cases of blindness this year.

Canine diabetes generally resembles insulin-dependent diabetes in humans, and its incidence has increased from 2.0 to 7.0 per thousand since 1970. Dr. Graves said the documented incidence is probably low: Just as one-third of the estimated 20 million Americans with diabetes are unaware that they are ill, he said many canines go undiagnosed. Clinical signs of insulin-dependent diabetes include increased thirst, urination, and appetite, weight loss, and cataracts.

A look at the odds ratios for canine diabetes shows a wide variation among breeds, from a rate of 32.1:1 for Australian Terriers to 0.07:1 for Boxers, but "it's important to realize that any dog can get diabetes," Dr. Graves said.

Hypothyroidism is caused either by autoimmune thyroiditis or idiopathic atrophy. But while it is the most commonly diagnosed endocrine disorder in dogs, it is also commonly misdiagnosed. Clinical signs include lethargy, weight gain, dry hair or shedding, hair loss, anestrus,

hyperpigmentation, cold intolerance, and low heart rates—but Dr. Graves maintained that the signs are often misinterpreted in the absence of sound scientific proof.

Golden Retrievers, Doberman Pinschers, Irish Setters, Miniature Schnauzers, Dachshunds, Cocker Spaniels, and Airedale Terriers are all known to be predisposed to hypothyroidism. But diagnosis is not as simple as it is in humans, where a shortage of the thyroid hormone thyroxine (T4) and a high level of thyroid-stimulating hormone (TSH) is almost 100% diagnostic. But most dogs with low T4 levels have some other disease, and canine TSH tests are neither sensitive nor specific. The ultimate marker for canine hypothyroidism is a combination of reduced total T4, free T4, and total triiodothyronine (T3), combined with elevated TSH.

Dr. Graves questioned the common practice of supplementing thyroid hormones to see if a dog will get better. While any animal will probably lose weight and grow some hair in response, the treatment can also suppress normal pituitary function, cause a thickening of the heart muscle, and increase the heart rate. “The endocrine system is very complicated, and hormones interact with each other and feed back on each other,” he warned. Unwarranted thyroid treatment may also allow an undiagnosed disease to progress while the veterinarian conducts a “therapeutic trial of a thyroid hormone.” He said the key to successful diagnosis is to watch for clinical signs, rather than relying solely on lab results.

A participant asked whether it’s reasonable for a breeder to screen pro-actively for thyroid antibodies and put dogs on hormone supplements before hypothyroidism occurs. “It’s extremely unreasonable,” Dr. Graves replied, since dogs with other diseases can have positive antibodies and normal thyroids. Another audience member asked whether an antibody test should be used to remove otherwise healthy dogs from the gene pool. Dr. Graves said there is no scientific evidence to support the practice.

Similarly, he argued against routine thyroid screening at national specialties in the absence of clinical evidence that the disease is present. “I think there’s a role for veterinary clinical acumen and evidence-based medicine rather than just racking up a bunch of numbers,” he said.

A participant stressed the importance of knowing the lab where a test is being conducted. “There is no such thing as a perfect test,” she said. “You should be looking at clinical signs, the total dog, at all times when you’re doing any of these tests.”

Another audience member said Dr. Graves’ advice ran counter to everything she had heard in recent years. Dr. Graves acknowledged that “there are really, really smart people who disagree with me, and there are people who really believe that hypothyroidism is rampant in just about every breed. My message is that that has not been established.”

A Reliable Test for Labrador Muscular Myopathy

Marilyn Fender, PhD, Professor Emeritus, at the University of Wisconsin, traced the development of a genetic test that permits easy, reliable screening for the mutation that leads to

muscular myopathy in Labradors—which was recently renamed Centronuclear Myopathy (CNM) to reflect a better scientific understanding of the condition.

The test was the result of a collaborative effort between the Alfort School of Veterinary Medicine and the Pasteur Institute in France, and enables researchers to replace muscle biopsies with cheek swabs to confirm diagnosis.

Although the test is a major achievement, Dr. Fender stressed that “finding the gene is not all there is to it. You then have to implement it, in our case internationally, in order to make good use of it.” She stressed the need to build owner and breeder awareness of CNM, adding that not all veterinarians know it when they see it.

Clinical signs of CNM appear at the age of one month and include weight loss and an absence of tendon reflex. Age of onset for the disabling phenotype is two to five months, with decreased exercise tolerance and generalized muscle weakness. The dogs can live 8.5 years with the condition and retain the ability to reproduce, but they never recover mobility. Cell biopsies of affected muscles show that 10-70% of fibers have centralized nuclei, compared to normal dogs with very little of the nuclei showing.

A number of national winners have been carriers of Labrador CNM, including one of Dr. Fender’s dogs. “When you have a national winner of this caliber, they will have bred a lot,” she explained, and the defect is quite common in the field, as well. CNM first appeared in the 1970s, was described in 1992 by Dr. Stéphane Blot, and became more prevalent when some of the lines began crossing back into each other to produce duplications. A decade of research in France has received support from the French Association for Myopathies, a human health research organization that recognizes the genetic similarities between canines and humans. Dr. Matthew Breen confirmed the relevant chromosomal assignments in 2002, with research funding from CHF, the Alfort School released its test in October 2004, and the research teams in the U.S. and France have developed contacts in Canada, Germany, the United Kingdom, and Australia.

But as late as 2004, Labrador owners and breeders had no idea that CNM was so prevalent. Earlier this year, Dr. Fender and her colleagues began publishing articles in breed specialty magazines. A website, www.labradorcnm.com, was launched in the spring and includes a “white list” of Labradors that have been cleared for the condition. A pilot CNM testing project began at the breed’s National Amateur Field Trial Championship Stake in June. The research team in France released a reliable diagnostic assay over the summer, and full implementation began in September, with electronic forms available on the website and *Retriever Field Trial News* distributing brush kits for sampling.

Dr. Fender underscored the need for DNA testing of animals that might be affected. “Among healthy dogs, we want to be able to identify the carriers for the mutation,” she said. “Those Labs are at high risk to transmit the deleterious copy of the gene to their litters.” Cleared dogs are placed on the “white list” unless their owners object, but the names of dogs that are carriers or affected are kept confidential unless the owner releases the information. Certification is based on a rigorous, three-step procedure that involves careful identification of dog and swab by a vet who has no financial interest in the animal.

For breeding purposes, Dr. Fender said, the obvious best combination is two clear dogs. But carriers can be bred to clear dogs if they have other good characteristics that benefit the breed. “It’s a mistake to eliminate all carriers from a very small gene pool, because we will lose as much good as bad,” she said.

Experience shows that it’s possible for a breed to eliminate an unwanted disorder, she noted. In the UK, the proportion of Irish setters that were carriers for Canine Leukocyte Adhesion Deficiency (CLAD) declined from 20% to near zero with the use of DNA testing. The process will be more difficult for Labs because the population is so much larger, but the test program is now in full implementation and expanding globally.

In reply to a participant’s question, Dr. Fender said the “white list” is already generating peer pressure to test. While some breeders who should be testing “hardly answer my phone calls and emails, others are coming to me and saying, ‘I really need to know this.’ So there’s a mix of reactions.”

Genetics of PAA in the German Shepherd and Dermatomyositis in the Shetland Sheepdog

Studying canine genetics may lead to improvements in both human and canine lives, said **Keith Murphy**, PhD, Texas A&M University. The dog is a model for dissection of human hereditary diseases and other traits. Genetics is the study of heritable variation, and the dog has a range of phenotypic variation unique among mammals.

Pancreatic acinar atrophy (PAA) is a degenerative disease of the exocrine pancreas. The disease damages pancreas cells producing enzymes that are necessary for digestion. “When these cells essentially cease to function, the enzymes that are supposed to be produced are no longer produced, so the dog cannot digest its food,” Dr. Murphy said.

The disease occurs predominantly in German Shepherds, and also in Rough Collies. Symptoms include weight loss, steatorrhea (high fat content in fecal matter), and poor hair/coat.

The disease is diagnosed by looking for a specific pancreatic enzyme. The test is 100% specific.

“The great thing about this disease is that 95% of the dogs can be treated—just give them enzyme supplements,” Dr. Murphy said. He added that it can be expensive and about 5% of dogs don’t respond to treatment.

The Department of Defense uses German Shepherds and has provided Dr. Murphy’s research team with a lot of samples from dogs with PAA. But in the field—say, Afghanistan or Iraq—it’s not possible to keep up the enzyme treatment necessary.

Dogs with PAA require a low fat diet in addition to the enzyme supplements.

PAA is a hereditary disease, caused by a recessive gene. Because it is a late onset disease, it is not possible to identify carriers by symptoms before they breed. PAA does not occur in humans, so there is no already identified human gene candidate that might correspond to a canine gene.

Dr. Murphy said his research team wanted to identify a molecular signpost, something that's close to the gene involved in the disease. They conducted a whole genome screen to find if there is anything always there or always missing in affected dogs. By using microsatellite markers, they determined that the area of interest is on chromosome 3 in the German Shepherd.

The team used microarray analysis to find 244 genes that were different in the pancreas of affected and unaffected dogs. With PAA, 231 genes in the pancreas were turned on and 13 genes turned down, including one gene, gp25L, that was turned down 500 fold. It already was known that PAA is caused by a single recessive gene, not by the combination of 244 genes. The research team mapped the gene turned down so dramatically and found it was on chromosome 3, already recognized as the place to look for the cause of PAA.

The CHF funded a study based on this information.

Dr. Murphy said that in sequencing data in the CHF-funded study, his team has not found any difference that could be associated with this disease. That doesn't mean this gene isn't involved, merely that there's no mutation in the area that codes the protein. The team now is looking at the regulatory regions.

Dr. Murphy also is working on dermatomyositis, a degenerative skin and muscle disease of Shetland Sheepdogs and Collies. This has some similarities to a human disease, and the Muscular Dystrophy Association is following the results of this study.

The earliest symptoms of dermatomyositis include focal areas of crusting and scaling on the face and extremities. Stress exacerbates the condition, so the disease waxes and wanes. Muscle function may be affected, causing difficulty eating, drinking, and walking.

“Muscle lesions may or may not occur, however, some of these can be very severe and require that the dog be euthanized,” Dr. Murphy said. The lesions are far more common in Collies than in Shelties.

Researchers looked at Sheltie pedigrees and also studied Shelties that did not have pedigrees, Dr. Murphy said. He is looking for the chromosome that causes dermatomyositis and also looking at the same time for the chromosome abnormalities related to merle coloring. They have determined that a gene on chromosome 35 controls both these conditions and research continues to determine what it is.

To determine if dermatomyositis is an autoimmune disease, the study is comparing disease-damaged tissue to normal tissue. The research team also is examining tissue samples to look for antibodies that attack the cells.

In other work going on now in Dr. Murphy's lab, researchers are examining a marker for PRA in the Alaskan Eskimo dog, the effect of genes involved in aging, alport syndrome in Cocker Spaniels, and cholesterol levels in dogs with high stroke rates.

Measuring Behavior and Temperament in Dogs

It is important to study behavior in dogs, said **James Serpell**, PhD, University of Pennsylvania, because behavior problems are health problems. Bad behavior is not a pathogen, but it is a major cause of euthanasia. Temperament eliminates 30% to 50% of service dogs, and dog bites are a public health hazard.

No standardization exists for measuring behavior or temperament. Different experts will view the same problem behavior in dogs and describe or label it differently.

Three methods are available to researchers for identifying behavior traits in dogs, and all have drawbacks:

- Long-term systematic observation of dogs in their usual environment: This may not identify behavior problems that are serious but infrequent, it is difficult to do without the researcher actually moving into the household, and it means observing not only the dog but also the dog's relationship with its owner, which may affect behavior.
- Temperament tests: These are time-consuming, and researchers don't know if a test is reliable or if dogs are consistent in their responses from one day to the next. Temperament tests even may be stressful to dogs, especially puppies.
- A questionnaire completed by a dog owner or handler: This method of getting information is quick and economical, but researchers must rely on observation by another person—the owner or handler—and responses may not be reliable.

The goal of Dr. Serpell's project was to develop a reliable instrument to measure temperament and behavior, then test its accuracy and reliability. The project started with two assumptions: The person living with the dog knows it the best, and by asking the right questions the right way, it is possible to get accurate behavior information from that person.

Dr. Serpell developed the Canine Behavioral Assessment and Research Questionnaire (C-BARQ) of 152 questions, with a scale of five responses from "never" to "always" for each question. He sent the C-BARQ to 2,000 regular dog owners, 1,093 breed club members, and 200 owners of problem dogs. All dogs were one year old.

This was not breed specific study, but some breeds (Basset Hound, Dachshund, English Springer Spaniel, Golden Retriever, Labrador, Poodle, Rottweiler, Shetland Sheepdog, Siberian Husky, West Highland White Terrier, and Yorkshire Terrier) prevailed because the breed club lists were used. Both sexes and both neutered and sexually intact dogs were included.

Data from responses was subjected to factor analysis, grouping responses to similar questions. Based on the responses received, Dr. Serpell's team identified 11 temperament traits common to most dogs, regardless of breed, age, sex, or neuter status:

- stranger-directed aggression
- owner-directed aggression
- stranger-directed fear
- nonsocial fear
- dog-directed fear/aggression
- separation-related behavior
- attachment and attention-seeking
- trainability
- chasing
- excitability
- touch sensitivity

To assure inter-observer/inter-rater reliability, two people in the same household were asked to observe and rate the dog without conferring. The questionnaire was tested for internal consistency. On 10 of the 11 traits identified, the related questions received highly consistent responses. On questions about touch or body sensitivity, the consistency was slightly lower than desired, but still good.

The researchers also checked the questionnaire's validity by comparing its results for dogs that previously had been identified as exhibiting problem behavior to the veterinarians' diagnosis, such as stranger aggression. Dr. Serpell said he believed the questionnaire's validity was good.

Breed differences in behavior were apparent, Dr. Serpell said. Dachshunds and Rottweilers scored highest on stranger-directed aggression, for example, and Siberian Huskies scored lowest.

Owner-directed aggression is not a frequent behavior, and it is selected against in the dog population. "That's because historically dogs that bit their owners didn't live very long," Dr. Serpell said. Although it is not common in the dog population, it is a trait that is important to owners and therefore shows up more often in behavior clinics than some other more common behavior problems.

The C-BARQ survey also was used to examine line differences in behavior problems, focusing on lines in the English Springer Spaniel breed. That breed was chosen because there were concerns about rising rates of aggression in the breed. An earlier study reinforced those concerns, especially among dogs bred for conformation. The C-BARQ questionnaire confirmed higher rates of stranger-directed aggression, owner-directed aggression, and dog-directed aggression among dogs bred for conformation than among dogs bred as field stock.

The C-BARQ also found that male dogs had more aggression behavior problems and that females were more fearful. These differences were even more extreme when looking at only neutered animals, even after excluding animals neutered for behavior problems. Dr. Serpell considers these differences disturbing and said additional study was needed.

Dr. Serpell said the next step is to use the C-BARQ to survey additional breeds. Then researchers can determine the role the C-BARQ can have in screening and selecting service dogs, use the C-

BARQ to examine the efficacy of treatment for behavior problems, and begin mapping genes associated with these behavioral traits.

Canine Vaccination and Risk: What Do We Know?

Belief is not the same as knowledge, said **George Moore**, DVM, PhD, Purdue University, adding, “It is possible to be sincerely wrong.” People must test their beliefs, including their beliefs about vaccine safety and protocols.

Two companies recently have published information showing that vaccines for canine hepatitis, distemper, and parvovirus are good for three years instead of the one year previously recommended. These claims will now be subject to testing.

Both the safety and efficacy of vaccines should be evaluated.

“Essentially, as we improve the quality of our vaccines, we also improve the number of vaccines,” Dr. Moore said. There are many more animal vaccines and accompanying implications now than there were 20 or 30 years ago. When vaccines are successful in decreasing infections, then it is time to decrease vaccine-associated adverse events (VAAE). As the number of adverse events rises, people stop vaccinating, the disease recurs, and people increase vaccination again to control the disease. For example, a recent outbreak of canine distemper in Chicago occurred because people had stopped vaccinating their dogs against the disease.

Safety trials are required before licensing a vaccine for animals, Dr. Moore said. The test involves giving two doses of a vaccine to 500 to 1,500 animals, with a follow-up in less than 30 days. Not looking at repeat vaccinations, having only one follow-up, and having that follow-up within a relatively short time limits the ability of these vaccine trials to recognize adverse events.

“All of a sudden now we get a false sense of security about what might be the safety record of that vaccine, and that’s true about vaccines for people as well as about animals,” Dr. Moore said.

With human vaccines, by law, doctors must report adverse events to the Food and Drug Administration or Centers for Disease Control. That kind of reporting is not required for animal vaccines. The USDA gets about 500 to 600 reports on VAAE a year, mostly on dogs and cats, although more livestock than small animals are vaccinated.

Veterinarians are more likely to report VAAE to the vaccine manufacturers than to regulators. Government surveillance on animal vaccines is more passive than active.

Dr. Moore said that prudent questions about VAAE are how often they occur and the frequency for different types of vaccines.

VAAE studies must follow a large population over long period. Dr. Moore and his research team looked at the vaccination records of dog patients at Banfield, The Pet Hospital, from January 1, 2002, to December 31, 2003. They considered the breed, age, sex, and neuter status. Vaccines

administered included bordetella, borrelia, coronavirus, giardia, rabies, parvovirus, and a multivalent distemper-adenovirus-parinfluenza-parvovirus-leptospirosis (4 serovars).

The team searched the animals' records for ailments occurring up to three days post vaccination and checked records for the nature of the reaction. This two-year study, examining 3.5 million doses of vaccine and 1.2 million dogs, found 4,678 adverse events. In 65% of those, the veterinarians called the adverse event a "vaccine reaction," and in 32% an "allergic reaction."

The most common reactions involved facial edema or edema around the eyes, wheals/urticaria, generalized pruritis, or vomiting. The incidence of allergic reaction was greater in smaller dogs. VAAE rates were higher in one-year-old dogs than in dogs two to nine months old, and were greatest in two-year-old dogs. Neutered dogs had higher rates of adverse events than sexually intact dogs.

The rate of VAAE also varied by breed. In each of 42 breeds, more than 5,000 dogs were vaccinated over the two-year study period. Dachshund, Pug, Boston Terrier, Miniature Pinscher, and Chihuahua breeds showed the highest rate of adverse effects.

Rates also increased by almost 25% for each additional vaccine given on the same occasion. The increase was slight but statistically significant in large dogs, with a greater increase in small dogs.

Three dogs died in the study; all received four or more vaccines on one occasion.

Many dogs that had vaccine reactions did not have repeat reactions with subsequent vaccinations. The risk of VAAE may be higher on these subsequent vaccinations than if there had been no previous reaction, but actual rates of subsequent reactions are not yet known.

More research is needed on adverse reactions, Dr. Moore said. Some of the limitations of the Banfield study were that all vaccines were from one manufacturer, there were no checks for adverse effects more than three days after vaccination, and the study did not consider records of previous vaccinations.

In questions following the presentation, an audience member asked about the benefits of distemper/measles vaccine to prevent the clinical problem of respiratory disease.

Dr. Moore said that because most dogs get good protection against these diseases from their mothers and because there is a low incidence of these diseases there doesn't appear to be as much benefit from this vaccine. It is possible that the vaccine helps protect dogs against other respiratory diseases, but there is no conclusive information at this time.

Asked about his recommendation on vaccinating for leptospirosis, Dr. Moore said he currently is involved in a study on the disease. It appears to be established in the wildlife population and now is seen in dogs that never leave their yards. As cities spread into formerly wild areas, dogs get the disease from wild animal contamination. Although the vaccine has side effects, the hazards of the disease—15% to 20% mortality rate from acute renal failure—outweigh the dangers.

The lepto vaccine appears to offer long-term protection. Even with undetectable titers, immunity appears to continue.

Closing Remarks

Steve Remspecher, Director of Marketing, Nestlé Purina PetCare, concluded the meeting by thanking the audience, speakers, financial supporters of the Canine Health Foundation, researchers, and breeders.

“As the proceedings come to a close, we hope that it has sparked a renewed interest in genetic research and the promise that these studies and findings represent,” he said.

He added, “Together we are working for longer and healthier lives for our canine companions.”