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‘Genes, Dogs and Cancer’
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Cancer is one of the leading causes of death today, in both dogs and humans. As witnessed by the Rottweiler Health Foundation website section, ‘Shared Real Stories’, over 75% of the stories submitted by Rottweiler owners involve the loss of their Rottweiler due to a form of cancer. Researchers are finding dogs to be a remarkable model to study many of the diseases that also affect humans, including cancer. In addition to their traceable pedigrees and compressed life span, dogs live in the same environment as humans, breathe the same air and have similar diseases, making them ideal candidates for health studies.

The American Kennel Club Canine Health Foundation began ‘The Cancer Initiative’ two years ago and to date has raised over one million dollars to help fund a multi-faceted research program targeting cancer in purebred dogs. The process by which research is funded begins when an investigator submits a pre-proposal to the Canine Health Foundation. A peer board of review then assesses the merit of the pre-proposal. If deemed worthy, a full proposal is requested. The full proposal, containing much more detail, is reviewed again and must be approved before funding is sought. The cancer research which is being done today, funded by us all, has great potential for making a big difference for our dogs, as well as ourselves.

Although funding is necessary for continued cancer research, without the participation of the Rottweiler community, research will have limited results and benefits. The research described in this report has resulted in new knowledge about cancer. As purebred dog owners we have the opportunity of assisting in future cancer research advances. Our initiative to become more involved can begin by simply talking to our veterinarians and other Rottweiler owners about these cancer research studies. A more permanent initiative would be the establishment of a DNA database containing significant numbers of Rottweilers. As one of the conference speakers pointed out, he had much more success collecting blood samples and pedigrees of healthy dogs, before any health problems occurred. This particular practice, collecting blood samples for a database when our dogs are healthy, is one which the Rottweiler community should seriously consider initiating.

The second annual ‘Genes, Dogs, and Cancer’ Conference was sponsored by: Nestle Purina PetCare Company, The Kenneth A. Scott Charitable Trust, American Boxer Charitable Foundation, Golden Retriever Club of America, Golden Retriever Health Foundation, Rottweiler Health Foundation, and Pharmacia Animal Health. It was a gathering of some of the top researchers in canine and human cancer research from around the world, as well as interested breed club representatives. John Studebaker, First Vice President of the American Kennel Club Canine Health Foundation, gave welcoming remarks. The Canine Health Foundation is currently funding fourteen projects in the area

of cancer. Recently the National Advisory Council for Human Genome Research reported that they would give the sequencing of the canine genome a high priority. This has enabled researchers to have a valuable tool for studying the molecular basis of cancer in dogs and will lead to exciting new therapies in the treatment of canine cancers.

Carol Krickeberg noted the real title of this report could easily be “The Second Annual Canine Cancer Conference as viewed from 20,000 Leagues Under the Sea”. Reading the degrees attached to the presenters’ names were somewhat intimidating: a group comprised of medical doctors, veterinarians, Ph.D.s, geneticists, and statisticians. Nonetheless, at the end of the two-day conference, each of us were very encouraged by the information offered and agreed that we need to share these important issues with the Rottweiler-owning public.

Many of the findings presented have implications for both human and canine cancers. The human and canine genomes are 90 percent similar. Dogs suffer many of the same diseases as humans; virtually all of the 400 known canine diseases have human counterparts. A word of forewarning: much of what follows includes medical technology terms and references, and has been included for those that are interested. A [general overview of the conference](#) and our input can be found at the end of this report.

“Training Stem Cells To Home: The Role of Drug Resistance Gene Transfer”

The keynote address was given by Dr. Stanton Gerson, MD, Chief of Hematology-Oncology at University Hospitals of Cleveland. Gerson’s talk focused on some of the latest research in the area of stem cell transplantation. His studies involved utilizing the drug-resistant gene, MGMT, in a mutated state, with extracted bone marrow stem cells from mice. Once the extracted stem cells are injected with mutant MGMT, the cells then become sensitive and therefore resistant, allowing expansion of stem cells, and a greater toleration of chemotherapy. Thus, it is possible to selectively replace the bone marrow, and perhaps other organs, with the transduced stem cells following intravenous infusion and drug treatment. Dr. Gerson’s team is also evaluating this model to discover whether or not stem cells can repopulate the lung, liver, and brain and whether this may be enhanced with tissue injury. Dr. Gerson indicated a clinical trial will begin soon with cancer patients.

“Examination of the Population Genetics and Inheritance Patterns of Cancer in the Flat-Coated Retriever”

Dr. Terri King, a statistician from the University of Texas Health Science Center in Houston, spoke on canine cancer epidemiology, and more specifically, malignant histiocytic neoplasms (or soft tissue cancer) in the Flat-Coated Retriever. In 1993, the parent club established a tumor registry to look at an emerging cause of death in the Flat-Coated Retriever, cancer. In 1995, the parent club conducted a health survey focused exclusively on cancer issues in the breed. They received 298 responses: 121 males and 137 female dogs, including information on 174 dogs that were still alive and 83 deceased dogs. From that survey they determined the average onset of cancer in the Flat-Coated Retriever was at 7.7 years of age, with a small population of animals developing cancer at 3.5 years of age.

They launched their first study collecting pedigrees and tissue samples. In one single pedigree, it was reported that there were 24 affected dogs. Within the single pedigree, it was discovered: (a) 4 parent-child transmissions, including one 3-generational transmission; (b) 2 sibling pairs; (c) 3 animals appear in 92% of the pedigrees collected; and (d) 2 are siblings. This type of incidence strongly suggests an inherited basis of soft tissue cancers in the Flat-Coated Retriever.

A telephone survey was done to obtain specific information from owners who submitted samples, so that a consistent information data set could be captured and a structured analysis could be performed.

Analysis is still on going, but they hope that through segregation analysis, leads can be obtained on the population genetics and the effects of inbreeding, as well as the soft tissue cancer's effect on the current gene pool and those implications on breeding stock. It was stressed that it was sometimes difficult to get blood samples on affected dogs, making it difficult to perform lineage analysis. Dr. King commented that one solution would be to capture blood samples on a large segment of the population prior to the onset of cancer. This study should prove to be an interesting one to follow in the future.

Dr. King's research has added 3,000 Flat-Coated Retriever genealogy records to the previous 7,043 records, generously provided by the Flat-Coated Retriever Society of America. The importance of participation and buy-in from the canine community is essential to the research's success. Certainly, the inclusion of over 10,000 genealogy records represents a huge commitment by the Flat-Coated Retriever community.

“Genetic Mapping of Cancer Susceptibility Genes In Dogs”

The next speaker was Dr. Frode Lingaas of the Norwegian School of Veterinary Science, in Oslo, Norway. In recent years, Dr. Lingaas' research has focused mainly on inherited diseases in dogs, especially cancer; as well as genetic mapping of the canine genome and inherited diseases in dogs. Dr. Lingaas addressed the subject of genetic mapping of cancer susceptibility genes in dogs. Again, it was pointed out that dogs are a great model to study many diseases because they are made up of less dissimilar parts than humans. Dogs, with their shorter life spans, develop many cancers as they get older and actually serve as a genetic surveillance or 'watch dog' for human society.

In 1989 Norway began a Canine Cancer Registry and currently has 15,000 histological samples and over 30% of these are mammary carcinomas. It was pointed that the breeds showing the highest incident in order were: Boxer, Flat-Coated Retriever, Rottweiler, Bernese Mountain Dog, and the Daushund.

Dr. Lingaas is currently involved in a large study called “Feeding, Growth Speed, and Bone Disease.” The project involved more than 600 family-owned dogs from four breeds. All dogs in this project were thoroughly followed from birth. Estimated feed intake, growth and skeleton-diseases, including osteosarcomas, were recorded and blood was collected from all dogs. Osteosarcoma is a cancer of large breed dogs with the Irish Wolfhound and the Rottweiler being the breeds with the highest predisposition for the malignancy. More than 40% of the dogs presented to the clinic had metastasis at the time of diagnosis. Interestingly, osteosarcoma is 4 to 5 times more common in the dog than it is in man.

Dr. Lingaas also sited a problem obtaining pedigrees and blood samples on affected dogs. In Norway they have started taking blood samples and pedigrees on young healthy dogs before they have any problems and then follow these dogs. Owners are far more interested in giving samples when the dogs are healthy. DNA samples on these dogs can be checked to see if they carry any precursor genes prior to onset of disease and then can be reexamined if the dog is later affected with a disease. Without a doubt, this collection will serve as a unique tool kit for future genomic studies.

Using a resource family of German Shepherds, thus far Dr. Lingaas has been able to isolate and map a specific kind of renal cancer syndrome to a region of the canine genome, which corresponds to a region on the human genome, containing a gene associated with a similar kind of human renal cancer. The model provides a powerful resource for genetic studies and underscores the merit of canine models for identifying cancer genes.

“Comparative Approaches To Understanding Metastases: Dependence of Osteosarcoma Metastasis On Ezrin, A Membrane-Cytoskeleton Linker Protein”

Dr. Chand Khanna of the National Cancer Institute presented some exciting work on a comparative study being done in osteosarcoma in dogs and children with bone cancer. Osteosarcoma in dogs is generally a disease of older dogs. In man, osteosarcoma is more prevalent in children, however the genetic profile of the disease is similar in both species. For this reason, the National Cancer Institute has set aside funds to run these comparative trials looking at new therapeutics for treating the primary and metastatic disease.

Working with cDNA micro arrays, Dr. Khanna has already identified a gene called ezrin, a membrane-actin cytoskeleton linker protein. The gene ezrin was found to be three-fold over-expressed in an aggressive model of canine osteosarcoma compared to expression levels in normal bone tissue. To examine the relevance of ezrin in osteosarcoma, tissue arrays using canine and human osteosarcoma samples (consisting of normal tissues, primary osteosarcoma, and osteosarcoma metastases) was constructed. The expression of ezrin was detected in 58% of dog osteosarcoma samples, with significant higher amounts in pulmonary metastases than primary tumors. Additionally, the study suggests a shorter survival for dogs with ezrin expression in the primary tumor, compared to those with no ezrin expression (213 days and 379 days, respectively). The over expression of ezrin in canine osteosarcoma has been linked to poor overall prognosis, as well as closely associated with progressive metastasis.

Follow-up from this work also showed that ezrin was unregulated in four out of four pediatric osteosarcoma cases that were examined. This is yet another example of how our research can benefit both our dogs and ultimately, man.

Future works showing such a comparative approach will be part of the mission of the proposed Comparative Oncology Program at the National Cancer Institute. One of the things that we can do to support this effort is to encourage our State Senators and Representatives to support this endeavor, as it will ultimately require federal funding.

“Molecular Cytogenetic Analysis of Recurrent Chromosome Aberrations In Canine Multicentric Lymphomas”

Significant attention has been drawn to the identification of recurrent chromosome aberrations associated with almost all forms of human cancer. However, the extent and identity of chromosome aberrations associated with canine cancers remains largely unknown. Rachael Thomas, Ph.D., of the Oncology Research Group Animal Health Trust, in the United Kingdom, along with Matthew Breen, Ph.D., of the Department of Molecular Biomedical Sciences at North Carolina State University, presented their very complicated molecular cytogenetic analysis of chromosome mutations in canine lymphoma. During the past two years, an extensive collaborative study funded by the Canine Health Foundation has been underway to complete the canine genetic map. Elaine Ostrander has been the moving force behind this program and as a result, the canine map is now complete. Thomas and Breen have extensively used this map to identify mutations in chromosomes in 25 cases of canine lymphoma. Studies have shown that a gain in chromosome function on chromosome CFA13 correlated with a good prognosis for a dog. Mutations in tumor suppressor genes cKIT and MYC were associated with poor prognosis clinically. Much of this work is still on-going with new techniques constantly being developed in the field of identifying chromosome aberrations of canine cancer cases, which will ultimately contribute to a future break through.

“Canine Histiocytic Neoplasia: Cell Lineages and Disease Classification”

Peter Moore, Ph.D., of UC Davis School of Veterinary Medicine, reported on canine histiocytic neoplasia cell lineages and disease classifications. Histiocytoma is a common, benign, cutaneous neoplasm of the dog. The tumor originates in the epidermal layer of the skin. Most canine histiocytic diseases are represented in cells of dendritic (structured as a tree branching out from a main feeder cell) lineage.

Histiocytes differentiate from CD34+ committed stem cell precursors. Histiocytic neoplasia that originates at a single site is called histiocytic sarcoma, or HS. This form is often encountered on the extremities and has its best prognosis if treated early by surgical excision or amputation of limb. When the disease spreads to distant sites, it is referred to as disseminated histiocytic sarcoma and is more likely to be found in the spleen, lungs and lymph nodes. The HS complex of diseases is most commonly found in Bernese Mountain Dogs, in which a strong familial association has been found. It was pointed out that the Rottweiler, Golden Retriever and Flat-Coated Retriever are also predisposed to the disease. Doreen LePage noted that she traveled back to the airport with several UC Davis vets, and they commented that they felt this would be the next serious health problem in the breed, as they are now seeing as many new cases in Rottweilers as they do in Bernese Mountain Dogs. They felt the incidence of histiocytic sarcoma was the same as osteosarcoma in our breed. You may visit their website at: www.histiocytosis.ucdavis.edu.

“Gene Therapy For Cancer”

The next speaker, David Argyle, BVMS, Ph.D., MRCVS, originally from Scotland, but now stationed at the University of Wisconsin School of Veterinary Science, spoke about the development of gene therapy as a means of supporting or replacing the known, rather crude therapies such as surgery, radiotherapy, or chemotherapy. In simple terms, gene therapy is the introduction of nucleic acid into a cell to improve a disease process. Gene therapy holds many promises but there are still technical hurdles to overcome before it can become accepted clinical practice.

Among the domestic species, the canine population has the highest rate of malignant tumors (166 cases per 100,000 per year) and is second only to the horse for the benign tumor rate (134 cases per 100,000 per year). The need for a therapy other than, or in combination with the standard surgical or chemotherapy procedure is evident. Successful gene therapy would involve the introduction of potentially toxic genes into cancer cells, yet requiring the expression of that gene be limited only to cancer cells, sparing the normal tissue, and therefore preserving the vital structures and protecting them from toxicity.

Ideally, in cancer gene therapy, any tissue specific promoter used should have activity restricted to the target tissue, without affecting other tissues. In reality though, many tissue specific promoters have low level background activity in other tissues.

Dr. Argyle’s laboratory has focused on a number of systems that rely on the expression of genes in cancer cells that are silent in normal cells. Studies have shown that many human malignancies have implicated the loss of the ‘p53’ tumor suppressor gene function. Interestingly, recent evidence suggests that ‘p53’ may also play an important role in the development of domestic animal tumor growth. Although mutations in the ‘p53’ gene are well recognized in human and veterinary oncology, there are still a large proportion of cancers that do not show abnormal ‘p53’ expression. A central common mechanism though, underlying the phenotypic cancer cell has become known as the differentiating factor between normal and tumor cells. This common agent, known as telomerase, is an enzyme that maintains the protective structures at the ends of chromosomes, called telomeres.

Telomere will eventually die and not replicate in normal tissue, but does not die in cancer tissues and cells. It is now well documented that the level of telomerase in malignant tissue compared to normal tissue is much higher.

As Dr. Argyle concludes, it has been only 12 years since the first human clinical trial in gene therapy, which is very short in comparison with the development of classical drug therapies. Many of the hurdles facing gene therapy revolve around cancer tissue/cell and the design of new systems that can target metastasis in a controlled fashion. For the time though, it is apparent that gene therapy will be treated as a supplemental treatment to the conventional drug therapy. It is easy to become euphoric with new breakthroughs and discoveries made in gene therapy, but Dr. Argyle underscores the importance of learning from previous laboratory testing to ensure the science is in place before embarking on the clinical phase.

“The Canine Hereditary Urothelial Malignancy Study (CHUMS)”

Dr. Frederick Leach of Baylor University gave an exciting overview of the Canine Hereditary Urothelial Malignancy Study (CHUMS), that indicated the study may be a potentially useful approach to understanding human urothelial malignancy. The lifetime risk of cancer in dogs is 43% and 38% in man, and is the second leading cause of death in man. Cancer statisticians estimate in the year 2002, urothelial malignancies will be diagnosed in 56,500 American men and women and 12,600 patients will die from advanced disease.

Knowledge of genes that are associated with malignant cells will give us insight into tumor biology and ultimately better therapies. Certainly, therapies that can regulate cells from becoming malignant are of special interest. Dr. Leach believes that the ability to study hereditary predisposition of urothelial malignancies through the use of a dog model, provides a useful and important means of learning of the genetic traits and mapping of hereditary renal cancer.

The Scottish Terrier has proven to be a good hereditary model to study bladder cancer. Using the tools of pedigree analysis, lineage analysis, cytogenetic analysis of candidate genes and immunohistochemical analysis of tumor specimens, they have been able to identify genes responsible for this disease. An accomplishment such as that, should not be taken lightly, especially when statistics show that 40% of the breed is affected.

The Scottish Terrier parent club has established a DNA bank so that they can have good genetic material to study not only bladder cancer, but other health problems affecting their breed. Again, it is truly time that we consider the establishment of an invaluable DNA bank for the Rottweiler. For those of you that are wondering ‘exactly what can a blood sample from my dog do for future research?’: from 8-10 ml of blood taken from a dog, researchers could perform between 1000-3000 PCR tests on the 300 ug of DNA that they could derive from that one blood sample. The value of one sample is quite impressive.

“Focused Expression Profiling of Cyclin and Cyclin-Dependent Kinase Integration Complex Components and Regulators in a Spontaneous Model of Canine Breast Cancer”

Dr. Curtis Bird of Auburn University then addressed canine breast cancer, focusing on the expression profiling of the cyclin and cyclin-dependent kinase integration components and regulation. Protein kinases are enzymes that play key roles in cell signal transduction, regulating cell growth, differentiation, survival and death. Expression profiling of many canine breast carcinomas have shown that these tumors have mutant tumor suppressor gene P16. Tumor suppressor genes are involved in cell cycle checkpoint control. When these genes are mutated, cells grow out of control, a hallmark of

cancer development. Dr. Bird’s work again confirmed the similarities seen between human and canine cancer. Using focused gene array analysis with cDNA from canine cancers, Dr. Bird showed that Erb2, CDK4 and cyclin C genes were unregulated in canine mammary tumors. These three genes have been known to play a role in breast cancer in women.

“Kinase Inhibitors In The Treatment of Canine Cancer”

The next speaker, Dr. Cheryl London of UC Davis, also spoke about kinase, although in the form of kinase inhibitors. Kinase inhibitors are ‘anti-angiogenesis’, inhibiting the growth of blood carrying vessels into a tumor, thus starving it and effectively preventing further tumor growth. Working for a major pharmaceutical company, Doreen LePage points out that kinase inhibitors are part of the exciting new therapies currently being studied at most major pharmaceutical companies. Many human clinical trials, utilizing kinase inhibitors, are currently in place.

Dr. London discussed several clinical trials she was conducting in dogs using the Sugen anti-angiogenesis compound SU11654. A tumor cannot grow beyond about a 3 mm size without angiogenesis, because the tumor needs blood vessel formation to supply itself with nutrients to grow. These agents are relatively non-toxic to the host and are available for oral administration so that dogs can be treated as outpatients. In her Phase I trial on mast cell tumors, multiple myeloma, mammary carcinomas and soft tissue sarcoma, the drug, SU11654, reportedly was well tolerated and 34% of the dogs had a partial response to the drug. It was determined however, the monotherapy would not be sufficient to arrest tumor growth. Dr. London is now conducting additional trials focused on combination therapy utilizing anti-angiogenesis inhibitors, coupled with chemotherapy. As Doreen agrees, clinical trials in humans have indicated that the best results are recognized when a combination of therapies are used. Doreen traveled back to the airport with Dr. London and discussed her perspective on this topic, as well as the typical cost for experimental therapy for a Rottweiler. Dr. London replied that treatment cost is \$1,000 per treatment and the Rottweiler would typically require 6-9 treatments.

Tetrathiomolybdate Therapy For Cancer (and Other Things!) in Dogs (and Other Species!)

The good friend of dogs, Dr. George Brewer of University of Michigan Medical School spoke next. Dr. Brewer has contributed so much of his life to researching canine health issues. He has developed a compound called tetrathiomolybdate (‘TM’) as an anti-copper drug for Wilson’s disease in humans. Because of angiogenesis (or tumor feeding) is dependent on copper, he felt that the drug had potential if it were used in cancer patients.

Using a mouse model of breast cancer Dr. Brewer showed that TM therapy could produce marked reduction in tumor growth in mice. Problems though were cited, as the drug did not work on big bulk tumors, having its best efficacy when treatments were started on small size tumors. Apparently, this is very typical of anti-angiogenesis compounds, as the best results are realized when treating small metastatic disease. Further recent studies have shown that some cytokines that promote inflammation and fibrosis are copper dependent. Clinical trials are currently underway at UC Davis looking at TM as a therapeutic agent for cancer in dogs. A side effect of anemia was noted in some patients, most likely due to the lack of copper, which bone marrow needs to remain healthy. Although reasonable success has resulted, TM therapy will most likely do best when combined with another therapy, such as radiation or chemotherapy.

“Inhibition of Angiogenesis and Tumor Growth by Interleukin-12 In A Canine Hemangiosarcoma Xenograft Model”

Dr. Stuart Helfand from the University of Wisconsin School of Medicine then spoke about the inhibition of angiogenesis, using Interleukin-12 (IL-12) in a canine hemangiosarcoma xenograft model. Restricting the ‘food supply’ for cancerous tumors involves some of the most promising work in cancer research today. Dr. Helfand demonstrated the ability of a cancer cell to produce ‘cytokines’ that would stimulate their growth. This survival mechanism of tumors has been demonstrated in the progression of human cancer as well.

IL-12 is a potent anti-angiogenic and has shown to have anti-tumor effects in some of his mouse models. In human clinical trials, IL-12 has been tested extensively, with mixed results. Treatment with IL-12 resulted in an increase in interferon gamma level in the blood, which is critical to several immunomodulatory processes in the body. Doreen points out, the idea of immunotherapy, or the ability to boost one’s immune system to attack their own tumor, is a hot area in human cancer biology.

Due to the difficulty of getting IL-12 to the tumor, Dr. Helfand had to use an antibody (manufactured by Abbott Labs), LM609, that he conjugated with IL-12. The antibody targets specific cells in the tumor with IL-12 therapy. Although Dr. Helfand has had reasonable success using Interleukin-12 therapy in mice, considerable testing must be done before the therapy can be used as an effective therapy in dogs. To date, IL-12 therapy has not worked in human cancer.

“Dietary and Environmental Risk Factors for Transitional Cell Carcinoma of the Urinary Bladder in Scottish Terrier Dogs”

Dr. Larry Glickman of Purdue School of Veterinary Medicine then addressed the dietary and environmental risks for transitional cell carcinoma of the urinary bladder in Scottish Terrier Dogs.

Transitional cell cancer is the most common form of bladder cancer in dogs. Scottish Terriers are 18 times more likely than the average dog to get TCC (transitional cell carcinoma). At the time of diagnosis, 20% of the cases have metastatic disease (meaning the cancer has spread to other areas), chemotherapy is not effective, and the disease is terminal in 50% of the cases, with a survival time of 2-6 months.

Dr. Glickman’s research involved test dogs divided into two separate groups: the first set was proven to have TCC via biopsy or histopathology; and the second set (of the same age as the first set) tested negative for TCC. The dog’s owners completed questionnaires and Dr. Glickman presented the following data based on his study:

- Females had a 2.8 time greater risk of disease
- Second hand smoke or passive smoke from owners was not considered to be a risk factor
- Overweight or obese dogs have a higher risk of disease
- Dogs exposed to flea dips had a 2 time greater risk
- Dogs living near a marsh where mosquito sprays were used had a 3 time greater risk
- Dogs whose diet was supplemented with Vitamin E and C, had a 50% lower incidence
- Dogs whose diet included cruciferous vegetables (such as broccoli, cabbage, and cauliflower) had a 75% lower incidence
- Dogs who were administered NSAIDS (such as aspirin), had a 50% lower incidence
- Dogs who drank chlorinated water, had a 26% greater incidence
- Dogs who had access to chemically-treated lawns, had a 100% greater incidence
- Dogs who had exposure to herbicides had a 400% greater incidence
- Dogs who had exposure to phenoxy herbicides had a 100% greater incidence

- Dogs who worn flea collars, had used flea/tick dips, shampoos, sprays, or powders had a 300% greater incidence. It was also cited that a dog using a combination of three of these products, the incidence was even greater

Dr. Glickman then spoke briefly about the typical composition of products used to kill insects and pests. Typical pesticides are comprised of ‘active’ ingredients and ‘inert’ ingredients. An inert ingredient is any ingredient, other than the ‘active’ ingredient. For example, in some flea sprays, pyrethins are listed as the active ingredient, which comprise only a small percentage of the product, while inert ingredients can sometimes be as much as 97% of the product. Many inert ingredients are known to be hazardous as environmental carcinogens. Examples of inert ingredients: toluene, xylene, benzene, and petroleum distillates. Dr. Glickman pointed out that companies who manufacturer pesticides, herbicides, and insecticides are not regulated by the federal government to list a product’s ‘inert’ ingredients, which typically comprise a great percentage of the product.

Please keep in mind that Dr. Glickman’s research is only in its eighth month, so what was presented should be labeled as preliminary. In many cases, Glickman made very broad range claims based upon a very small sample size. The real ‘pressure test’ for any data generated in a scientific study is to use a statistical analysis to determine if the results were significant and not just a matter of chance. Many of Dr. Glickman’s claims did not have sufficient numbers to be statistically significant. As Doreen notes, the group of scientists she traveled back to the airport with, felt that very little could be taken from Dr. Glickman’s preliminary data.

Although Dr. Glickman’s study cannot be considered statistically significant, certainly it creates an awareness of environmental influences and how they may be potentially harmful. In addition, as bladder cancer is on the rise in both dogs and man, our dogs do serve as a sentinel for the future of society.

After Dr. Glickman’s address, Carol and I spoke to Dr. Jaime Modiano, who is currently spearheading the study on ‘Dogs, Genes, and Cancer’. Dr. Modiano made a humorous comment: ‘Does this mean that our clients are going to be asking us if they can spray their yards if they feed their dogs broccoli?’

“Regulation of COX-2 Expression In Canine Cancer”

The next speaker, Dr. Monique Dore of the University of Montreal, spoke about COX-2 expression in canine cancer. Cyclooxygenase (COX) is the first enzyme in the prostaglandin biosynthetic pathway. An isoform of COX, COX-2, appears to correlate with an increase in prostaglandins, which has angiogenic factors and decreases immune response. Mounting evidence suggests that COX-2 plays a role in various cancers.

Many human cancers over express COX-2, such as human breast cancer. In dogs, COX-2 is induced in approximately 50% of mammary tumors. The use of COX-2 inhibitors, such as aspirin and NSAIDS, has shown to decrease the incidence of colon, breast and prostate cancer in man. Dr. Dore showed that COX-2 in the canine has strong homology to COX-2 in man.

These strategies suggest that anti-COX-2 strategies should be useful for the treatment of some canine cancers. In addition, as Doreen points out, human clinical trials utilizing a class of agents called COX-2 inhibitors have been very promising thus far.

“Of Mice & Men (and Dogs): Development of a Xenogeneic DNA Vaccine Program for Malignant Melanoma”

Dr. Phillip Bergman from the Animal Medical Center in New York City was the final speaker. He spoke about a xenogeneic DNA vaccine program for canine malignant melanoma. Dr. Bergman’s talk was hope inspiring as to improving the lives of his canine melanoma patients.

His clinical trial involved nine dogs with advanced malignant melanoma who received four bi-weekly intramuscular injections of DNA encoding human tyrosinase. These dogs were very ill, and had little to loose. The results were very good, with no toxicity or induction of autoimmunity seen. The survival time of the dogs treated was significantly higher (i.e., 389 days) as compared to historical controls. In addition, one dog experienced complete clinical response by developing antibodies and is still alive. The trial is so successful that the FDA has permitted human trials to start.

Conference Overview – Potential Benefits For Both Humans and Dogs

- In a recent clinical trial using an orally administered drug called SU11654, which inhibits tumor growth by cutting the blood supply, 91% of dogs with mast cell tumors experienced tumor regression or stability.
- The results of recent clinical trials on 42 human patients and 13 dogs with a variety of advanced and metastatic cancers, Tetrathiomolybdate (“TM”) therapy which creates a copper deficiency, shows a marked ability to inhibit tumor growth as well as to suppress inflammation.
- A xenogeneic DNA vaccination of dogs has been shown to be a potentially safe and non-toxic therapeutic method of treating canine malignant melanoma. A clinical trial for human cancer patients with malignant melanoma is also in currently in the works.
- Through studies of the genetic basis of bladder cancer in the Scottish Terrier, utilizing both pedigree and molecular analysis of affected dogs, it is expected to eventually identify the gene that predisposes Scotties to urinary tract cancer. Once this gene is formally identified, researchers believe that the comparable gene that causes this type of cancer in humans can be identified.
- Through the development of a comparative map of canine and human genomes, researchers expect useful information into many canine and human diseases.
- Current therapies, utilizing kinase inhibitors (which inhibit the blood supply to tumors) such as COX-2, show promise as partial treatment of some canine cancers. In fact, current human clinical trials utilizing COX-2 inhibitors show much promise.

In conclusion, several key points were driven:

1. The dog is a sentinel for our environment.
2. The dog is a good model for human disease.
3. The work being done by researchers has a ‘xenogeneic’ benefit.
4. We are all benefited by our participation in this research.
5. Although trial results have been encouraging, the best treatment method appears to be the utilization of a combination of therapies.

While Doreen, Carol, and I joined together for dinner, we discussed strategies of how we might disseminate this important information to the rest of the Rottweiler world and then engage them to become more involved in the future collection of research samples. It is clear that the general Rottweiler-owning public should participate by providing a simple blood sample and pedigree from their dogs(s). The key to the success of future scientific research targeting both effective cancer treatment and the prevention of cancer can be realized through the utilization of significant, statistical

data. It is certainly thought provoking to think that by donating blood to an established database, may not only help the Rottweiler(s) you own, but also humankind.

This is a very exciting time in cancer research and the future is very promising. As Rottweiler owners and members of various clubs funding specific research projects in canine cancer through the American Kennel Club's Canine Health Foundation, we should be very proud of our contributions to this cancer initiative project. Scientific break through will not only benefit our beloved dogs, but also help man. By a better understanding of tumor biology, better therapies will ultimately be developed and hopefully crack the complex mystery of this horrible disease.