# Ask The Health & Genetics Committee:
# Hemangiosarcoma FAQ's

Linda Shipman (Juneau, Alaska) wrote to the H&G to request the most current information about hemangiosarcoma in Golden Retrievers. She graciously provided a number of questions below, paraphrased from an Internet discussion List, that are on the minds of many Golden owners. We appreciate her help in directing this discussion toward frequently asked questions.

**What is hemangiosarcoma, and how common is it in Goldens?**

Hemangiosarcoma (HSA) is a cancer of the cells that line blood vessels, called endothelial cells. Since blood vessels are in nearly all tissues in the body, this cancer can arise in nearly all tissues. However, the spleen is the most common site for HSA tumor development, accounting for 50-65% of HSA tumors. Other common sites for HSA tumors are the heart, liver, lungs, brain, and skin. Hemangiosarcoma of the skin or underlying tissues is called cutaneous hemangiosarcoma, and hemangiosarcoma of the organs and deep tissues is called visceral hemangiosarcoma. Data from the 1998 GRCA/GRF Health Survey (http://grca.org/pdf/health/healthsurvey.pdf) indicate that 18.7% of Golden Retrievers (nearly one in five) die from hemangiosarcoma at an average age of 10.3 years old.

**What are the symptoms of HSA? It seems like they are very healthy and then 'boom,' they're gone literally hours later. Is it true that they will have a rash on their tummy? I've also heard that it can have signs that show up on an eye exam. Other people describe refusing food, weakness, and pale gums**.

The clinical signs of HSA can vary with the part of the body affected. Tumors of the spleen and other internal organs often rupture, causing bleeding into the abdomen; or in the case of a cardiac tumor, into the sac around the heart (pericardium). Sometimes bleeding into the abdomen causes weakness, pale gums, lethargy, and loss of appetite for a few days, but gradually the lost blood is resorbed and the dog regains the appearance of good health. This waxing and waning of symptoms may be repeated through several episodes over the course of a month or more. Other signs of visceral HSA may include difficulty breathing, weight loss, abdominal distention, and generalized depression. Particularly with cardiac tumors, the first sign of disease may be sudden collapse and death; or abnormal heart function can cause weakness, pale gums, and labored breathing. In addition, the majority of dogs with hemangiosarcoma have blood clotting abnormalities at the time of diagnosis.

Cutaneous HSA may present as a "rash" on the abdomen, which is typically dark or purple in color, and often raised. It can also appear as a red or dark mass in or under the skin, which may or may not be ulcerated.

Many systemic diseases can be detected as nonspecific abnormalities during an eye exam, which is one reason that yearly eye examinations are recommended for dogs even long after their breeding careers are over. Some manifestations of HSA might be detected on an eye exam, and though this would alert the owner to seek follow-up care, it would not be diagnostic.

**What are treatment options with HSA?**

Unfortunately, treatment for visceral HSA currently is of very limited effectiveness. Surgical intervention to remove an accessible mass will provide relief from the clinical symptoms associated with internal bleeding for a period of time. Chemotherapy usually increases survival time, and may be offered as single agent therapy (typically doxorubicin) or multi-agent therapy. Newer immunotherapy protocols are available at some treatment centers.

With no treatment, survival time from the discovery of visceral HSA ranges from less than a day to about 8 weeks. Surgery alone increases survival time to approximately 3-4 months, while surgery plus chemotherapy has been reported to increase median survival time to more than 5 months (Sorenmo et al., 2004; Ogilvie et al., 1996). Early results with immunotherapy report median survival time of 273 days (Withrow and MacEwen, 2001).

Cutaneous HSA has a better prognosis. With small lesions that are restricted to the upper layers of the skin, surgery with wide margins may be curative. With deeper or larger lesions, surgery plus chemotherapy may be recommended (Ward et al., 1994). However, when metastatic disease is present, chemotherapy is not curative.

As with all veterinary care, individual treatment decisions are best made between an owner and the treating veterinarian. When circumstances permit, owners may wish to consult with a veterinary specialist such as a board certified oncologist (http://www.acvim.org) to discuss options that may not be available at a general veterinary practice.

**Does it ever happen that the spleen is removed due to HSA, and the dog is cured? Does the disease always metastasize? Is it ever recommended to remove an "at risk" dog's spleen to prevent HSA?**

Though one hesitates to use absolute words like "never" and "always" to describe biological processes, in this case, it is very nearly certain that removing a spleen with an HSA tumor will not cure the disease. Further, removing a healthy spleen will not prevent this disease. Let's examine the disease process in greater detail to understand why.

Many people are aware that in humans, it is estimated that a breast cancer usually has been growing for an average of 8-10 years before the tumor reaches a size where it can be detected. Likewise, current theories in visceral hemangiosarcoma (and other cancers) estimate that the first mutant cells become cancerous several years before the tumor reaches detectable size (Etzioni et al, 2003; Wulfkuhle et al, 2003; Laird, 2003). Because the cancerous hemangiosarcoma cells may arise in any blood vessel in the body, they have ready access to circulating blood and can migrate freely through the body in the blood stream.

At some point a primary tumor site develops, and this is typically in a highly vascular organ such as the spleen, liver, or heart. In some malignant tumors, factors associated with the primary tumor actually suppress the growth of tumors that originate from cancer cells that have escaped into the blood from the primary tumor (O'Reilly et al., 1994). So although malignant cells from the primary tumor have nearly always spread elsewhere in the body, they may temporarily remain dormant while the primary tumor is growing. However, removal of the primary tumor is

essential to prevent additional shedding of malignant cells, and to prevent problems associated with tumor enlargement and rupture. Unfortunately, in model systems, removal of some primary tumors can actually increase the growth rate of metastases because removing the tumor also removes the source of the factors that suppress the growth of secondary tumors (Barbour and Coventry, 2003; Ouatas et al, 2003). Thus, it is extremely likely that visceral HSA will have spread before the primary tumor is detected and it is even possible that removal of the primary tumor will actually increase the growth rate of HSA in the distant (metastatic) sites.

In addition, although a large proportion of primary HSA tumors occur in the spleen, there is only limited evidence that the original mutation to cancerous cells occurs in the spleen. Since the spleen functions as a filter to remove abnormal blood cells from circulation, a likely scenario is that hemangiosarcoma cells originating elsewhere are captured by the spleen, and then develop into the primary tumor. It is unlikely that removal of the spleen would prevent HSA, because the primary tumor can develop in alternate sites such as the liver or right atrium of the heart (obviously not candidates for prophylactic organ removal). Further, the spleen functions to aid the body to fight infections, and is certainly not a "disposable" organ that can be removed with no consequence to the dog.

**At the 2000 National, a seminar was presented on HSA. Someone asked if there was any way to detect hemangiosarcoma with regular ultrasounds. The answer was that even twice-yearly ultrasounds might not catch rapidly spreading cancers, because they could develop in a dog's body and kill it within as short a stretch as six months. In response to this, a breeder shared that they had ultrasounded a Golden in late August, showing a normal heart. Then in mid-December, there was a lesion visible on the heart, which was confirmed as hemangiosarcoma. The dog died in late January. The earlier ultrasound showed a splenic mass, but the pathology report indicated a benign hematoma, not hemangiosarcoma. What use is ultrasounding when the cancer spreads and kills so quickly anyway?**

As discussed above, current research indicates that by the time a tumor is large enough to be detected on ultrasound, the disease has existed for some time, and metastasis has already occurred. Even monthly ultrasounds would not "catch" HSA prior to metastasis.

However, periodic ultrasounds might discover a primary HSA tumor prior to rupture, permitting removal of the tumor before it has spread its contents into the abdominal cavity (which may contribute to additional metastasis). This may add several months to the dog's survival time, and of course, will prevent sudden collapse and death due to tumor rupture. However, approximately one-half of splenic tumors are benign, and these generally cannot be distinguished from HSA without surgery (Clifford et al, 2004). Thus, the potential benefit of discovering an HSA tumor prior to rupture, must be balanced against the possibility of surgery for a benign tumor. There are reasons that removing a benign tumor may also be of benefit, but we have found no studies comparing the risk and benefits of surgery for benign splenic masses. As always, the attending veterinarian is in the best position to make recommendations for the most appropriate health care and diagnostic procedures for the individual dog.

**What research is going on that might help us with HSA?**

There are a number of hopeful lines of research in HSA. First, hemangiosarcoma is an excellent naturally occurring animal model of a process that occurs in all solid tumor cancers, called angiogenesis (Fosmire et al., 2004). Angiogenesis is the process by which cancers create a blood supply so they can grow. This makes it of great interest to scientists working on human cancers,and therefore, substantial research money, time, and talent is being devoted to HSA. By understanding how cancers create their own blood supply, scientists hope to learn to impede that process, and thereby control the growth of tumors. This would have potential therapeutic benefits to a very wide variety of cancers.

Investigators are also working to develop other ways to treat hemangiosarcoma. In addition to the antiangiogenesis therapies discussed above, these include immunotherapies, vaccine therapies, newer chemotherapeutic agents, modified treatment schedules with existing chemotherapeutic agents, and different delivery methods for chemotherapy (Akhtar et al., 2004;Clifford et al, 2000;Sorenmo et al., 2004). Some of these studies are conducting clinical trials that are available to eligible dogs (http://www.grca.org/pdf/health/cancerdonation.pdf) for referrals.

Another promising line of research is in the area of developing earlier methods of detection of HSA (Clifford et al., 2001; Rossmeisl et al., 2002). As a general rule, the earlier a cancer is detected, the greater the effectiveness of treatments.

Epidemiologists are examining environmental factors that may influence the development of hemangiosarcoma and other cancers. They are considering such factors as food and dietary supplements, various chemical exposures, parasitic exposures, vaccination protocols, and other environmental conditions.

Finally, scientists are also investigating the role of genetics in hemangiosarcoma. They are looking for tumor suppressor genes and oncogenes (genes that promote cancers) that may contain germ-line (inherited) mutations that could predispose dogs to cancers. Finding such genes might lead toward DNA tests to help breeders identify dogs that are at higher or lower risk of certain cancers, or dogs that may produce offspring with higher or lower risk of certain cancers. Identifying these genes may also lead toward more effective targeted therapies to treat HSA. An example of success in this area is that a gene which plays a causative role in a rare cancer (hereditary multifocal renal cystadenocarcinoma and nodular dermatofibrosis) of German Shepherd Dogs has recently been identified (Lingaas et al, 2003). For a number of reasons,finding genes that play a role in hemangiosarcoma susceptibility will be much more difficult than the example with GSD's, but there are some preliminary suggestions (Jeglum, 2001) that increased familial susceptibility to cancers may exist in some lines. However, until these genes are identified and DNA tests can be developed, cancer in an individual Golden Retriever cannot be classified as sporadic (due to chance events), environmental, or familial (having inherited tendencies).

The AKC Canine Health Foundation funds and monitors a number of canine cancer studies with the support of many breed Clubs and funding organizations, including the Golden Retriever Foundation and Golden Retriever Club of America. Abstracts from these studies are available online at http://www.akcchf.org/research/grants/disease/c.htm#Cancer.

**At what age is cancer considered to be a by-product of old age?**

As implied in this question, some scientists consider cancer to be an expected occurrence as part of the aging process. Cancers develop when multiple sporadic (non-heritable) mutations permit cells to divide out of control, or not die when they are supposed to. Each time a cell divides, there is an opportunity for a mutation that contributes to cancer to occur; and the more cell divisions there are, the more chances there are for a cancer to begin. Obviously, an older animal has had more cell divisions in its lifetime than has a younger animal, and thus, the odds of accumulating cancer causing mutations rise as an animal ages.

In addition to numerical odds being in their favor (because of fewer cell divisions), younger animals are also protected against mutations better than are older animals. These protections permit time for animals to reproduce. Loss of these protections also contributes to cancers that occur in older dogs.

So at what age is cancer "normal" and at what age is it too young? There is no single answer, because we really don't have sufficient data yet to determine what assessments might be most valuable for predicting risk to the future generations of Goldens. One way to consider the question might be to examine the average age of death from certain cancers in this breed – for example, 10.3 years for hemangiosarcoma, and 8.5 years for lymphoma. One might feel that when these cancers occur after these ages, it is better than the norm for those cancers. Or, one could use the average life span in the breed (10.7 yrs for males, and 11.3 yrs for females), and make a case that only cancers that occur after those ages can be considered old age cancers.

As a very general rule, cancers that occur in young animals have the highest likelihood of a more significant heritable genetic component.

More information on cancer and aging is available in some recent scientific publications (McMurray and Gottschling, 2003) or online http://www.infoaging.org/feat15.html or http://www.skcc.org/thoman.html).

**How much cancer can be attributed to environment and how much to genetics?**

Science is still far from answering this question in dogs, as we are only beginning to glimpse the intricate interactions between genes and the environment. Since much more is known about this topic in humans than in dogs (although not nearly fully understood in humans either), perhaps we can draw some understanding from human medicine.

In some human cancers, such as breast and colon cancer, it is known that a person's risk of developing those cancers is increased if he/she has multiple first-degree (parent or sibling) or second-degree (grandparent, aunt, uncle) relatives with the disease. Yet, the vast majority of affected persons **do not** have a family-history risk factor. So while there is a genetic component, clearly something else is going on too. Some of those other factors have also been identified, and include a high fat diet and a sedentary lifestyle. Yet not all sedentary people who eat a high fat diet and have affected family members get breast or colon cancer. In fact, most don't. And many

active people who eat moderate fat diets and have no family history, **do** get breast or colon cancer. So again, clearly something else is going on.

Examining this in greater detail, it is widely known that researchers have identified certain specific genes in humans that contribute to cancers, such as the *BRCA1* and *BRCA2* genes, which can play a significant role in breast and ovarian cancers, and several other cancers. For example, a woman with one of these genes faces a 3- to 7-fold increase in her risk of developing breast cancer, and will often develop cancer at a younger age, as compared to the general population. And yet, only 5-10% of American women with breast cancer have these genes. (Data used in this and the previous paragraph is from The National Cancer Institute, available online at http://www.nci.nih.gov/) It is likely that for many affected people, their breast (or colon) cancer arose at least in part as a result of unlucky sporadic (chance) mutations, or other factors which are not yet understood.

As we learn more about cancers in dogs, it is very likely that we will find a similar puzzle emerging. One piece of the puzzle may include one or more genetic risk factors, another piece may include some environmental or lifestyle risks that are identified, and other pieces will include factors that aren't identified. As with most breast and colon cancers in humans, it is likely that that no single factor plays a predominant role. And then there is luck – or lack of it – played out over the lifetime of the dog each time a cell divides.

However, there are several important clues that lead to some basic theories of cancer genetics in Goldens. First, it appears that the overall incidence of cancer in Goldens in the US and other countries such as the UK is elevated as compared to all dogs. For example, the overall rate of death due to cancer among US Goldens (66% of males, and 57% of females, according to the 1998 GRCA/GRF Health Survey) is higher than is the death rate from cancer among all dogs (Craig, 2001). In the UK, the incidence of lymphoma is 162% higher in Goldens than in all dogs, and the incidence of mast cell tumors is 190% higher (Edwards, 2004). These elevated rates of cancers in Goldens are a strong indication that there is a heritable component to overall cancer susceptibility within the breed.

However, hemangiosarcoma does appear to have an increased incidence in the US as compared to the UK. (Edwards, 2004) This is an indication that specific gene pools or lines may possibly be implicated as having increased genetic contributions to the development of HSA in US Goldens.

And finally, some differences at the cellular level of specific cancers have been identified that seem to segregate within certain breeds of dogs, including Goldens. This is another indication that there may be a heritable component to specific cancers within our breed.

Taken all together, a working theory has emerged. It is possible that early Golden Retrievers had genes that confer an elevated degree of cancer risk, and that these genes have become common and widely dispersed over countless generations of breeding within a closed gene pool. According to this model, the inherited susceptibility for cancers is widespread throughout the breed, and it is possible that no lines are exempt from a certain degree of elevated risk (as compared to all dogs). However, some lines within the breed also may be at additional increased

risk for specific cancers, including hemangiosarcoma. The mechanisms behind this increased genetic risk for cancers can include inheriting some of the steps in the progression toward cancer, or inheriting an increased susceptibility to environmental triggers of cancer causing mutations (Cavenee and White, 1995; Feigelson et al., 1996; Minamoto et al., 1999; Knudsen., 2001; Kamb et al, 1994). (For a more detailed discussion, see http://grca.org/pdf/health/perspectives.pdf)

**What has changed to explain the increase in cancer in recent years? Has it always been there and just been undiagnosed?**

Unfortunately, we really do not even know if there has been an increase in cancer in recent years. Certainly, our dogs are not succumbing to infectious diseases at the rate they were many generations ago, and this has contributed to a long term trend toward alternate causes of death. And there may be a greater likelihood of accurate diagnosis in recent years, though this is not certain either. One factor that may influence the perception (real or not) of more cancer, is the current use of chat Lists to share information. As a result, most of us have heard many more anecdotal accounts of affected dogs than we would have been likely to hear even 10 yrs ago. Even popular online databases give us access to more information than we would have had in previous generations.

The good news is that the 1998 GRCA/GRF breed Health Survey has now given us some baseline data with which to compare and track future trends in cancer and other diseases. This promises to be very useful, and it is likely that a new health survey will be conducted in the near future.

Although not directly a cancer statistic, the 1998 survey does indicate that the average lifespan of Goldens (11.3 years for bitches and 10.7 years for dogs) is very similar to the 10 years reported for mixed and purebred dogs in one Danish study (Proschowsky et al., 2003) and the 11.1 years reported in a British study (Mitchell, 1999).

**Does hemangiosarcoma occur more often in close relatives? What breeding recommendations are there for a dog that had a close relative die from HSA?**

This is another question about which we do not have good data. There is a common perception that certain lines have an increased incidence of hemangiosarcoma, and this may, in fact, be the case. However, even disturbing circumstances such as several littermates diagnosed with HSA, may not be too far outside the norm. For example, with a rate of 18.7% HSA in the breed, on average, a litter of 10 pups would contain one to two affected dogs. And even a third affected littermate may not be numerically extreme. If one were to extend the consideration to all cancers, on average, this would amount to 6 of the 10 littermates succumbing to cancer. It is very difficult for breeders and scientists to accurately understand what is really going on with these pedigrees, especially when examining small or incomplete data sets (such as only a couple of litters by a prolific sire, or only a few littermates out of a larger litter).

To better illustrate the complexities of accurately understanding family histories, it might help to consider once again the human examples of breast and colon cancer. Extensive studies have led to very specific guidelines to assist patients and physicians in determining who is likely to have

inherited risk factors for certain cancers. Note that the guidelines (reproduced below from Murff et al, 2004) are different for each cancer, and are much more detailed than simply knowing that "several relatives" had a certain cancer:

**Example 1 Hereditary Nonpolyposis Colon Cancer (HNPCC)**

All of the following criteria should be present:

- At least 3 relatives must have cancer associated with HNPCC (colon, endometrial, ovarian, stomach, small bowel, hepatobiliary, ureter, renal-pelvis, brain)
- One should be a first-degree relative of the other 2
- At least 2 successive generations should be affected
- At least 1 of the relatives with cancer associated with HNPCC should have received the diagnosis before age 50 years.

**Example 2 Hereditary Breast/Ovarian Cancer**

Any of the following criteria should be present:

- Two breast cancers in a first- or second-degree relative and mean age at diagnosis of 40 years
- One breast cancer and 1 ovarian cancer in a first- or second-degree relative and a mean age at diagnosis of 41 to 50 years
- Two or more breast cancers and 1 ovarian cancer in a first- or second-degree relative
- Ovarian cancer in 2 relatives
- Identified relatives for all of the above must be on the same side of the family (either maternal or paternal relatives)

Clearly, we are very far from these kinds of precise guidelines to help us make sense of canine pedigrees (family histories) as they pertain to hereditary risks of cancer. So how can breeders approach the problem of understanding pedigrees as they pertain to risk of cancers? There are several steps that are likely to help in the long run, though results may be frustratingly slow.

First, breeders can keep records on the dogs they produce, and owners should inform their breeders of cause of death. Obviously, cause and age of death records can only be accumulated over the long term, but if one does not start somewhere, one will never get anywhere. Necropsies should be performed on dogs for whom the cause of death is not known, and it is important to keep medically accurate records that include the specific kind of cancer diagnosed, and age at diagnosis or death. A common error is that owners sometimes note only the organ that contained the primary tumor ("spleen cancer"), rather than identifying the cancer as a hemangiosarcoma or other specific neoplasia. A tissue sample sent out for a pathology report may be necessary to obtain an accurate diagnosis.

Second, it does little good if each of us keeps records, but does not share that information. Islands of data are much less meaningful and reliable than are networks of data. Unfortunately, disclosure of information through open health registries or directly to individuals to whom it may be relevant, takes courage and conviction in the current dog breeding culture – which leads to the next point.

If we really want to have a chance at improving our understanding of family histories, it is important to resist the impulse to: 1) point fingers 2) spread rumors 3) condemn 4) keep secrets 5) leap to the most negative conclusion possible 6) over simplify this complex disease 7) shun those who disclose information 8) accept "I don't know" for an answer, and 9) automatically reject pedigrees with negative data, without considering all of the nuances. If we want a culture of openness that will ultimately benefit our dogs, we are all equally and individually responsible for creating it – every time we pick up the phone, send an e-mail, or talk ringside.

Unraveling the pedigree genetics of cancers will take a mature, selfless, committed, long-term, and united effort. There are no quick or easy answers here. As breeders embark on this task, there are several important genetic concepts to understand. First, as with any complex genetic trait, complete or nearly complete vertical pedigree data (sibling data) is at least equally as valuable as is horizontal pedigree data. (For a full discussion of vertical pedigrees, see http://www.offa.org/hovanart.pdf) That means that information on the "invisible" dogs that went into pet homes may add up to be more important than data on the "visible" dogs that went into show homes, since there are typically far more of the former than of the latter.

Finally, with all of that as background, we return to the question of what breeding recommendations there are with regard to a dog whose close relative had hemangiosarcoma. Begin by putting this in the perspective that since approximately one in five Goldens gets HSA, if this cancer is randomly distributed thru the breed, accurate data on at least 10 close relatives over the age of 10 years (parents, siblings, aunts, uncles), would suggest that most Goldens have a close relative with HSA. From there, compare the most complete pedigree data available to what is known to be average for the breed. Include the nuance factors such as age of onset (cancer at 12 yrs old may not be weighted the same as cancer at 6 yrs old), and number and ages of dogs on which data is available (a dog that has produced 100 offspring of older ages will usually have more affected offspring than will a dog that has produced 25 offspring that are still young). As this data comes together, sometimes a pattern may emerge which may make it appear that the line is average, above average, or below average in its incidence of HSA (and other cancers).

The genetic significance of such a pattern cannot be stated with certainty, but it is possible (and supported by a lower incidence of HSA among Goldens in the UK) that there are Golden lines with a stronger genetic susceptibility to hemangiosarcoma and perhaps to other cancers. If the data leads in that direction, such lines should be bred sparsely and cautiously, and efforts should be made to choose alternative lines in breeding programs. However, dogs from these lines are ideal candidates for inclusion in studies which seek to identify genes that may predispose Goldens to hemangiosarcoma. Through participation in research, these dogs have the opportunity (and their owners have a special responsibility) to make a contribution toward potentially developing DNA tests that may help breeders reduce the incidence of hemangiosarcoma in the future.

**Are there studies which show that cancer happens more often in dogs with high COI's? If so, what is the recommended percentage at or under which we should breed?**

There are few studies examining cancer rates for dogs with various coefficients of inbreeding (COI's). One study (Dorn et al, 1976) compared the COI's in purebred dogs with mammary cancer, other cancers, and healthy dogs; and the COI's in the three groups ranged from .000 to .535. While the two groups with cancers did have numerically higher average COI's, it was not considered to be a statistically significant difference. (A statistically significant finding is a one that is not likely to have happened by chance.)

Taking a broader view of health considerations, many studies in commercial animals such as cows and pigs, have shown that inbreeding depression can result in reduced fertility, slower growth, higher neonatal mortality, and other specific findings such as decreased milk production in cows. A small study of Bouvier des Flanders in the Netherlands (Ubbink et al, 1992) showed higher average COI's for dogs with several genetic diseases than for the normal controls, but this study did not note any results specific to cancers. Very highly inbred strains of laboratory mice (such as brother x sister breedings for 100 generations) usually have decreased overall life spans as compared to outcrossed strains.

There has long been a concern that repeated inbreeding (high COI's) may result in such significant loss of genetic diversity that highly inbred animals may be extremely vulnerable to infectious and other serious disease. This is of particular concern to conservationists attempting to preserve species that have been reduced to dangerously low numbers. However, as often happens with scientific theories, the data is not always as straightforward as the theory, and it turns out that Nature may have some tricks up her sleeve to preserve essential genetic diversity under even extreme circumstances.

A very recently published study (Aguilar et al, 2004) of the San Nicholas Island fox found surprising results. Approximately 10-20 generations ago (1970's), the isolated fox population on this island was reduced to under 10 individuals (probably about 5). It has since rebounded and repopulated the island to over 500 foxes, but with an entirely inbred population with extremely high COI's. It is the most monomorphic population in a sexually reproducing animal ever reported, showing no variation in most of the genetic markers examined. Yet geneticists were startled to find remarkably high levels of variation in the Major Histocompatibility Complex (MHC), which are genes that influence disease resistance. Of course, natural selection guided those breeding choices, not Man, and that is a very significant difference. But this example at least serves to remind us of how much we don't fully understand yet.

**Are tight line-breedings (high COI's) the main contributors to cancer or are there other issues, such as the use of popular stud dogs and the result of not being able to find pedigrees without some risk factor? What about heavy linebreeding on dogs that don't appear to have cancer in their pedigrees? Is that even safe from the threat of increased cancer?**

Although from the above discussions it should be clear that we do not understand all there is to know about how linebreeding and high COI's affect cancer, it would probably be safe to say that

we cannot "blame" cancer on modern day linebreeding and high COI's. Data on cancer as a cause of death in dogs varies greatly, but one study (Bronson, 1982) indicated that 39% of all dogs succumb to cancer. By age, this ranges from 20% of dogs at 5 years of age, and increases to 40-50% of dogs from 10 years of age onward. This study included both mixed-bred and purebred dogs, so COI's also ranged widely, and low COI's did not protect these dogs from cancer. On the other hand, a study in Denmark indicated that purebred dogs – which by definition have some degree of inbreeding and thus higher COI's than most mixed bred dogs – have a slightly decreased median lifespan of 10.0 years relative to mixed breeds with a median lifespan of 11.0 years (Proschowsky et al., 2003). However, this finding was not absolute, as some small purebred breeds had a longer lifespan than the mixed breeds, and a few breeds had a much lower median lifespan of 7 years. This study indicates that lower COI's might offer some advantage toward overall longevity.

It is not known whether Golden Retrievers with higher COI's have any greater risk of developing cancer than do Goldens with lower COI's. However, since many human cancers and at least some canine cancers can have hereditary tendencies (Padgett et al., 1995; Lingaas et al, 2003), a prudent approach might include avoiding repeated line-breeding or inbreeding, especially using dogs or lines that may be suspect. As discussed previously, however, it is impossible to identify such dogs and lines without a great deal of data. It is not enough to note a few related individuals with hemangiosarcoma and conclude that a dog or a line is at higher risk than average. (In fact, such premature conclusions are exactly the kinds of reactions that people fear when they make decisions not to disclose information.)

The converse is also true when investigating pedigrees that might have a lower than average risk of cancer. It is not enough to know a dog and his parents all lived to 13 with no cancer, because many of the siblings and aunts and uncles may have been affected, bringing the line into the average range in its rate of cancer. Unfortunately, such extensive data is not typically available.

However, when substantial amounts of data **do** indicate a higher than average incidence of hemangiosarcoma (or other cancers) in specific lines, it is the responsibility of those involved to take steps to reduce the genetic contribution of those lines. No one sets out with the intention of producing dogs with cancer, and it is nothing to be ashamed of when a dog is diagnosed, or even when multiple dogs are diagnosed. But conscientious breeders step forward at these difficult times to accept appropriate responsibility, disclose relevant information, and change direction if necessary to improve the health of the breed.

**What can we do to give our Goldens the best chance of not succumbing early to cancer? Please address such factors as less vaccinations, stress, pesticides, radio and microwaves, systemic medications like Heartgard & Frontline, better nutrition, etc.**

Epidemiological studies published earlier this year (Raghavan et al, 2004; Glickman et al, 2004) examined the relationship between a common genetic cancer (bladder cancer) in Scottish Terriers, and exposure to spot-on flea and tick products, and exposure to lawn chemicals. Results showed no increased risk for dogs exposed to spot-on flea and tick products, no increased risk for dogs exposed to lawn insecticides, and no increased risk for dogs exposed to nonphenoxy

herbicides. Exposure to phenoxy herbicides was associated with an increased risk of bladder cancer in Scottish Terriers.

The 1998 GRCA/GRF Golden Retriever Health Survey found a **decreased** risk of hemangiosarcoma (and lymphoma) in association with use of spot-on flea and tick products. It also indicated no increase in cancer in Goldens exposed to lawn chemicals.

There is no evidence at this time to suggest that vaccinations, stress, radiowave or microwave exposure, or heartworm preventative are associated with hemangiosarcoma or other cancer in dogs. However, there is evidence to suggest that dietary manipulation may have very beneficial effects.

First, there are a few foods and supplements that which may have some protective benefits against cancer. The antioxidants beta-carotene, lycopene, and vitamins A, C, and E, and the mineral selenium may be of benefit. In addition, supplementation approximately three times per week with broccoli, cauliflower, or cabbage may have protective effects. (For a more complete and referenced discussion of this topic, please see the Jul-Aug '04 GRNews, p 54 *"Preventive Health Care Thru Risk Management"*)

One of the healthiest things that any of us can do for our dogs is to grow our puppies slowly by strictly limiting food intake, and to keep our dogs very trim throughout their lives. Slowly grown puppies, kept trim as adults, showed significantly reduced rates of cancer, and an older age of onset of cancer, as compared to their littermates that served as a control group (Kealy et al, 2002). Overall, the trim dogs enjoyed a median life span that was 22 months longer than the littermates. In addition, the food-restricted dogs had lower rates of osteoarthritis, liver disease, and false pregnancies than did their pair-mates. Restricted food studies have shown similar results in a variety of other animals including mice and rats, and preliminary results in rhesus monkeys. **There are no breeding selection factors that are known to have as great an impact on overall longevity as this study indicated is possible with calorie restriction.**

Finally, there is another important way that owners can help reduce the toll that hemangiosarcoma and other cancers take on Golden Retrievers. The Golden Retriever Club of America (http://www.grca.org), The Golden Retriever Foundation (http://www.goldenretrieverfoundation.org), and AKC Canine Health Foundation (http://www.akcchf.org) are actively involved in supporting and promoting numerous research studies investigating several kinds of cancer. As funding organizations, GRF and CHF have devoted a significant proportion of their resources to canine cancer research, with resulting papers regularly appearing in scientific journals. The achievements have been impressive, especially considering that privately funded canine cancer research was almost nonexistent just a few years ago.

Of course, expectations should be kept to a realistic level. It's been over 30 years since President Nixon first declared "war on cancer" in humans, and some people probably wonder sometimes if we're winning or losing that war. But although cancers continue to be a major human health concern, progress against the disease has been remarkable. Many, many cancers that were once deadly have become curable or manageable over the last three decades. Further, a number of genes that influence a person's risk of specific cancers have been identified and developed into

DNA tests. Comparable tests in dogs would offer breeders a powerful tool to help guide breeding decisions. Progress against human cancer is made on a daily basis, though usually in small increments rather than in leaps and bounds. This should be our expectation for canine cancer research too.

Still, canine cancer research **is** moving forward toward an ever brighter future for our dogs. And to a great extent, the process is driven by money – the greater the resources available to fund the research, the more research that will be done. Thus, concerned owners have it in their power to influence the pace of this research and increase the potential benefit to dogs by donating to Golden Retriever cancer research via the GRF Zeke Fund (http://goldenretrieverfoundation.org/zekefund.html). The Golden Retriever Foundation has recently produced an excellent video, with copies provided to each local Golden Club. The Health & Genetics Committee highly recommends that each Club show this video at meetings or other events, and perhaps consider using it to spur new fund raising efforts to support the Zeke Fund.

In addition, owners can contribute toward progress against canine cancer by permitting their dogs to participate in research. This usually involves supplying a pedigree, blood, and/or a tumor sample, as required by individual studies; or in some cases, dogs may participate in clinical trials of new therapies. Yet despite notices in every issue of the GRNews, and on the GRF and GRCA web sites (http://grca.org/pdf/health/GRresearch.pdf), recruitment for participation in these studies is far below where it could and should be. Nearly every Golden breeder at one time or another, has the sad but hopeful opportunity to refer dogs to these studies, but only a small percentage of the GRCA membership actually does so. This is another area in which there is an opportunity to make a real difference – perhaps not for one's own Golden, but for those of future generations.

The H&G hopes that this information and discussion of hemangiosarcoma in Goldens will help owners and breeders better understand the many challenges that this disease presents. We also hope it will empower and motivate owners and breeders to make choices and take action toward meeting those challenges.

The GRCA Health & Genetics Committee

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