WESTIE FOUNDATION OF AMERICA, INC

Leading the Way to Westie Health

The Westie Health E-Book

Common Health Problems, How To Recognize Them, and What To Do About Them

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About this "E-Book"

Welcome to the second edition of the Westie Health E-Book, sponsored by generous support from the Westie Foundation of America. This electronic book is meant to serve as a source of information for Westie owners, breeders, veterinarians and for anyone who loves Westies.

The E-Book is organized as depicted in the Table of Contents. Links within the Table of Contents will take you to the topic of interest with a click of a button. The material is organized by topics of general interest, and then by specific diseases that often affect Westies. To help tie them together, the diseases are arranged according to the system of the body affected. Within the discussion of each disease, is information intended for all readers; where appropriate, we have included new illustrations and photographs to help clarify specific points. We also have included brief reviews of selected recent scientific publications related to each disease; this information may be of particular interest to veterinarians and scientists, but we've done our best to ensure that the major points are understandable by everyone. Finally, we have included lists of recent reference materials relevant to each topic area.

Health and Disease in Dogs – A Brief Overview

Dogs are amazingly hearty and healthy. The owner of any new puppy is amazed at the number of "delectable" items puppies eat – and how they grow and prosper.

There are several things that determine the health of all dogs. First, and foremost, dogs need a nutritionally adequate and complete diet, plenty of clean, fresh water, and a safe environment (See *Diet and Environment*, below). Second, dogs need humans to attend to their health problems. Owners of dogs are the front line in providing regular visits to the veterinarian for vaccinations and physical examinations (See *You and Your Veterinarian*, following page). Third, the breed of dogs can have a very strong influence on the development of some health problems. We know that some types of health problems, such as cancer or skin disease, are more common in some purebred dog breeds than others. One example of this is an increased incidence of bladder cancer in Scottish Terrier breeds, such as the Scottie and Westie (See *How Breed Influences Health in Dogs*, following page).

Diet and Environment

Revision by Korrin Saker, DVM PhD DACVN

Dogs prosper on many different diets. How can you be assured the diet you choose will provide adequate nutrition for your dog? The American Association of Feed Control Officials (AAFCO) has developed policies for regulating the manufacture, labeling, distribution and sale of animal feeds. The Nutrition Claim or Nutrition Statement on all pet food labels will indicate if and to what extent the manufacturer has followed AAFCO guidelines in formulating and testing that diet.

You will be able to ascertain, to some extent, if the diet is appropriate for your dog at a particular lifestage. Most commercially available diets (dry, semimoist, or canned) are formulated to provide "complete" nutrition for a specific life stage. A separate category of commercial diets, termed "therapeutic or prescription diets", are formulated to address specific health concerns. Diets that are formulated to provide "complete and/or balanced nutrition" do not require supplementation with vitamins, minerals or other nutrients for maintaining adequate health. Some owners prefer to prepare the diet for their dog using ingredients from the market. While homemade recipes have their place in pet nutrition, they can easily be incomplete or "unbalanced". Therefore, it is important that you discuss your dog's diet with your veterinarian to ensure that it provides all the nutrients the dog needs to maintain good condition. The National Academy of Sciences, Board on Agriculture and Natural Resources has created a 400-page report that summarizes the daily nutrient and calorie requirements for dogs and cats. The site also provides free access to the Science-Based Guide for Pet Owners, that is an excellent summary of relevant information. The website is worth a visit if you have questions about nutrition and diets for your Westie: www.dels.nas.edu/banr/petdoor.html

In general, most dogs thrive on the same diet – day after day. In fact, some dogs don't do very well if their diet is changed, and will sometimes develop stomach upsets and diarrhea when this happens. Most owners realize that there are some dietary nono's – too much food (exceeding body needs and leading to weight gain), doggie junk food and snacks, and fatty scraps. Although they love them, many dogs will get upset stomachs and diarrhea if they eat bones. Soft bones, such as those from poultry, may actually be a danger to dogs. These bones can be broken into sharp pieces during chewing and injure the digestive tract and mouth of dogs. All of these should be avoided.

Virtually all pet food companies maintain very good information on dog nutrition on their websites. They also provide information for dog owners on their products. Pet food websites and product information can be obtained by accessing the American Academy of Veterinary Nutrition (AAVN) website: www.aavn.org

Dogs need clean, fresh water. Dogs should have their water changed several times daily, and regularly checked by their owner for debris, cloudiness or discoloration that might indicate the water is unpalatable or potentially contaminated. Water bowls made of stainless steel are generally easier to keep clean and to resist chewing by enthusiastic dogs.

One of the most important things owners can do to ensure the health of their animal is to keep it in a safe environment. Dogs that are allowed to run free potentially may encounter other dogs with infectious diseases. Although Westies have the courage of African lions and will stand their ground against much larger dogs, they may get severely injured in dog or cat fights. Dogs that run free also run the risk of being struck by automobiles, ingesting dangerous substances (like antifreeze, for example), or being injured from falls or from malicious acts. So, keep your Westie safe!

You and Your Veterinarian

You and your veterinarian function as a team dedicated to maintain the health of your Westie. After completing undergraduate courses and being accepted into a veterinary school, they must spend the next four years in classes and being mentored during practice experiences before they are able to take licensing examinations and begin to practice veterinary medicine. Most new veterinarians will work with more seasoned practitioners to hone their skills. Some veterinarians will take additional years of training (as in internship and residency training programs) to learn a veterinary specialty like dermatology, cardiology, neurology, oncology (the study of cancer), or orthopedic surgery. If you are interested in veterinary training or in the scope of the veterinary profession, several very good websites are maintained by The American Veterinary Medical Association (www.avma.org) and the American Animal Hospital Association (www.healthypet.com). These websites also contain a wealth of information on the health of companion animals (such as dogs, cats, and horses) and are worth a visit.

Regular visits to your veterinarian are critical in maintaining the health of your Westie. These visits allow the veterinarian to get to know your dog and to know you. The visits allow you to communicate to the veterinarian what a special dog you have and to allow the dog to understand the environment and examination procedures. It is well known that dogs that know their veterinarian and the practice environment are more at ease with visits. This lowers the stress levels your dog might have when going to a place where there are other dogs and cats, unfamiliar people and strange smells.

Regular visits also help the veterinarians in the practice do a good job in assessing the health of your dog, because they can develop a baseline of health and potential medical problems, detect diseases at early stages, and, most importantly, gain the trust of you and your Westie (***Figure 1***).

Figure 1 - Regular visits to your veterinarian's office will allow him/her to assess your dog's health status.

Figure 2 - Spaying and neutering your dog has many health benefits, as well as helps reduce pet overpopulation.

How often you and your Westie visit your veterinarian depends on the age and the health of your dog. Most veterinarians would like to see your dog frequently (every few months) as a puppy, for vaccination against infectious diseases, to provide information on diet, to detect early signs of health problems, and to assess whether or not your puppy is affected by parasites. When dogs become mature, visits to the veterinarian may only be needed every 6-12 months. Of course, you and your dog should always see the veterinarian if there are any health problems, so they can be accurately diagnosed and treated.

Most dogs in the United States are now regularly maintained on medication to prevent the development of canine heartworm disease ("dirofilariasis"), a disease spread from one dog to another by mosquito bites. Veterinarians may also recommend the use of medications applied regularly to minimize the effects of fleas and ticks on dogs that go outdoors.

Breeding, Spaying and Neutering

Breeding, spaying and neutering are critical topics for discussion between you and your veterinarian.If you are an experienced dog breeder, you have a wealth of knowledge regarding breeding – perhaps more than your veterinarian. Most veterinarians will readily acknowledge this and will be happy to learn from your experiences. They may also have questions and observations that will foster dialogue, including discussions about the optimum timing for breeding, frequency of breeding, suggestions about nutrition for dam, sire and pups, vaccination schedules and protocols (to optimize puppy immunity), and a number of other topics. The ultimate outcomes of the dialogue between a breeder and veterinarian are happy, health Westie pups, Westie moms, and their human families!

The topic of spay/neuter is a personal decision, it is encouraged to follow your veterinarians recommendation as to timing. The benefits of early spay/neuter are obvious and do have some health advantages such as reduced mammary and testicular cancer. Recent literature, especially in large breed dogs, encourages sterilization after sexual maturity to prevent some common orthopedic injuries.

Spaying your female dog ("ovariohysterectomy") removes the ovaries and the uterus of the dog, so that she will not have puppies. Neutering male dogs removes the testes, and these dogs are sterile. These operations are done by your veterinarian in the hospital. Veterinarians first examine your dog to ensure that the dog is healthy enough for surgery, and then schedule the operation. Dogs that are spayed/neutered are placed under general anesthesia and prepared for sterile (aseptic surgery - *Figure 2*). After the operation, dogs will have a portion of their fur shaved, a sutured/stapled surgical site, and will require observation and aftercare. This will all be discussed with you by your veterinarian.

As noted above, there are important health consequences of spaying and neutering. Several studies have noted that the incidence of uterine infections ("pyometra") and mammary gland tumors is markedly reduced in female dogs that have been spayed. The beneficial effect on the development of canine mammary gland tumors is seen in dogs that are spayed in the first year of life and somewhat in dogs spayed between 1-2 years of age. Female dogs of any age have a reduced risk of developing pyometra, as the spaying operation removes the uterus.

The benefits (aside from preventing pet overpopulation) of neutering male dogs may be a reduction in the incidence and growth of some types of skin tumors ("perianal gland adenoma"), decreased incidence of perianal fistula and problems associated with benign enlargement of the canine prostate, including prostatic cysts and abscesses. The results of recent research has not shown that neutering of male dogs decreases prostatic cancer in dogs; in fact, some findings indicate that neutered male dogs may be at a slightly increased risk for developing this very uncommon tumor.

The effect of spaying and neutering on the development of other diseases and on pet behavior (such as aggression) is less clear cut. Once again, a discussion of these topics with your veterinarian will help you make important decisions on pet breeding and pet neutering.

How Breed Influences Health in Dogs

One of the many things that are very important in determining the health of every dog is genetic makeup. Each cell in every dog contains a "blueprint" for the cell and for the dog. These "blueprints" are made up of DNA, formed into specific genes contained in chromosomes. The entire set of genes that contain the "blueprint" for each dog is known as its genome. The genome specifies how cells are made, how the cells form tissues, and how the tissues (such as the heart or skin) function.

Selective breeding of dogs, following domestication from wild dogs and wolves, has resulted in the evolution of specific dog breeds, like the West Highland White Terrier. The genome of one Westie is likely to be very similar to other Westies, because selective breeding over several hundreds of years has focused the genome on certain desirable characteristics that make them Westies. For example, the pale and white coat color of Westies, the shape of the body, and even things like their lifespan are encoded in their genome. Interesting, Westies tend to live longer than Great Danes!

It is very likely that the differences between the genome of Westies and those of other dog breeds are small and caused by the variable expression of certain key genes. These variations in gene expression are termed "polymorphisms" or "mutations" by genomic scientists. Many such variations in the genome are beneficial, conferring selective advantages in appearance, performance and health. On the other hand, some variations are not advantageous for dogs. It is well known that cancer, for example, is the result of mutation in certain specific genes that control cell growth, cell division, and cell lifespan.

How does this relate to Westies?

There are some diseases that occur more commonly in Westies than in other breeds. The reason for this is undoubtedly tied up in the genome of the breed. Selective breeding over hundreds, if not thousands of years, has developed the Westie with certain characteristics such as size, stature, coloration and even personality. At the same time that these desirable characteristics were selected by careful breeding, other less desirable characteristics also developed. Some of these less desirable mutations were linked (literally, in the DNA and chromosomes) to more desirable breed characteristics – sort of 'hitching a ride' in the Westie genomic pattern. Because of these linked mutations, Westies are predisposed to the development of some diseases, just like Golden Retrievers are predisposed to develop malignant lymphoma and Bulldogs get more brain tumors. We know that while dogs may be predisposed genetically to developing some diseases, there are also many identified and unidentified environmental influences on disease development, expression and severity. This complex interplay between genome and environment is an area of intense scientific study.

A very good first step in making progress in understanding which diseases are common and for beginning the study of genomeenvironmental relationships are health surveys, conducted by the Westie Foundation of America and also the West Highland White Terrier Club of America. The results of recent studies serve as an excellent starting point for discussion of diseases that follow.

It is now our job to find the specific genes in the Westie genome that are related to common diseases. Once this is done, more effective treatments for these diseases can be found, and concerned breeders, owners, veterinarians and scientists can work together to eliminate these problem genes, while maintaining happy, healthy populations of Westies for centuries to come.

Common Diseases of Westies

In 2005, the Westie Foundation of America and the Health Committee of the West Highland White Terrier Club of America conducted a study to determine the owner-reported prevalence of 27 diseases in West Highland White Terriers using an anonymous survey distributed by mail to approximately 6,000 homes owners and breeders in 2005. Follow-up mailings to non-responders were not conducted, as no effort was made to track returns. This was the result of a decision to make the surveys completely anonymous in an effort to increase response rates and the validity of reported information.

The results of that study were made available in 2007 on the Foundation's website. In the report prepared by Dr. J. Kevin Grayson, author of the report, the following conclusions were made:

The prevalences of targeted diseases remain essentially unchanged between the 2000 and 2005 surveys. For some common diseases, such as: atopic dermatitis, deafness, luxated patella, and Legg-Perthes disease; the prevalences have actually increased. For others, such as: aggression, deafness, diabetes, and pulmonary fibrosis; modest decreases were realized.

Progress is being made at many veterinary schools on determining the mode of inheritance and new treatments for many of these conditions. Continued financial, data, and case material support for these programs will greatly benefit the breed in the future. Some of the interesting findings of the 2005 study are summarized below.

An ongoing health Survey (2012-present) can be found at www.offa.org. The WFA and West Highland White Terrier Club of America conducted the survey as a joint project. We encourage all Westie owners to participate in this survey answering for dogs both past and present. This information determines how the WFA designates how research dollars are spent.

Comparison of prevalence of targeted diseases in 2000 and 2005:

2000
Atopic Dermatitis
Aggression
Luxated Patella
Dry Eye
Legg-Perthes Disease
Craniomandibular Osteopathy
Pulmonary Fibrosis
White Shaker Syndrome, Addison's Disease, Diabetes

2005
Atopic Dermatitis
Luxated Patella
Aggression
Inflammatory Bowel Disease
Legg-Perthes Disease
Dry Eye
Addison's Disease
Lymphoma
White Shaker Syndrome

Targeted diseases ranked by prevalence among dogs by sex in 2005:

Females
Atopic Dermatitis
Luxated Patella
Aggression
Dry Eye
Inflammatory Bowel Disease
Legg-Perthes Disease
Addison's Disease
White Shaker Syndrome
Pulmonary Fibrosis

Males
Atopic Dermatitis
Luxated Patella
Aggression
Inflammatory Bowel Disease
Dry Eye

Targeted diseases ranked by prevalence among deceased dogs in 2005:

2005
Atopic Dermatitis
Pulmonary Fibrosis
Conjestive Heart Failure and Lymphoma (tied)
Diabetes
Dry Eye (Keratoconjunctivitis sicca)
Luxated Patella and Inflammatory Bowel Disease (tied)
Copper Toxicosis, Aggression and Bladder Cancer (tied)

Aggression in Dogs: What does it mean for Westie owners?

John Robertson, VMD, PhD

One of the most controversial issues for owners, breeders, veterinarians, and the public is canine aggression. This chapter is written not only from the viewpoint of a dog owner and veterinarian, but also with unfortunate personal insights; I was 11 years old when severely mauled by a German Shepherd. This chapter is not written by an animal behavior expert, but contains the current thinking of a number of behaviorists. One point needs to be emphasized – Westies, as a group and statistically, are not a breed of dog for which there are profound public concerns over aggressive behavior! In a word, Westies are solid and predictable canine citizens (***Figure 1***).

Problem Dogs

An old adage is that there are no bad dogs, only bad owners. However, each year, millions of dogs are surrendered at shelters and many/most of these dogs are euthanized. According to shelter managers, dogs are surrendered to them primarily for one of four reasons:

- Dogs are aged or ill, or both.
- Dogs are homeless or ownerless.
- There was a weak bond between the dog and owner (the dog did not fulfill the expectations of the owner).
- Dogs are not good pets because of behavioral problems (40% of dogs surrendered).

There have been major strides in reducing the number of unwanted animals surrendered to shelters. Public education and outreach campaigns by animal welfare organizations, veterinarians, and governments have raised public awareness about pet animal overpopulation and the need for neutering pet animals. However, even as these campaigns succeed, many dogs are still taken to shelters. In a survey conducted at 12 animals shelters, adolescent and young adult dogs comprised a significant proportion (29-31%) of the dogs surrendered (Arkow, 1991). While many dogs surrendered at shelters are of mixed parentage, roughly 30% are purebred animals. Many professionals and concerned groups note that even if pet overbreeding and overpopulation were virtually eliminated, many dogs would still end up in shelters and would be destroyed.

Shelters receive "ownerless" dogs from animal control officers and from the public. Homeless dogs may be strays (have escaped from owners), abandoned, or may be truly feral (breeding and roaming without human intervention or ownership). Dogs that roam individually or in groups are problematic, as they may suffer from starvation, disease and trauma. Ownerless dogs may harbor infectious diseases that can spread to other ownerless dogs or to pet dogs. Ownerless dogs may catch and eat wildlife, livestock and pet animals while searching for food or raid waste bins. In many cases, ownerless (feral) dogs may avoid human contact – like other "wild" animals such as coyotes. At times, ownerless dogs may threaten or attack humans or pet animals. The public health problem associated with biting dogs is discussed more fully below.

In a study of socialized pet dogs presented at 12 humane shelters, Salman et al, (2000) noted several common behavioral problems that were the cause of surrender. Most common was inappropriate elimination (dogs resist learning or observing housebreaking and soil the home). Dogs that could not be housebroken were 7 times more likely to be taken to shelters than other dogs. Some dogs displaying inappropriate elimination may, in fact, be marking territory within homes. This normal behavior, while completely appropriate out-of-doors, is definitely not desirable indoors.

Aggression was the second most common behavioral problem that resulted in dogs being surrendered for adoption or euthanasia at shelters (Salman, et. al., 2000). Ten percent of all dogs relinquished had displayed aggression toward people and of the dogs surrendered, 69% had bitten at least one person. Eight percent of all dogs relinquished had displayed aggression toward other animals. Several studies have shown that approximately 40% of dogs presented for evaluation and treatment of 'behavioral problems' at veterinary practices are displaying aggression, with a majority of dogs showing aggression toward people (***Figure 2***).

Dogs that bite people are a significant public health problem. According to information provided on the Centers for Disease Control's website, approximately 4.5 million dog bites occur each year in the US. Of these, they estimate that 1 out of 5 bites become infected. Dog bites are both a financial and legal burden for owners of dogs that inflict the bites.

In 2001, an estimated 368,245 people sought acute treatment for dog bites at hospital emergency rooms. The rate and severity of injury were highest among children aged 5-9 years old, and 42% of dog bites occurred in children less than 14 years old. The incidence rate was significantly higher in boys than in girls, probably a reflection of outdoor and unsupervised contact. The injury rate declined with increasing age; adults are much less likely to be bitten than children. For persons over 15 years old, there was

Figure 1 - Westies typically are loving dogs, with very predictable behavior patterns.

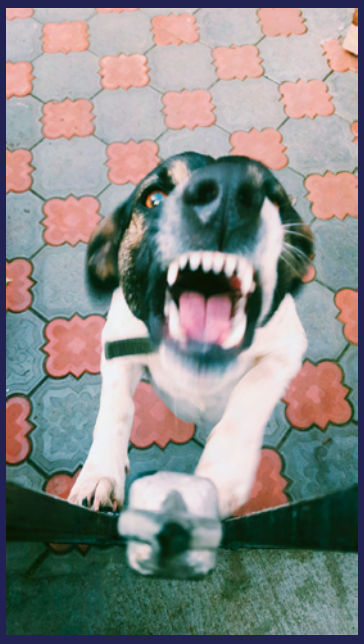

Figure 2 - Aggressive dogs should be approached carefully to minimize biting incidents.

no difference in incidence between males and females. Biting incidents increased slightly in the warmer months (April to September, peaking in July). Between 4-7% of dog bite-related injuries were work-related (delivery and service people, staff and professionals involved in animal care; CDC, 2003).

The most common sites of injury included bites to arms and hands (45% of all injuries), legs and feet (26%) and head and neck (23%). While the majority (65%) of the injuries to children less than 4 years old were head and neck injuries, the incidence of extremity injuries increased with age. The types of injuries inflicted included punctures, lacerations, contusions and hematomas, infections, and crush/amputation injuries, and fracture/dislocations (CDC, 2003). About 98% of all people seeking care at emergency rooms for dog bites are treated and released.

Between 1979 and 1996, more than 300 people were killed as a result of unprovoked dog attacks, according to data collected by the Humane Society of the United States (Sacks, et. al., 2000). In a study of 227 human fatalities for which breed information and attack data were available (1979-1998), Sacks and co-workers demonstrated that 25 breeds of dogs (including crossbreds but with a predominating phenotype) were involved. Pit Bull Terrier/Pit Bull Type dogs, Rottweilers and German Shepherd Dogs accounted for 147/227 fatalities. In the 20-year study period, there was one fatality due to a West Highland White Terrier. Single fatalities were also recorded for Yorkshire Terriers and Dachshunds. A majority of deaths (58%) involved an attack by an unrestrained dog on the owner's property. Most fatalities (160/227) were caused by an attack from a single dog. A trend was noted in the number of attacks and breed popularity. When Rottweilers and Pit Bull Terrier type dogs increased in breed registrations, the number of attacks attributed to these dogs went up.

Nature Versus Nurture: Is there a genetic connection to behavior?

I think there is a popular perception that dog behavior can be predicted fairly well by the breed of the dog. Jack Russell Terriers are feisty, Golden Retrievers are great with children, and Rottweilers are stalkers. And as everyone knows, Westies are Lovers! Let's take a look at evidence and opinions about breeds and behavior.

The influence of genetics and breeding on canine aggression and other behaviors has been studied for thousands of years. It is very clear that domestication of dogs was a process of selecting not only desirable body shape and size, but also selecting useful behaviors including guarding, hunting and herding. Roughly 100 years ago, scientists began to collect observations and perform studies to determine potential genetic links to behavioral characteristics. As early as 1921, MacDowell noted differences among litters of Dachshund

puppies in their reactivity to visual and auditory cues. Whitney (1926) noted that some behaviors were characteristic of certain breeds and that these behaviors were inherited independently from phenotype (physical appearance). Some of the traits studied included shyness, intelligence, levels of energy and aggression (defined as a tendency to bite). Whitney concluded that while some behavioral traits seemed to show classic patterns of inheritance (caused by expression of dominant and recessive genes), many traits were complex and probably inherited as expressions of multiple genes.

Mahut (1958) studied the differences in emotional responses in 10 breeds of dogs. In a standardized test setting, young dogs were evaluated for curiosity, response to 'teasing' (approaching and pawing/mouthing objects), approach-avoidance (excitement at seeing objects and stalking them), wariness (tensing and trembling, growling), and frank avoidance. She classified dogs studied as belonging to one of two groups. Fearful dogs (Collies, German Shepherds, Poodles, Corgis, and Dachshunds) had high scores for wariness and avoidance. The other group was classified as 'fearless" based on low scores for wariness and avoidance. Fearless dogs included 'fighters, ratters, and killers' such as Boxers, Boston Terriers, Bedlington Terriers, and Scottish Terriers. Mahut found that the environments dogs were raised in significantly affected the display of behavioral traits.

Animal behaviorists consider the work of Scott and Fuller (1965) to be a cornerstone of our understanding of the genetic basis of dog behavior. Work they conducted in a very controlled environment, over decades, showed that within each breed of purebred dog studied, there is a wide variation in emotional responses to various stimuli. They suggested caution in 'accepting the idea of a breed stereotype' of emotional behavior.

Many other studies (too numerous to list here) on heritable behavioral characteristics in purebred dogs have yielded contradictory and sometimes confusing results. Studies of lineages and pedigrees of several breeds of dogs have appeared to clearly demonstrate a heritable link of aggression. This was shown in studies of Golden Retrievers (Van den Berg, 2006), Cocker Spaniels (Podberscek, et. al., 1996) and English Springer Spaniels (Reiner, et. al., 2005). While some authors believe that there is a heritable tendency toward excitability, fear, or nervousness in some dog breeds, other authors feel that factors such as length of time puppies stay with dams, sex of dogs, and early experiences are just as important as parentage.

The influence of early socialization cannot be ignored. A significant number of dog breeders feel that the more time a puppy can spend in the controlled environment of the breeder, the more predictable the puppy's behavior will be. There is ongoing (and probably unresolvable) debate about the optimum age for puppy adoption. Many breeders believe that adoption between 6-8 weeks of age does not allow for adequate dog:dog and dog:human socialization. It would seem clear that delaying adoption of puppies might allow breeders to more easily identify puppies with potential behavior problems and to decide how best to manage these dogs. On the other side of the debate, many veterinarians and some behaviorists believe that an optimum time for bonding of puppies with their new owners and environment is between 6-8 weeks. This debate is not going to be settled unless there are objective research studies that demonstrate how best to socialize puppies. Additional thoughts on this are to be found below where prevention of aggression is discussed and also in Dr. Meyers-Wallen's topic on breeding practices.

Pfleiderer-Hogner (1979) analyzed the heritability of performance from records of 2046 evaluations conducted on a total of 1291 German Shepherd Schutzhunden (i.e., 'protection dogs'). Dogs were evaluated with the standard measures of Schutzen performance, including tracking, obedience, man-work and character. A correlation was found between man-work (such as guarding and commanded confrontation) and character, but not other traits. She concluded that there is little heritable basis for performance and that early evaluation of dogs for performance could not predict behavior. The very comprehensive review authored by MacKenzie et al, (1986) exhaustively covers these controversies (***Figure 3)***.

Hart et al, (1985a, 1985b) discussed behavioral profiles of 56 dog breeds and factors that might influence selection of purebred dogs as pets. A panel of 96 'authorities' (48 small animal veterinarians and 48 obedience trial judges) expressed opinions that were used to score breeds of dogs on 13 traits, including such things as excitability, snapping at children, watchdog barking, and affection demand, among others. A very complex scoring system was developed and tested statistically for validity.

Authorities were asked to determine a predisposition to excitability based on the following statements "A dog may normally be quite calm but can become very excitable when set off by such things as a doorbell ringing or an owner's movement toward the door. This characteristic may be very annoying to some people. Rank these breeds from least to most excitable." Data collected on Westies is interesting, for a number of reasons. First, Westies ranked highly as a breed in terms of excitability. In contrast, Bloodhounds, Bassett Hounds and Rottweilers ranked lowest in terms of excitability.

Figure 3 - Specific behaviors are desirable in some breeds of dogs, particularly those trained to be used as 'protection dogs'.

Figure 4 - It is very common for puppies to play out aggressive behaviors as they socialize.

Second, a separate behavioral category, watchdog barking, was analyzed. To assess this behavior, the following statements and scenario were given as a definition "Now we would like to find out your opinion regarding watchdog capabilities of these breeds. A woman living alone in a city wants a dog that will sleep by her bed and frighten intruders by barking if anyone breaks into the house in the middle of the night. Rank these breeds from least to most as to which will most consistently sound an alarm when it hears something unusual and will bark at intruders". Westies were ranked in the most effective watchdog category (with Rottweilers, German Shepherd Dogs, Doberman Pinschers, and Scotties).

Taken together, one might well argue that high scores in terms of both excitability (alertness) and watchdog barking, are a desirable combination in some circumstances (family protection) but a detriment in others (continual barking at sounds in an apartment environment). In terms of housebreaking (a measure of trainability), Westies scored in the middle of the rankings.

Hart and co-workers (1985b) used their data to create 'behavioral profiles' of breeds, based on scoring in all 13 categories. Using statistical tools including cluster and principal component analysis, they created a scheme that classified different dog breeds. Needless to say, their work suggested very strongly that although there were variances in individuals within breeds, there were inherited behavioral predispositions in breeds. They specifically concentrated on 'reactivity', 'aggression', and 'trainability' to cluster breeds. Reactivity was defined by the aggregate scoring of dogs in the following categories: affection demand, excitability, excessive barking, snapping at children, and general level of activity. Aggression was defined by the aggregate scoring of dogs in the following categories: territorial defense, watchdog barking, aggression to dogs, and dominance over owner. Finally, trainability was defined by the aggregate scoring of dogs in the following categories: obedience training and housebreaking ease.

Based on the analysis of all data, Westies were placed in a cluster of "very high aggression, high reactivity, and medium trainability". Other dog breeds in this cluster were Cairn Terriers, Scottish Terriers, Airedales, Miniature Schnauzers, Dachshunds and Fox Terriers. By contrast, German Shepherd Dogs, Akitas, Doberman Pinschers, and Rottweilers formed a cluster characterized by "very high aggression, very high trainability, and very low reactivity". We have to remember that this is an artificial system of data classification, based on interviews with 'authorities' and their subjective experiences and opinions with these breeds.

Hart and co-workers (1985b) also analyzed the effects of gender on behavioral characteristics. Not unexpectedly, they found several measures of aggression (snapping at children, territorial defense, aggression toward other dogs and dominance over owners) higher in intact male dogs than in intact female dogs. They felt that their data demonstrated that neutering of male dogs altered hormonally-driven

behaviors (mounting, urine marking, and aggression) in about half of dogs in which these undesirable behaviors created problems for owners. Neutering did not appreciably alter other behaviors such as playfulness, destructiveness, snapping at children, and territorial defense.

Scientists are just beginning to understand the relationship of brain anatomy and chemistry to behavior and aggression in dogs. Jacobs and his colleagues (2006) found actual differences in the centers in the brain that regulate emotion and reaction when they compared tissue samples from aggressive and non-aggressive dogs. Reisner and co-workers (1996) also found differences in neurotransmitter metabolites in aggressive and non-aggressive dogs, perhaps indicating a higher potential level of reaction to stimuli in aggressive dogs. This area of neurobiology is rapidly evolving. We can expect that more study of the triggers of dog behavior will lead to a better understanding of genetic factors controlling brain development and metabolism. This may lead to the development of drug and behavioral therapies for problem dogs.

What is canine aggression?

Aggression is broadly defined as a behavior that is manifested as growling, snarling, baring of teeth and biting (Scarlett et al, 2002). There are times when aggression in dogs is appropriate and times when it is not. Haug (2008) stated that there were three underlying reasons for canine aggression: fear; resource-guarding (territory, owner and other animal protection); and predation. There are not clear boundaries between these reasons and some dogs may display aggression for several reasons. Haug further noted that aggression may be normal and functional, or it may be normal but inappropriate or considered unacceptable, or it may be a frank behavioral abnormality, with dogs acting completely inappropriately in many situations.

It is possible to distinguish several forms of appropriate and predictable aggression. For example, puppies play out aggression as they become socialized in litters (***Figure 4***). Much of this controlled and playful aggression serves multiple purposes. Most breeders will readily acknowledge that dogs quickly establish a hierarchy within litters for attention, access to food, water, toys, and the most desirable places to sleep. In the past, this was broadly classified in terms of seeking and learning dominance.

Playful aggression is a component of socialization during the critical period of 4-14 weeks of age, when dogs learn about their relationships with other dogs (adults and littermates) and people (Scott, 1950). It is during this critical period of development that puppies also learn (in general terms) what they need to fear and what they do not need to fear. Many animal behavior specialists and veterinarians believe that the basis for much of the inappropriate aggression shown by dogs is fear-based, not dominance-based (Tynes, 2008). It is critically important to assure adequate socialization of dogs between 4-14 weeks of age and to help them overcome fear and anxiety. A study by Roll and Unshelm (1997) showed that about half (44%) of dogs that were aggressive to other dogs had not had a significant amount of contact with other dogs between 5 weeks and 5 months of age. Dogs that fail to understand their hierarchical position with owners, familiar and unfamiliar people, and other animals during the critical period of socialization may develop unacceptable behaviors later in life. Unfortunately, no one really knows how much early socialization is optimal for an individual dog.

There are appropriate and acceptable forms of aggression shown by adult dogs. A major value of dogs after domestication must have been protection of people and livestock from marauding animals and from unfamiliar people (resource-guarding). Barking to warn humans of impending threats and also displaying more direct forms of aggression (biting) were highly desirable (and rewarded) behaviors. Highly controlled aggression displayed by well-trained dogs in response to commands during field trials is highly desirable (***Figure 5***). In fact, aggression displayed in these circumstances is normal and is expected, based on training. It is critically important to understand that such aggression terminates on command and is therefore not problematic. Haug (2008) specifically notes, "All forms of aggression are modified by learning". In fact, if working dogs do not display aggressive performance, according to training and on command, they are considered to be behaving abnormally.

Animal trainers and behaviorists disagree about the source of aggression in working dogs. Some believe that some dog breeds possess inherited behavioral tendencies to aggression that can be exploited and controlled by training. This would appear to be in agreement with studies by Scott and Fuller (1965) and multivariate cluster analysis developed by Hart and co-workers (1985). However, Pfleiderer-Hogner (1979) was not able to show this with Schutzenhunden. Some trainers of protection dogs feel that aggressive tendencies are more individualized.

There is virtually no disagreement that dogs of any breed, subjected to unexpected stimuli that cause fear can create stress for the dog. Likewise, dogs that are abused learn to be fearful and learn aggression.

Inappropriate and Unpredictable Aggression: Familiar and Unfamiliar People, Dogs, and Situations

Haug (2008) wrote a comprehensive review of canine aggression directed to unfamiliar people and dogs. Fear of unfamiliar stimuli (people, dogs, situations) was considered the most common cause of aggression (also see Luescher and Reisner, 2008). The proximity of the stressful stimulus may be a factor. Some dogs will be observant and mindful when unfamiliar or unexpected stimuli are far from them, their owners, and their territory, but may become increasingly fearful as the stimulus moves closer. Haug notes that some dogs may display aggressive reactions (posturing, snapping, barking) while leashed or restrained, but not otherwise. Fear-related aggression may be well-developed by about 6 months of age, and this helps to differentiate it from territorial guarding and aggression that may not occur until at least 6 months of age or at a time of social maturity.

Luescher and Reisner (2008) reviewed the complexities of canine aggression to familiar people and situations – something of the greatest concern to owners and breeders. They note that the domestication of dogs and wolves from a common ancestor (roughly 12,000 years ago) was based on selection of many different traits. In terms of behavior, they believe dogs were selected to retain characteristics as adults that generally are seen in immature wolves. These 'immature characteristics' include playful behavior, the need for extensive physical contact, and highly social interactions (barking, pawing, licking and nuzzling). Adult wolves form structured hierarchical packs in which body language and conflict avoidance is important (feral dogs do not form such packs).

Luescher and Reisner define many different types of aggression, including:

- Fear-induced aggression
- Resource guarding aggression
- Conflict-related aggression ("dominance")
- Territorial aggression to unfamiliar people and animals
- Predatory aggression
- Play-related aggression
- Excitement-induced aggression
- Pain-induced aggression
- Maternal aggression
- Disease-associated aggression (with brain tumor growth, for example)

Many people (including veterinarians, owners, and breeders of dogs) believe that dogs that bite owners or family members do so to assert dominance, potentially challenging the owner for leadership. However, Luescher and Reisner question this. Citing data from a number of studies, they found that in many cases of aggression in young adult (2-3 year old) dogs, aggressive behaviors emerged in puppies and became amplified as the dogs aged. In many cases, early aggressive behavior was correlated to fearfulness and resource guarding, not to the evolution of social bonds and relationships that appear to form after 6 months of age.

Guy (1999) extensively studied aggressive behavior toward familiar people and other dogs (termed 'household aggression'). This study found that approximately 40% of dogs presented to veterinary practitioners for evaluation of inappropriate behavior had growled at family members, 20% had growled and snapped when owners tried to

Figure 5 - Highly controlled aggression can be displayed by well-trained dogs in response to commands during field trials.

remove food or toys from the dog (characteristic of resource guarding aggression), 15% of dogs had bitten owners, and 12% had bitten with sufficient force to leave a bite mark or penetrating wound.

For most dogs, conflict management and avoidance is important. Body cues that signal stress and conflict may include repetitive yawning (not related to sleepiness), gazing and gaze avoidance, and changes in body posture. Erect, heightened and rigid postures may be signs of stress, fear and potential conflict. Play bows, rolling, licking, whining, and submissive urination all may be strategies for avoiding conflict.

Luescher and Reisner (2008) advise owners, breeders and others in contact with known or potentially aggressive, stressed and fearful dogs, to watch for changes in body language that may indicate thoughts of conflict are escalating or that conflict is imminent. Dogs that display overt signs of offensive aggression (erect body posture, erect tail and ears, lip curling with display of canine and incisors) are sending clear signals that they may act out and bite in a short period of time. Many veterinarians and behaviorists note that confident, offensively aggressive dogs will stare at a potential target before initiating an attack. Dogs that display defensive aggression appear to have different body language; this is usually seen in fearful dogs, placed in unpredictable situations (veterinary clinics, unfortunately). Defensively aggressive dogs may withdraw, lower their hindquarters and overall body position, and may lip curl, displaying many teeth. It is important to lower levels of stress and fear in these dogs, to prevent escalation of aggressive behavior.

Prevention and Treatment of Aggressive Canine Behavior

Veterinarians and other professionals who deal with inappropriate aggressive canine behavior feel it is challenging to treat and that the prognosis for controlling or eliminating aggression is guarded.

Prevention of the development of aggressive behavior is critical for puppies and should be of great concern to breeders. Luescher and Reisner (2008) offer some guidelines and suggestions for development of well-adjusted puppies (growing, hopefully, into well-adjusted dogs). These guidelines include:

- Provide a safe, comfortable, and predictable environment, free of intense stimuli (noise would be one example) that might induce fear and stress
- Handle frequently
- Wean at an appropriate time; early weaning may induce stress and fear
- Be aware of health issues; some work has shown that early, severe illness can lead to fearfulness in adults
- Encourage controlled socialization and exposure to diverse, safe environments that will help puppies understand and overcome fear
- Be consistent in interactions and training
- Punishment-based training may induce fear and later aggression: physical punishment may have poor outcomes; when puppies are punished, and suffer physical discomfort, they may become more fearful and frustrated - an overview of effective training strategies can be found at http://veterinarymedicine.dvm360.com/client-handout-why-punishment-fails-what-works-better (cited in Tynes, 2008)
- Regular meal feeding, regular interactions with humans, and regular exercise set the stage for good human-dog interactions

You and your veterinarian must be a team when trying to help treat a dog with aggressive behavior. Some general guidelines for evaluation and treatment of canine aggression are outlined by Luescher and Reisner (2008) and Tynes (2008).

First, it is important to determine the basis for aggression in an individual dog, and not to assume it's "just something in this breed". In some cases, physical ailments (thyroid disease, inflammation and tumors in the brain, liver failure, infectious agents (rabies for instance) may be a cause of aggressive behavior. A study of 238 dogs examined for potential links between "itchiness" (pruritus) and either anxiety or aggression found no relationship (Klinck et al 2008). These authors did find that dogs treated with glucocorticoids ("cortisone") were more likely to be anxious and reactive when confronted by loud noises (thunderstorms or other noise). It is essential to diagnose these problems with a thorough case history, physical examination, and laboratory tests (hematology, serum chemistry and urinalysis).

Second, if aggression appears to be a primarily behavioral problem, veterinarians specifically trained in dealing with behavior should be consulted. Several professional organizations, including the American College of Veterinary Behaviorists (www.dacvb.org) and American Veterinary Society of Animal Behavior (www.avsabonline.org) can provide recommendations for certified veterinary behaviorists to help deal with problem dogs. Not all veterinarians in clinical practice are interested in or trained to treat behavior problems. It is very important for owners and breeders of problem dogs to find a qualified person to help.

> “There are times when aggression in dogs is appropriate and times when it is not.”

Third, owners and breeders should realize that problem behaviors like aggression develop and persist for many reasons (genetics, brain chemistry, fear, environment, etc.) and that controlling the expression of behavior is not a simple matter of giving a pill or subjecting the dog to ‘training’. Everyone should be wary of any person who represents themselves as a dog trainer who can ‘break’ an aggressive dog and whether they can actually achieve a positive outcome. I personally would advise caution in simply seeking someone who ‘trains dogs’ in dealing with an aggressive dog. I think there is a world of difference between teaching a well-adjusted pet to play FrisbeeTM and taking offensively aggressive dogs and transforming them into well-adjusted and predictable pets.
Fourth, veterinary behaviorists usually approach the treatment of aggressive dogs in a three-part approach (Luescher and Reisner, 2008).

1. Take a general history and assess normal environment and management of the problem dog. Perform physical examination and laboratory studies to detect underlying physical problems that may cause fearfulness and aggression.
2. Take a history that assesses how the dog interacts in the environment, with familiar and unfamiliar people and situations, and its attitude toward major daily events.
3. Study the actual aggression problem: when does it occur, how often, what triggers it, what does it look like and what has been attempted to treat it.

Once the nature of aggression is assessed, several approaches can be taken that seem to help. First, the dog has to have as much predictability in the environment as possible. For example, dogs should be fed regular meals twice daily rather than having unlimited access to food at all times. The setting of a regular mealtime creates predictability and structure for the dog.

Second, a commitment must be made on the part of the owner to regularly (at least twice daily) exercise the dog in a safe manner. It seems pretty obvious that owners should not take dogs that are aggressive to unfamiliar people and other dogs to places where they will encounter unfamiliar people and dogs! Many behavior specialists recommend walking the dogs with a head halter leash, which encourages owner control and dog attentiveness.

Third, dogs that are aggressive should be kept in environments that do not encourage fearful or territorial aggression. Some behavior specialists have noted that crating dogs may both prevent aggressive episodes and allow security for the dog. Crating should be used ONLY for limited periods of time each day and should not be used as a form of isolation and punishment.

Fourth, there is broad, uniform agreement that physical punishment is not effective in modifying the aggressive behavior of dogs. It should be avoided.

Veterinary behavior specialists (Yin, 2007) acknowledge that traditional training methods based on the concept of dominance and submission are outdated and may, in fact, make aggression worse, due to fear, frustration, and inconsistency. Instead, many advocate a system of rewarding desirable behaviors and not rewarding less desirable conduct. A bond between dog and owner is based on reward, trust, and a lack of fear of punishment (domination). As with all training methods and theories, it only works if the owner and dog work at it consistently, constantly, and to successful goals.

Displacement and desensitization training, done by capable professionals and committed owners, can help control aggressive behaviors of dogs. In this type of training, small changes are made in the environment or triggers that help dogs become less reactive. Luescher and Reisner (2008) discuss how dogs that act aggressively when food is offered or withdrawn can be subjected to gradual behavioral modification. One method is to simply place food in a room without the dog being present, allow the dog into the room to eat, and then remove the dog from the room after eating. This is thought to break down a connection of possession guarding (food) and the owner. Another method involves gradual feeding from a long-handled pot, so that the dog cannot attack the owner nor will it be able to guard its food. Once again, behavioral modification is a job for trained behaviorists.

Finally, let’s discuss drug therapy. It is well known that humans suffering from anxiety and depression can, in many cases, be treated effectively (clinical signs of illness decrease) with a combination of psychotherapy and drug therapy. In some cases, drugs alone can significantly help. We are just beginning to understand the complex neurochemistry associated with behavior in dogs. Several studies in this area were noted above. We are also just beginning to understand that some drugs, especially drugs known as selective serotonin reuptake inhibitors (SSRIs) may help modify the behavior of some dogs in some situations. For example, there

have been some preliminary studies done that support the use of the drug fluoxetine for treating anxiety disorders in some dogs. There is a presumption that this drug, given to some dogs, will modify the levels of critical neurotransmitter chemicals in the brain (serotonin), helping to calm dogs and decrease inappropriate behavior. There have been no carefully controlled clinical trials of this drug and it should not be viewed as a known effective treatment, especially for canine aggression.

There is a difference of opinion among animal behaviorists about the effectiveness of anti-anxiety drugs, like diazepam, in managing canine aggression. Some behaviorists, based on observations of individual dogs, have seen improvements in behavior. Other professionals caution that by changing an 'anxiety threshold' (essentially removing anxiety that is blocking behavior), such drugs might make aggression worse in some dogs (Crowell-Davis, et. al., 2006). In a recently published study (Herron, et. al., 2008), diazepam was judged only minimally to modestly effective in controlling some anxiety-associated behaviors and was often discontinued by owners who were unhappy with side effects (sedation, agitation/hyperactivity, increased appetite). Bottom line: there is a lot of work still to be done before effective drug therapy for canine aggression can be prescribed.

In summary...

Canine aggression is a significant problem, which is influenced by genetics, environment, upbringing and training. Dog breeders should be aware that there is a complex interaction between inherited breed traits, environment of adult and young dogs, active socialization, and learning that will create adult dog behavior. Responsible breeders should be alert to signs of fearfulness in puppies and to understand that the current thinking on canine aggression is that much of it is fear based. Several research studies have been able to link inappropriate adult behavior with specific breeding animals, but this is a largely unexplored field. Nonetheless, it is very important that breeders regularly follow-up with owners of dogs they have bred to see if there are physical and behavioral problems that emerge in some litters and from some pairings. Dog breeders, dog owners, and veterinarians should be knowledgeable about the importance of body language and conflict avoidance for dogs. Dogs displaying body language of offensive or defensive aggression should not be pushed to a point of acting out their aggression. By the same token, potentially aggressive dogs should not be physically punished, as this may actually heighten levels of fear and foster biting. Recent studies have noted that dogs may be acutely sensitive to human body language and even to human odors associated with emotional behavior. At times of potential conflict, humans should not escalate human behaviors that inappropriately aggressive dogs find threatening.

Problem dogs should be examined by veterinarians and by qualified animal behaviorists. Physical problems that may be associated with aggression should be actively investigated. With overtly healthy aggressive dogs, the dog, the owner, and the behaviorist all have to commit the effort needed to help the dog. It is absolutely mandatory that once an owner identifies an aggressive or potentially aggressive dog, they must control this dog so that it does not injure people or other animals.

There are no magic pills or quick training methods for treating or overcoming canine aggression. The science of using drugs to modify dog behavior and perception is in its infancy and it may take many years of study before drugs to predictably modify behavior are available. Dog owners should understand that there may be significant limitations of behavioral training in eliminating aggressive behavior.

As concerned dog owners and breeders, it is our responsibility not to create fearful, aggressive dogs, and to reach out and educate the public about proper dog behavior and upbringing (Reisner, et. al., 2008). Let's try to be sure that, within our power, we raise great pets and not subject any more children to dog bite scars for life.

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Complementary and Alternative Medicine

Stephanie Shrader, DVM and John Robertson, VMD, PhD

Introduction

Complementary and alternative medicine has been practiced in various forms for thousands of years, originating in ancient Asian and Indian cultures. Through trans-oceanic exploration and colonization, non-traditional medical treatments eventually spread to Western civilizations. Many of these therapies were, and still are, practiced by folk healers. The use of complementary and alternative medicine therapies has become an emerging niche in the fields of human and veterinary medicine in the past 30 years. In 1982 Carvel G Tiekert, DVM, established the American Holistic Veterinary Medical Association. According to the association's charter, holistic veterinary medicine combines conventional and complementary (or alternative) modalities of treatment. Diagnoses and treatments are based on physical examination, behavioral history, medical and dietary history, and consideration of the animal's environment (including diet, emotional stresses, etc.).

Complementary and alternative medicine therapies are considered to be so important in human medicine that one branch of the National Institutes of Health – the National Center for Complementary and Alternative Medicine (NCCAM) – was founded specifically to study them. The National Cancer Institute maintains an Office of Cancer Complementary and Alternative Medicine.

The Basics of Complementary and Alternative Medicine

The NCCAM defines complementary and alternative medicine as a group of diverse medical and health care systems, practices, and products that are not presently considered to be part of conventional medicine (also known as allopathic medicine). Complementary medicine, by definition, is used in conjunction with conventional medicine, while alternative medicine is used instead of conventional medicine. Complementary and alternative medicine can be divided into four general categories: mind-body medicine, biologically based practices, manipulative and body-based practices, and energy medicine.

Mind-Body Medicine

The first category, mind-body medicine, includes prayer, mental healing, and therapies that utilize creative outlets such as art, music, or dance. Oriental practices, such as tai chi, qi gong, meditation, and relaxation techniques are included in this category as well. This category has little practical relevance to the veterinary profession, although there is some research that supports the use of music to ease canine anxiety. One such study was conducted in Belfast, Ireland by Dr. Deborah Wells (Wells, et. al., 2002), a psychologist and animal behaviorist. The study focused on the influence of five types of auditory stimulation: human conversation, classical music, heavy metal music, pop music, and a silent control (i.e., no music). Results revealed that classical music had a calming effect on dogs in animal shelters when compared to the other types of auditory stimuli.

One of us (JR) has successfully used classical music therapy, in his practice, for dogs with obvious anxiety disorders, including dogs that are severely reactive to loud, sudden sounds (Fourth of July fireworks, for example). It is known that dogs have a considerably larger frequency range and increased perception of sounds compared to humans. Exposing dogs to regular, rhythmic, and complex sounds (symphonies, for example) at the same time that they are being rewarded and comforted, allows dogs, over time, to associate the music with positive and relaxing experiences. Playing music at times when dogs are experiencing stress (Fourth of July fireworks!) will relax them and also dilute perception of any sudden or unexpected background sounds. This type of therapy is inexpensive and allows owners alternatives to the uses of sedative, tranquilizers, and antidepressants for calming anxious dogs.

A web search reveals a number of companies that make and market CDs specifically for dogs that experience anxiety problems. Here is one such company's website:
www.throughadogsear.com/shelter-program/

Biologically Based Practices

Herbal medicine (also known as phytomedicine) has been used for thousands of years in the prevention and treatment of human disease. In recent years, it has become accepted as standard allopathic therapy to make use of substances found in flowers, roots, berries, and herbs (***Figure 1***). Many potent and effective therapies, in common use, were derived from plants. For example, corticosteroids were derived from the molecule diosgenin, originally isolated from wild yams (Dioscorea villosa). The cancer chemotherapy agent, vincristine, is derived from compounds found in periwinkles. Aspirin, a non-steroidal drug, is a salicylate related to compounds found in willow tree bark and cambium. Quinine, a preventative for human malaria, was also derived from Cinchona tree bark (Chevallier, 1996). Antibiotics, such as penicillin and streptomycin, came from molds and fungi. The drug digitalis, from purple foxglove (Digitalis purpurea), is a mainstay of therapy in dogs and people for treatment of heart failure.

It should be pretty apparent that substances derived from plants can also be extremely toxic. A small dose of aspirin may lower the body temperature in a person with a fever or help prevent blood clots from forming by keeping blood platelets from becoming sticky. Two or three times that small dose may cause heartburn, stomach ulceration, and bleeding tendencies. We pointed out (above) that some very common and useful antibiotics are derived from growing molds. The growth of other molds, like the fungus Aspergillus flavus on peanuts and grains, can produce mycotoxins which are capable of causing cancer (aflatoxin B) or destroying brain tissue (Fusarium toxin – fumonisin). Methylxanthines found in chocolate (derived from the cocoa plant – Theobroma cacao) are very toxic, even in small amounts for dogs. Dog owners should understand that the metabolism of dogs and people are very different. Herbal remedies that may be relatively safe for people, may not be safe for dogs. The doses of drugs used to treat disease in humans and dogs have been established through scientific studies. The doses of herbs for treatment of disease in dogs have not been well-studied.

According to the World Health Organization (WHO), in some Asian and African countries, 80% of the population still depends on traditional medicine for primary health care. The WHO also notes that herbal medicine is the most popular worldwide form of complementary and alternative medicine. Herbalists seek to treat a variety of human conditions, including arthritis, depressed immunity, Alzheimer's, asthma, depression, fatigue, skin problems, and a host of others.

Three common herbal remedies used in both humans and animals are St. John's wort, ginseng, and echinacea. St. John's wort (Hypericum perforatum) is used in humans as an analgesic, anesthetic and an anti-inflammatory agent. In dogs, it has been used to treat obsessive problems such as lick granulomas, aggression, barking, jumping, scratching, chewing and separation anxiety. Its use is contraindicated with antidepressant drugs.

Ginseng root, from the plant Panax ginseng, is native to North America and China. In Chinese, the word ginseng means "the essence of man." This is because it has been used to treat a wide variety of ailments. In humans, Ginseng is administered to treat fatigue and headaches, stimulate the appetite, and to increase both vitality and immune function (Kim et al, 1990), especially in older individuals. It is marketed to treat many of the same conditions in both dogs and cats.

Ginseng, when chemically analyzed, is shown to contain over 35 distinct chemical compounds (ginsenosides, triterpenoid saponins, panaxans, sesquiterpenes) that may have medicinal actions for humans (Chevallier, 1996; Blaylock, 2003). Studies have shown that ginseng will inhibit human tumor cell growth in tissue culture (Shinkai, et. al., 1996). Whether these findings can be extrapolated to dogs would require further studies.

Echinacea is a wildflower (Echinacea angustifolia and E. purpurea) native to the central United States. Its main uses are to improve the function of the human immune

Figure 1 - Herbal medicine makes use of substances present in specific flowers, roots, berries, and herbs

Figure 2 - Chiropractic can be used in the diagnosis and treatment of specific conditions involving the back, neck, and extremities, as well as pain associated with muscle spasms and certain injuries.

system, especially against the common cold and influenza. It can also be used to help wounds heal faster and decrease inflammation. In dogs, echinacea has been used to bolster the immune system, aid in the treatment of viral infections, and prevent cancer.

And now, a final word of caution and warning about herbal remedies and phytotherapy for your Westie. While plants and herbs have been used for literally thousands of years as folk remedies in humans, much less is known about the effects of plant-based compounds as therapies for disease in dogs. Before beginning any herbal remedy with your pet, always consult your veterinarian first. When in doubt, leave them out - as therapy for sick dogs.

Manipulative and Body-Based Practices

The use of chiropractic/osteopathic manipulation and massage are well-known forms of manipulative and body-based complementary and alternative medicine therapies. Osteopathic manipulation is used by osteopathic physicians, combined with physical therapy, in order to shorten patient recovery time. Reflexology, Tui Na, rolfing, the Bowen technique, Trager bodywork, and many other techniques are also included in this category. Most of these therapies are impractical for veterinarians and their patients, but there is a growing chiropractic movement within the veterinary field.

Formal animal chiropractic education began in 1989 with the formation of the American Veterinary Chiropractic Association (AVCA). The first courses were taught by the founder, Sharon Willoughby, DVM, DC. She began the practice of teaching Doctors of Veterinary Medicine and Doctors of Chiropractic side by side. Doctors of Veterinary Medicine receive a foundation of chiropractic theory and technique, and Doctors of Chiropractic learn common animal diseases, zoonotic diseases, comparative anatomy, and animal handling techniques.

The AVCA has a multi-tiered mission: to provide a professional membership group, to promote animal chiropractic, and provide certification for doctors who have completed animal chiropractic training. The AVCA also seeks to provide the public with access to doctors trained in animal chiropractic.

Animal chiropractors treat many different animals and a wide array of problems. Cats, dogs and horses are the most common patients, but chiropractic medicine is also used to treat zoo animals, wildlife, and exotics. A chiropractic exam includes evaluation of the patient's history (including prior radiographic results), a full neurological exam, and finally the adjustment of vertebral joints, extremity joints, and cranial sutures (***Figure 2***). Animal chiropractic has been used in the treatment of neck, back and extremity pain, muscle spasms, injuries, internal medicine disorders, and temporomandibular joint syndrome.

To find out more information or to locate an AVCA certified veterinarian, review the following website:
www.AnimalChiropractic.org

Most Westie owners know that their dog enjoys being petted and held. Some dogs seem to particularly enjoy massage, if they are acclimated to it and rewarded for 'participation'.

Dogs that have suffered injuries may be painful and resentful of manipulation and massage, but may benefit from the gradual introduction of common-sense physical therapies, including gentle massage and range-of-motion exercise, warm and cool compresses and even hydrotherapy. Most veterinarians receive little, if any, training in physical therapy and rehabilitation of their patients. However, they may work with you and local physiotherapists to custom design programs for dogs with injuries that would be helped by therapy. This should be discussed with your veterinarian.

Energy Medicine

Energy medicine, perhaps the least studied and least understood of all the complementary and alternative medicine therapies, involves manipulation of the energy fields that purportedly surround living beings and the use of electromagnetic fields for therapeutic outcomes. Energy medicine includes Reiki, Therapeutic Touch therapy, light and sound therapy, qi gong, homeopathy, acupuncture, and a host of other treatments. Although we have known some pet owners to practice Reiki and Therapeutic Touch therapy, the most common energy medicine techniques practiced by holistic veterinarians (and endorsed by the American Holistic Veterinary Medical Association) is homeopathy and acupuncture.

Homeopathic remedies date back to the time of Hippocrates, and include the use of plants, minerals, drugs, viruses, bacteria and/or animal substances to treat illnesses. Homeopathy involves treating an ill patient using a substance that can produce, in a healthy individual, symptoms similar to those of the illness. This substance is created through serial dilution of the normally toxic agent. For example, snake venom, poison ivy and opium have been used to make homeopathic remedies, but in high enough concentrations can cause serious problems. Homeopathy has been used to treat a wide range of problems in both humans and animals, but has not been studied scientifically to prove effectiveness or safety.

Acupuncture, by definition, is the Chinese practice of piercing specific areas of the body along peripheral nerves with fine needles to relieve pain, induce surgical anesthesia, and for therapeutic purposes (Dorland's Pocket Medical Dictionary, 25th ed. W. B. Saunders Co., 1995). Acupuncture dates back thousands of years and is considered part of traditional Chinese medicine. According to traditional Chinese medical theory, the qi (life force) flows through various meridians (channels) throughout the body. When this flow is disrupted, it manifests as pain, and other ailments. In the United States there are currently more than 50 schools

Figure 3 - The primary goal of veterinary acupuncture is to strengthen the dog's immune system.

and colleges of human acupuncture and Oriental medicine. Many offer masters degree programs and are accredited by or have been granted candidacy status by the Accreditation Commission for Acupuncture and Oriental Medicine. Here is a website for finding out more about the acupuncture schools in the United States and the programs they offer: www.acupunctureschools.com

The National Cancer Institute website for complementary and alternative medicine (www.cancer.gov/about-cancer/treatment/cam) provides a wonderful overview of the use of acupuncture as a treatment for individuals (humans) with cancer or cancer-related side-effects. Research supports acupuncture as an effective complementary therapy to reduce nausea and vomiting after surgery and chemotherapy, as well as an effective pain inhibitor. There are many studies currently underway involving acupuncture and its ability to relieve lower back pain, breast cancer, limb pain, menopausal symptoms, nausea, dry eye, and the list goes on, and on. One of us (JR) has undergone acupunture treatment of painful lower back spasms (due to disc prolapse) and will personally attest to its effectiveness!

A full list of current clinical trials involving human acupuncture can be found at: www.clinicaltrials.gov/search/open/intervention=acupuncture

There are a growing number of veterinary acupuncturists (***Figure 3***). According to the AVHMA, the main goal of veterinary acupuncture is currently to strengthen the body's immune system. The etiology of acupuncture's therapeutic effects, however, is not well understood. As you might imagine, dogs that are going to be acupuncture subjects may not understand what you and the acupuncturist are trying to accomplish – or how you are doing it. It takes little imagination to realize that your Westie might not think it is such a good idea to get stuck with one or more long needles and then to hold still for the therapy to work (5-30 minutes). It is probably a very good idea, if you are considering acupuncture therapy for some painful condition, to discuss this with your veterinarian and the veterinary acupuncturist. It may be worthwhile to get the names of clients who have had dogs treated with acupuncture and to contact them to see how the therapy worked. Remember: dogs don't seem to experience a "placebo effect" – there is no amount of talk that will convince the dog it is going to feel better!

To contact and/or locate a holistic veterinarian who practices homeopathy or acupuncture, check out the websites listed at the end of this chapter.

A Personal View of Complementary and Alternative Medicine – John Robertson

Imagine for a minute that you are sick. Perhaps suffering from arthritis and the ravages of age on our bones and muscles. How do you view your disease and suffering? The result of normal wear and tear? Perhaps the result of injuries sustained many years ago? Bad diet? Not enough vitamins? Poor posture, a bad mattress or old shoes? It is very hard to say if any or all of these factors are the cause of your current disease, but you know you want some relief. What are some things that might be effective?

- Anti-inflammatory drugs (cortisone, non-steroidal drugs like aspirin) to decrease joint inflammation and potentially slow the progression of disease
- Anti-inflammatory drugs to decrease pain, allowing more normal mobility and better quality of life, with normal daily activities
- Application of topical heat to sore joints and muscles, with or without application of heating and cooling topical gels and ointments
- Vitamin and mineral supplements, including calcium and magnesium, to help rebuild and maintain bone
- Vitamin supplements, including chondroitin-glucosamine, for helping the healing process
- A balanced program of exercise, perhaps including exercise in water, and stretching to gain/regain mobility, decrease stiffness, and increase a feeling of well-being
- New mattress and new shoes
- Better diet, coupled with sensible weight loss (if overweight)
- Rest in a comfortable place when tired
- Avoid repetitive injury than makes the arthritis worse

If you did all the things (ten of them) on the list, do you think you would feel better, especially if you did them over and over? At least 80% of the items on the list (the bottom 8 items) are not a pill prescribed by your doctor. Each, however, would be complementary to the occasional use of drugs (steroids and non-steroidal anti-inflammatory drugs). Complementary therapy provides a system of holistic healing, optimizing diet, exercise, and judicious use of drugs that have been proven to be effective. This would work for you and for your dog. And (I hope) you would accept that neither strict medical therapy (the drugs alone) nor the combination of medical and complementary therapies are going to cure your arthritis.

Suppose, now, that your dog has developed a serious cancer, such as malignant lymphoma. Malignant lymphoma is one of the most treatable forms of cancer in dogs. With multiagent chemotherapy, many (over 50%) dogs, even those with moderately to markedly advanced cases, may live 1-2 years. The drugs, however, do not cure the cancer, and virtually all dogs diagnosed with malignant lymphoma will succumb to the disease or complications of the disease. We know this from studying the outcomes of treatment of thousands of dogs that have developed malignant lymphoma. In general, about 10% of dogs getting chemotherapy (the treatment of choice for malignant lymphoma) will develop treatable side effects during therapy, including vomiting and diarrhea. Dogs with moderately to markedly advanced malignant lymphoma that do not receive multi-agent chemotherapy rarely live more than a few months.

What do you do? Treat? Not treat? Hard choices. Life and death choices. Some owners, concerned with the potential suffering that their dog might have, decide on humane euthanasia, and this is both a personal and rationale choice. Some other owners might decide to go ahead with chemotherapy, realizing it is expensive (perhaps $3,000 to $6,000), and that they may prolong life, good quality life, for up to a year or two. And that your dog is going to very likely die as a result of the cancer. For most owners, making this decision is very difficult and there is almost always sadness

and frustration for your canine friend and companion having an incurable disease. But, there are two rational choices – euthanize or treat.

In trying circumstances, some owners may reject rational choices, feeling that traditional allopathic and complementary medicine has failed them and their pet. When they ask the veterinarian to cure the incurable and treat the untreatable, they indicate that current medical and surgical practice has failed them. They may wish to avoid well-documented and supportive therapies in favor of treatments whose value, effectiveness, and safety have not been established. While it is quite normal to feel frustrated that our pets get ill and eventually die, it is not rational to reject proven therapies for unproven alternative therapies. I've lost eight dogs and as many cats to disease. As much as I hoped I could fix them, in the end I could not. There were no magic medicines, no secret herbs, and no intervention that would keep them with me. I've reflected on my limitations and failings quite a bit. In the end, I always come back to the same answer. As pet owners, as veterinarians, as scientists, we owe our pets the best possible life we can provide for them and we need to constantly work harder to make the years they have with us quality time, free of disease. We need to understand disease and develop better treatments, not harbor resentment over the limitations we now experience. In the end, it's all about understanding more and doing more, not rejecting treatments that aren't perfect or foolproof.

In summary...

There are many forms of complementary and alterative medicine that have a place with common and traditional medical and surgical therapies in treating disease in dogs. There is a lot of information available (see below) describing some tested and helpful therapies. Westie owners should be cautious about subjecting their dogs to unproven therapies and should reject stuff that promises unrealistic results (like curing or preventing cancer). Do not use toxic and potentially deadly plant/herb products.

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Related Websites

National Center for Complementary and Alternative Medicine: http://www.nccam.nih.gov/

Alt Vet Med, Complementary and Alternative Veterinary Medicine: http://www.altvetmed.org/

Academy of Veterinary Homeopathy: http://www.theAVH.org

American Academy of Veterinary Acupuncture: http://www.AAVA.org

Veterinary Botanical Medicine Association: http://www.VBMA.org

British Association of Veterinary Homeopathic Surgeons: http://www.bahvs.com/

World Health Organization: http://www.who.int/en/

Links to Practitioners of Complementary and Alternative Medicine

http://ahvma.org/

http://www.ivas.org/

http://www.holisticvetconsult.com/

http://www.holisticvetpetcare.com/

http://www.petsynergy.com/

http://www.AnimalChiropractic.org

The Basics of Dermatitis and Atopic Dermatitis in Westies

Updated by Valerie A. Fadok, DVM, PhD

The Basics of Allergic Dermatitis in Westies

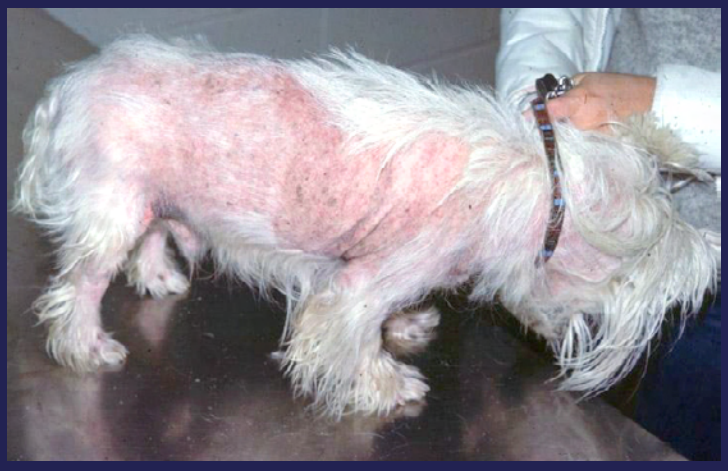
Dermatitis, or inflammation of the skin, is one of the most common medical problems affecting dogs. It has many causes, can take many forms, and can be difficult to diagnose and treat. Many Westie owners become frustrated searching for the underlying cause of the problem and for an effective means to control and cure it. To provide the basis for a discussion of atopic (allergic) dermatitis in Westies, this overview describes the basics of dermatitis, causes of dermatitis, and how veterinarians diagnose and treat dermatitis ***(Figure 1)***. Skin is a complex organ, consisting of several types of cells with a variety of functions. Many of these cells are involved in the body's natural, protective inflammatory response to stimuli in the environment. In fact, without this inflammatory response, people and dogs would not survive cuts, bruises and other daily traumas, as well as exposure to infectious organisms like bacteria and fungi. Common signs of acute inflammation include redness, swelling, heat and pain at the site of injury. While many things in the environment can initiate the inflammatory response in the skin, hereafter referred to as dermatitis, this overview will focus on dermatitis associated with reactions to food, inhaled substances, parasites, hormones and bacteria.

Types of Allergic Dermatitis in Dogs

Urticaria: Urticaria, also known as hives, is a type of dermatitis that occurs more often in humans than in dogs. Dogs with urticaria have dry, elevated patches of skin (called wheals) that are itchy and that may or may not be reddened. When wheals are group together they form larger flattopped patches called plaques. In a related condition, "angioedema", these patches become moist and swollen. People with severe allergies to substances like bee venom develop urticaria and angioedema when stung. It is a Type I hypersensitivity reaction that occurs when allergies bind to IgE (allergic antibody) on mast cells. This binding results in the release of histamines which cause vasodilation. This accounts for the redness and accumulation of fluid in the skin lesions.

Urticaria and angioedema occur in response to environmental irritants, such as food, medication, insects, and plants, time in the sun or extreme high or low temperatures. Treatment of urticaria and angioedema ideally involves avoiding the offending environmental stimulus and medicating the affected animal with epinephrine (anaphylaxis) and glucocorticoids and anti¬histamines. It is important to keep in mind that short coated dogs, such as English or French bulldogs, can suddenly develop bacterial infections in the skin. These infections can resemble urticaria, but require bathing and antibiotics for treatment. Occasionally, Westies can develop inflammatory skin infections than resemble urticaria. Consequently, it is important that owners consult with their veterinarians to ensure that lesions are true hives and not bacterial infections.

Parasitic hypersensitivity: Dogs with this condition develop dermatitis in response to the bites of parasites, such as fleas, ticks and other insects. The most common parasitic allergy is referred to as "flea allergy". Dogs that are sensitive to flea saliva become itchy and have large elevated domeshaped or flattopped lesions on their backs by their tails, the inner rear



Figures 1 and 2 - Canine atopic dermatitis in Westies (Photographs courtesy of Dr. William Miller, Cornell University)

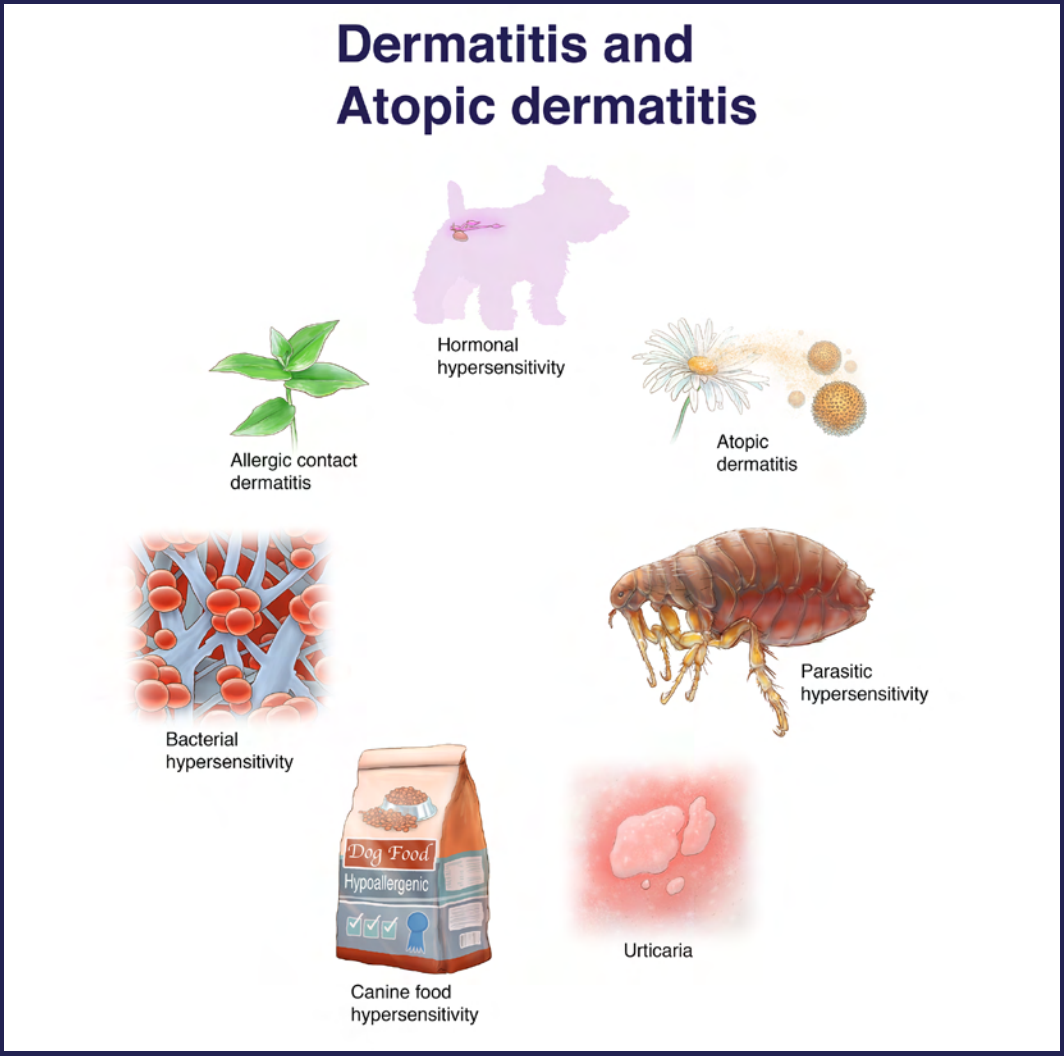


Figure 3 - An illustration depicting the most common causes of dermatitis and atopic dermatitis

thighs and abdomen. Tick bites can produce dead skin around the bite and ulceration and possibly itching as well. Dogs also can become allergic to the bites of mosquitoes and Culicoides spp ("no-see-ums"). Dermatitis can also occur in response to intestinal parasites, although this is rare. There does not appear to be any breed predilection for parasitic hypersensitivity.

While the underlying mechanisms responsible for parasitic hypersensitivity dermatitis remain to be identified, the condition is presumed to occur in a manner similar to other allergies, with the body producing allergenspecific IgE and mounting an inflammatory response; there are delayed immunologic reactions as well. Treatment of affected dogs requires parasite control. For dogs with flea allergy, year round flea control is essential. For acute flare-ups, glucocorticoids or oclacitinib can be given to relieve the itch.

Allergic contact dermatitis: This condition, which also is called contact allergy or hypersensitivity, differs from atopic dermatitis because the allergen is part of something, such as a plant, medication or fabric that has touched the dog's skin. Fortunately, allergic contact dermatitis is rare in dogs. However, when it occurs, the skin becomes reddened and develops either small flat lesions that are colored differently from the dog's normal skin, similar larger lesions or, rarely, large fluidfilled lesions. Over time, this type of contact dermatitis results in hair loss, greater skin discoloration and raw or thickened skin. The areas typically affected are the bottoms of paws, the abdomen and the outsides of the ears. In years past, the chemicals and plastics in flea collars were common causes of this type of dermatitis, with lesions appearing around the neck. Fortunately, the newer types of flea collars are far less likely to initiate contact dermatitis. Dogs that develop contact dermatitis may or may not be itchy, depending on the dog and the allergen.

Allergic contact dermatitis is an example of a Type IV hypersensitivity, which means it is a cell-mediated reaction

Common Clinical Findings
Itching
Scratching
Hair Loss
Thickened and Pigmentation of Skin

to an allergen or a delayed type hypersensitivity. Reactions occur usually 48-72 hrs after exposure to the contact allergen, making the offending allergen difficult to identify. The contact allergen interacts with specialized cells in the skin called Langerhan's cells, which then interact with T-lymphocytes. These T-lymphocytes then initiate the immune and inflammatory reaction. Although the precise mechanisms underlying allergic contact dermatitis remain to be determined, this condition is best treated by avoiding the allergen, if it can be identified, and medicating the dog with glucocorticoids, oclacitinib, or pentoxyfylline, drugs that reduce the inflammation.

Bacterial hypersensitivity : This type of dermatitis is a condition in which affected dogs are highly sensitive to a group of bacteria known as Staphylococcus. These dogs have itchy skin, with discrete pusfilled lesions. Based on these lesions, this condition also may be referred to as "pyoderma," which means "pusfilled skin". They also have crusts, and epidermal collarettes (circular lesions with a rim of scale). Although mechanisms responsible for bacterial hypersensitivity have yet to be identified, some dogs with recurrent pyodermas make IgE and IgG antibodies to Staphylococcus organisms. Treatment of bacterial hypersensitivity relies on bathing with chlorhexidine shampoos, and the use of antibiotics when necessary. Because of the emergence of methicillin resistance in canine Staphylococcus pseudintermedius, repetitive antibiotic use is to be avoided. For some dogs, treatment with staphylococcal bacterins can be helpful.

Yeast (Malassezia) hypersensitivity: Some dogs will become allergic to the yeast on their skin. Malassezia hypersensitivity results in intense itchiness in dogs and the infections often recur. Most dogs with recurrent yeast infections in the ears and skin make IgE (allergic) antibodies to the organism. These dogs require frequent bathing and treatment with oral antifungal agents. Some dogs will benefit from an allergy vaccine containing Malassezia extract.

Hormonal hypersensitivity: This rare condition is associated with apparent responses to the animal's sex hormones. Affected animals include intact females and males. With the increased use of topical hormone replacement therapy in humans, this condition can occur in neutered animals as well. Therefore, people using this form of therapy should apply the creams or ointments with gloves and to parts of the body their dog cannot contact. Affected dogs are itchy and have small elevated lesions on their rump, inner back of the thighs and in the genital and anal areas. Enlargement of the vulva and nipples is common. While it currently is not known how the skin becomes inflamed, the condition is successfully treated with neutering.

Canine food hypersensitivity: Food allergy in dogs is also known as adverse food reactions, primarily because some reactions to food are not actually allergic. In fact, pure food allergies, where the dogs' clinical signs are controlled completely with changes in the diet, are relatively rare. It is more common for a dog with atopic dermatitis to have reactions that are triggered by food as well as pollen or other substances. The immunologic basis of food allergy is complex, as some dogs appear to have a Type I hypersensitivity, making IgE antibodies to food triggers, while other dogs do not. Some of the same immunologic abnormalities seen with atopic dermatitis are associated with food hypersensitivity in dogs.

Dogs are most commonly allergic to animal proteins in their diets; grain allergies are less common. Affected dogs typically have itchy, flaky skin, though some may develop thickening of the skin, changes in coloring, scales, crusts or redness. The ears, rump, lower legs and groin are the most commonly affected areas.

There is no diagnostic test for food allergy. There are serum tests that can be done, but they are not accurate enough to predict which foods will be safe to feed. The only reliable way to make a diagnosis is to eliminate specific components of a dog's and then challenge with that component. 'Limited ingredient diets' available over-the-counter are not sufficient as a diagnostic test because they are contaminated with chicken, beef, soy, and other ingredients not listed on the label. These diets are not prepared to the same level of stringency as a veterinary prescription diet. Diet choice should be based on what the dog has eaten before. If a veterinary prescription diet is not appropriate, then a home-cooked diet balanced by a veterinary nutritionist can be fed. Presently, 96% dogs can be diagnosed with an 8-week food trial; during this trial, no treats, table scraps, rawhides, or flavored medications should be fed without consulting with the veterinarian first. At the end of the 8-week period, if improvement is seen, then diet challenges should be done to identify the triggers. At that point, the dog can be transitioned to an over-the counter diet for long term maintenance. The itchiness associated with food allergies can be controlled during the trial with oclacintinib or glucocorticoids (steroids).

Atopic dermatitis: This is a genetically predisposed hypersensitivity to environmental allergens to which normal dogs do not respond. These allergens include pollens, molds, dusts, danders, insects and mites (house dust and storage mites). Some dogs become allergic to Staphylococcus and Malassezia, and some dogs become allergic to proteins in their food. Genomic diagnostic tools are being used to identify the genes associated with the development of atopic dermatitis in dogs.

Two types of genes are involved: 1) those associated with the immune system and 2) those involved with the skin barrier. Dogs with atopic dermatitis have a dysregulated immune system, causing immune cells to produce the cytokines (protein messages that cells use to communicate with each other) that underlie the dog's clinical signs. These clinical signs include itchiness and inflammation. As a result, IgE antibodies are developed that are directed against specific allergens. Some of these cytokines, such as IL-31, bind directly to nerves to cause itch.

The other genes of importance cause the top surface of the skin, also known as the skin barrier, to be defective. This skin barrier consists of corneocytes (cells) embedded in layers of lipid (fats, particularly ceramides, cholesterol, fatty acids). When functioning normally, this barrier keeps the skin moisturized and prevents the penetration of allergens and microbes. Dogs with atopic dermatitis have a disrupted barrier, causing water to leak from the skin and allergens and microbes to be absorbed. The allergens and microbes activate the defective immune system, resulting in the itch and inflammation. Since allergens are absorbed directly through the skin, lesions are most evident on parts of the body that are sparsely haired. Interestingly, there are breed differences in some of the genes affected, with many breeds having a defect in a skin gene called filaggrin; Westies, however, do not!

There is no diagnostic test for atopic dermatitis. It is diagnosed based on history and clinical signs, and by ruling out other causes of itch (parasites, infections). Allergy testing is only done if immunotherapy (i.e., allergy vaccine) will be used. It has been demonstrated that response to an allergy vaccine can be just as good with a serum test as with an intradermal test. The key to success with an allergy vaccine is to be patient and give it at least a year to work. In the meantime, other approaches are taken to keep the dog comfortable.

Treatment of Atopic Dermatitis

Treatment of atopic dermatitis requires addressing the disease from multiple perspectives; this is called a multimodal approach. Although this disease is lifelong and not curable, it is manageable using a combination of the following five treatments.

First, we avoid what we can avoid. Practically speaking, this means controlling exposure to ectoparasites and known food triggers, Consequently, all dogs with atopic dermatitis should be on good flea control throughout the year, because exposure to fleas makes their disease flare. It is not uncommon for atopic dogs to get other ectoparasites, including scabies mites, so vigilance for ectoparasites is very important. Clearly, there's no way to avoid access to pollens and other allergens.

Second, we recommend allergy testing and immunotherapy (i.e., allergy vaccine), particularly for dogs with clinical signs that occur regardless of the season. Immunotherapy is the only treatment available that changes the abnormal immune response in this lifelong disease. Fortunately, this can be achieved using sublingual immunotherapy (allergy drops) which can be just as effective as injections. However, it is unrealistic to expect that an allergy vaccine will control all clinical signs in all dogs. Use of an allergy vaccine should be considered successful if it reduces the dog's need for daily medication. In many cases, the allergy vaccine will help the medications work better. If an allergy vaccine can be used in young dogs when the immune system is most malleable, it may be needed for only 3-5 years. It is important to recognize, however, that some dogs may require their allergy vaccine for life.

Third, infections can be controlled with bathing and the use of antibiotics and antifungal agents when needed. Bathing

is the primary approach to infection control because of the emergence of methicillin resistance (antibiotic resistance) in canine Staphylococcus pseudintermedius. Bathing allergic dogs every week helps remove allergens from the skin. A veterinary formulated shampoo containing 2-4% chlorhexidine is best, and shampoos containing lipids (phytosphingosine, ceramides, fatty acids) can prevent the drying effects of baths and help repair the skin barrier. If needed, antibiotics can be given. For dogs with yeast infections, oral antifungal agents can also be used.

Fourth, the abnormal skin barrier can be repaired by optimal nutrition and by the application of lipids directly to the skin. A high quality diet with the right balance of omega-6/omega-3 fatty acids is recommended. Over time, these fatty acids can help the skin repair itself. Topical application of lipids (phytosphingosine, ceramides, and/or fatty acids) also is recommended; these can be in the form of shampoos, sprays, foams, and spot-ons. Many dogs may require twice weekly baths initially, but the frequency can be reduced to a manageable level (e.g., twice monthly).

> “It is important to control inflammation and itchiness to give other treatments time to work.”

Fifth, it is important to control inflammation and itchiness to give other treatments time to work. Medications traditionally used for this include glucocorticoids (steroids), cyclosporine, oclacitinib, and a monoclonal antibody directed against the molecule (IL-31) underlying the itch. When used alone, antihistamines are rarely effective. However, they can help some dogs when used in combination with other medications.

Glucocorticoids (steroids) have been used traditionally because they work quickly to reduce itch and inflammation. Nearly every cell in the body has receptors that bind glucocorticoids, hence the wide array of potential side effects. Glucocorticoids

Multimodal Approach to Treatment

Avoid What We Can Avoid

Allergy Testing and Immunotherapy

Optimal Nutrition

Bathing and Antibiotics

Control Inflammation and Itchiness

affect metabolism, immune function, skin barrier, muscle and ligaments, the Gastro-Intestinal (GI) system, and behavior. They are not ideal for long term use. Even in the short term, increased thirst, increased urination with accidents in the house, and behavioral changes (lethargy, aggression) can be seen. Dogs needing glucocorticoids to live should be administered them every other day. Glucocorticoids given orally or by injection could have a negative impact on pregnancy, so they are not used in pregnant or lactating dogs. Glucocorticoids will interfere with intradermal testing and some serum testing for allergies, so treatment needs to be stopped several weeks before these tests are performed. Glucocorticoids inhibit almost all inflammation, so the presence of infections can be masked.

Cyclosporine (Atopica®, Elanco), a drug that decreases the production of cytokines and that is used in human transplant patients, has been used over the last decade in atopic dogs. It is given orally daily for 4-6 weeks, then slowly reduced to the frequency that controls the disease. Some affected dogs may need to take it daily for best effects. The most common side effects are vomiting and diarrhea (30-40% dogs), but severe infections have occurred in rare instances. The efficacy of cyclosporine is dependent on a microemulsion process that makes it more absorbable. Other formulations of the drug may be less effective for dogs, particularly those that are compounded. While this drug should not be given with a full meal, a small amount of food will not inhibit its efficacy. Cyclosporine has not been studied in breeding, pregnant, or lactating dogs. Cyclosporine does not interfere with intradermal or serum testing for allergies. It is not likely to work well in dogs that have fleas or infections.

Oclacitinib (Apoquel®, Zoetis) is a medication that works by inhibiting an enzyme (Janus kinase 1) that blocks the intracellular signal that occurs after the cytokine binds to its receptor. In essence, it is a small molecule that enters the dog's cells where it blocks the messages that initiate inflammation and itchiness. It is approved for use in dogs one year of age or older, and can be given twice daily for up to 14 days, then once daily. Vomiting and diarrhea are the most common side effects, but these occur in less than 5% of dogs. Very rarely, serious infections have been associated with this medication. Its use has not been studied in breeding, pregnant, or lactating dogs. This medication can work in any type of allergic itch and inflammation. Oclacitinib does not does not interfere with intradermal or serum testing for allergies. Like cyclosporine, it is not likely to work well in dogs that have fleas or infections.

Caninized monoclonal antibody directed against canine IL-31 (Cytopoint®, Zoetis), the molecule that initiates itchiness in atopic dermatitis, is a biologic agent rather than a drug. It is approved for use in dogs that have a diagnosis of atopic dermatitis to help reduce itch and inflammation. Because it is a monoclonal antibody and not a drug, it can be used to treat dogs of any age, and dogs being treated with other drugs. It can also be used in dogs with serious infections (e.g. pneumonia, septicemia), cancer, or other medical conditions for which glucocorticoids, cyclosporine, or oclacitinib would not be used. It is given by injection every 4-8 weeks by a veterinarian. This monoclonal antibody does not interfere with intradermal or serum testing for allergies. Monoclonal antibodies, while used routinely in human medicine, are new to veterinary medicine. For more information, visit www.cytopoint4dogs.com

Current Research on Atopic/Allergic Dermatitis

Due to the clinical impact of atopic/allergic dermatitis in dogs, it is important that both basic and clinical research be performed on these diseases. In this section, three recent articles that provide clinically relevant information about these conditions will be reviewed.

Gonzales AJ, Fleck TJ, Humphrey WR, Galvan BA, Aleo MM, Mahabir SP, Tena JK, Greenwood KG, McCall RB. IL-31-induced pruritus in dogs: a novel experimental model to evaluate anti-pruritic effects of canine therapeutics. Vet Dermatol. 2016 Feb;27(1):34-e10.

Dogs with atopic/allergic dermatitis develop itchy skin that then requires treatment, typically with medications that alter the inflammatory/immune responses to allergens. The purpose of this study was to determine if an experimental model of allergic skin conditions could be developed by administering a specific inflammatory mediator called interleukin-31, that often is present in dogs with naturally-occurring skin diseases. After successfully inducing the itching behaviors that occur in dogs with these diseases using this approach, the investigators then were able to compare changes in the dogs' behaviors after administration of different anti-inflammatory compounds (prednisolone, dexamethasone and oclacitinib). As a result of this study, it now is possible to test the efficacy of new compounds in a reproducible way.

Hensel P, Santoro D, Favrot C, Hill P, Griffin C. Canine atopic dermatitis: detailed guidelines for diagnosis and allergen identification. BMC Vet Res. 2015 Aug; 11:196.

This paper is open access and can be freely downloaded. The International Committee for Allergic Diseases in Animals has reviewed the veterinary literature and developed guidelines for the diagnosis of canine atopic dermatitis. The diagnostic approach is to rule out other skin conditions with clinical signs that resemble or overlap with atopic dermatitis, to carefully interpret the history and clinical signs of each dog affected with atopic dermatitis, and to utilize allergy testing with the primary purpose of pursing allergen-specific immunotherapy.

Olivry T, DeBoer D, Favrot C, Jackson HA, Mueller RS, Nuttal T, Prelaud P. Treatment of canine atopic dermatitis: 2015 updated guidelines from the International Committee on Allergic Diseases of Animals (ICADA). BMC Vet Res. 2015 Aug; 11:210.

This paper is open access. It reviews the literature published since the publication of the 2010 guidelines. It summarizes those guidelines and updates them where necessary. Emphasis is on individualizing the program for each dog and using multimodal therapy.

Michels GM, Ramsey DS, Walsh KF, Martinon OM, Mahabir SP, Hoevers JD, Walters RR, Dunham SA. A blinded, randomized, placebo-controlled, dose determination trial of lokivetmab (ZTS-00103289), a caninized, anti-canine IL-31 monoclonal antibody in client owned dogs with atopic dermatitis. Vet Dermatol. 2016 Dec;27(6):478-e129.

This paper describes the first use of a caninzed monoclonal antibody in the treatment of atopic dermatitis. The monoclonal antibody is directed against canine IL-31, a major cytokine that mediates the itch and inflammation seen with AD. When given subcutaneously, dogs experienced significant relief compared to those dogs treated with placebo, and this relief persisted for at least one month.

Acknowledgements

Mr. Matthew Crotts and Ms. Stephanie Pfeiffer, medical illustrators in Educational Resources in the College of Veterinary Medicine at the University of Georgia, created the illustrations used in this chapter.

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Idiopathic Pulmonary Fibrosis – "Westie Lung Disease"

In order to appreciate the effects of pulmonary fibrosis, it first is important to understand the basic anatomy and physiology of the pulmonary system. The pulmonary system is comprised of the airways and the lungs. The airways include the trachea, the bronchi and their divisions into the very small bronchioles. The lungs are comprised of the alveoli (air sacs) and their surrounding capillaries, where exchange of oxygen and carbon dioxide take place, and the tissues and spaces that surround the alveoli. Collectively, these latter components of the lung, which are called the interstitium, are made up of elastin, collagen, smooth muscle cells, mast cells and a few other types of less common cells. The purpose of the interstitium is to provide both structure and strength to the lungs.

Breathing problems can arise from a number of factors including developmental problems, injury, obstruction of airways, circulation problems, viral, bacterial and fungal infections, and interstitial disease. Acute interstitial pneumonia is a disease affecting the interstitium in which the cells and fibers comprising the interstitium are damaged and eventually are replaced with scar tissue. The body's response to injury that results in scarring is called fibrosis. Consequently, the disease is called pulmonary fibrosis. Because the underlying cause for the injury remains unknown, the disease also is referred to as idiopathic ("unknown cause") pulmonary fibrosis, This disease, which also is known as "Westie Lung Disease", prevents the lungs from functioning normally, resulting in difficulty breathing and, eventually, death. In a recent study of affected Westies with this disease, the median survival time from onset of clinical signs was 32 months. This condition primarily affects middle-aged to older Westies, and individual survival time varies considerably. A similar chronic and ultimately fatal disease also affects humans.

While it was once thought that idiopathic pulmonary fibrosis was the result of an inflammatory reaction to an individual injury, it is now understood that fibrosis most likely occurs as the result of repeated injuries caused by some unknown agent or agents. It may be that these agents are a combination of allergens in the air, pollution, and infectious organisms. The body's natural response to injury is to replace damaged cells and fibers with fibrous connective (scar) tissue. While the scar tissue fills in the space where damage occurred, it leaves the area less flexible and less functional than normal. Excessive and repeated scarring, as occurs in pulmonary fibrosis, leaves the lungs unable to expand fully or to contract properly. As a result, they lose their ability to bring oxygen into the body or to expel waste gases. There appears to be a genetic component to pulmonary fibrosis and Westies appear, in particular, to be at risk.

The Westie Foundation of America (WFA) sponsored a 1-day meeting in October 2007 at Purdue University. As a result, a paper "An Official American Thoracic Society Workshop Report: Comparative Pathobiology of Fibrosing Lung Disorders in Humans and Domestic Animals" was published and is available online (http://www.atsjournals.org/doi/full/10.1513/AnnalsATS.201309-321ST). The purpose as cited in this publication was "to improve awareness and communication regarding spontaneous progressive fibrotic lung disorders in mammals and to stimulate interaction between human and veterinary medical professionals".

Common Clinical Findings
Difficulty Breathing (Dyspnea)
Coughing
Exercise Intolerance
Abnormal Lungs on Radiographs

As a next step, the WFA fundraised approximately $125,000 to host a second meeting "Fibrosis Across Species Workshop" on April 27-29, 2014 convening almost 70 human and veterinarian pulmonologists, pathologists, geneticists, radiologists, immunologists to discuss the "One Health" concept comparing disease in the Westie breed and humans. Several research studies resulted from this meeting to determine if pulmonary fibrosis in the Westie is comparable to the disease in humans. Continued research using the Westie as a naturally occurring model of pulmonary fibrosis will further treatment options in humans as well as our beloved Westies. A paper of this meeting is forthcoming and planned for both veterinary and human scientific journals.

Clinical Symptoms and Diagnosis

The major symptom of dogs with pulmonary fibrosis is difficulty in breathing – a clinical symptom known as "dyspnea". Some canine patients will also cough frequently and may have a fever. These dogs tire quickly and lose their ability to do strenuous activities, such as running around or going up and down stairs. Veterinarians will note that lung sounds heard through a stethoscope are abnormal, and the heart will enlarge as the disease progresses. The part of the heart that pumps blood into the lungs, the right ventricle, enlarges the most. This occurs as that part of the heart works harder to pump blood into the increasingly resistant lungs. Because of dysfunction of their heart and blood vessels, affected dogs may also have blood become congested in the veins around their organs.

Hypersensitivity pneumonitis, a chronic condition in which a dog has an allergic reaction to inhaled organic dusts, results in symptoms that are very similar symptoms to those associated with pulmonary fibrosis and can lead to debilitating scarring of the lungs. If hypersensitivity pneumonitis is the cause of the problem, it can be prevented by eliminating exposure to the allergen. In some cases, skin testing may be used to identify the allergen responsible (see previous section on *Atopic Skin Disease*).

The diagnosis of idiopathic pulmonary fibrosis will be made based on the clinical signs, history, results of lung function tests and findings on radiographs (x-rays). Radiographs of the thorax typically reveal abnormalities in the lungs (e.g., loss of clear air space) and evidence of right ventricular enlargement.

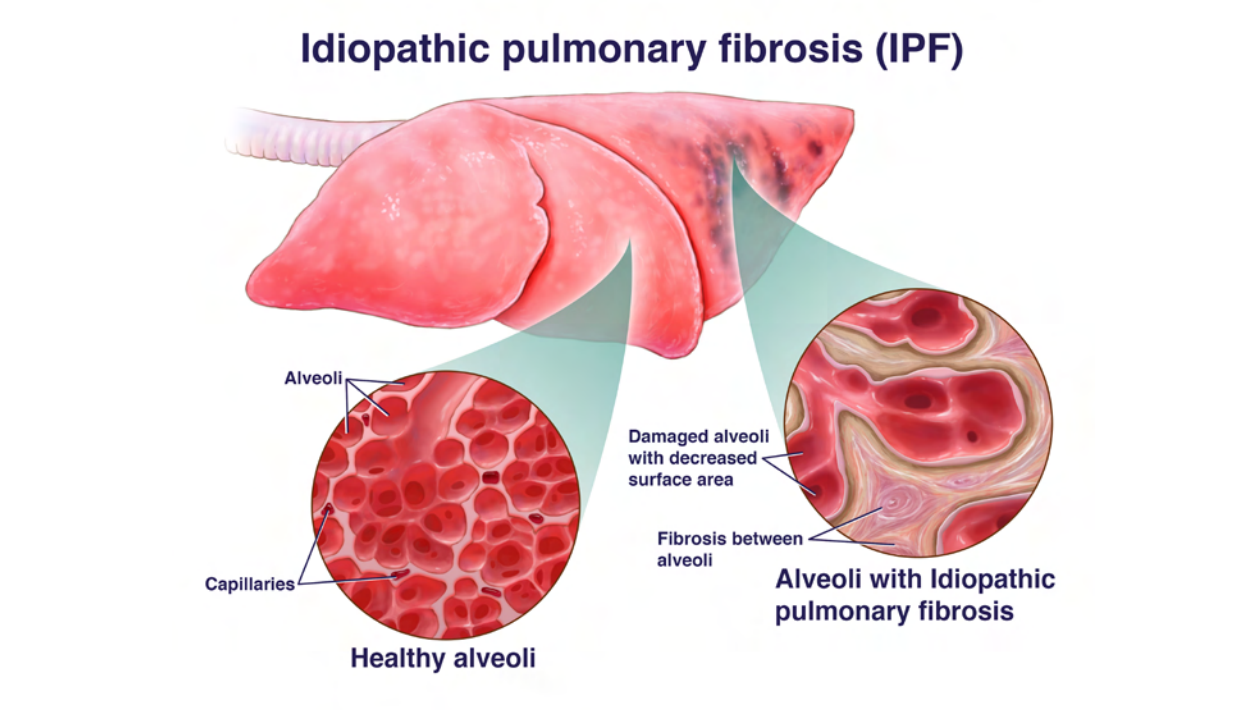

Figure 1 - In this illustration, differences between normal healthy alveoli within the lung are contrasted against those affected by idiopathic pulmonary fibrosis. The scar tissue between the alveoli and reduces alveolar surface area compromise the ability of the lungs to oxygenate the blood.

The veterinarian also may decide to measure the levels of oxygen and carbon dioxide in the patient's arterial blood.

In some cases, veterinarians may consider doing a lung biopsy, to collect tissue for microscopic examination and interpretation by a veterinary pathologist. In fact, biopsy of lung tissue is the gold standard used to make the diagnosis of idiopathic pulmonary fibrosis in humans.

While this procedure is invasive (it requires sedation /anesthesia and surgical preparation, at a minimum), it is the only way to examine the lung itself for abnormal changes indicating disease. Veterinarians may also use a technique called bronchiolar lavage to collect cells from inside the bronchioles and alveoli. This diagnostic procedure involves sedating the dog, instilling dilute physiologic sterile saline solution into the patient's lungs, and then suctioning it out with a syringe. When the fluid sample is then retrieved, it contains cells and debris from the lungs and airways. Experienced veterinary clinical pathologists can then examine the cellular makeup of this fluid to learn more about the types of disease that may be present. In many dogs with idiopathic pulmonary fibrosis, this fluid contains an increased total number of white blood cells, principally macrophages, neutrophils and mas cells. Typically bacteria are not isolated from the fluid.

Prevention and Treatment

Idiopathic pulmonary fibrosis is a serious and progressive disease that primarily affects older Westies. Because of the strong breed predisposition for this disease, prevention of this devastating disease starts with careful decisions regarding breeding. Current research studies are being performed to identify which of a particular dog's offspring are at risk for developing the condition. While in most affected dogs pulmonary fibrosis remains idiopathic, smoking is a common cause of the disease in humans. The hot gases from cigarette smoke damage lung tissues and this leads to scarring, lung remodeling and emphysema. Living with a human who smokes will dramatically increase any dog's risk of developing pulmonary fibrosis and other lung diseases.

> "The body's natural response to injury is to replace damaged cells and fibers with fibrous connective (scar) tissue."

There is no cure for pulmonary fibrosis, and treatment is difficult. Currently, affected dogs can be helped by the use of corticosteroids, which reduce inflammation, suppress the immune system and help interrupt the cycle that leads to fibrosis. Non-steroidal anti-inflammatory drugs, such as aspirin or ibuprofen, have not been shown to be particularly effective in reducing the signs of disease or arresting the progressive scarring associated with the disease. Without a good understanding of the cause of this disease, therapies are not specific to the disease and do not completely alleviate symptoms. Bronchodilators, such as theophylline, and cough suppressants may help make some patients more comfortable, but there is evidence that different dogs respond differently to therapy. In recent years, pirfenidone, a drug that has antifibrotic, antioxidant and anti-inflammatory effects, has been used in human patients with the disease. The results of a small number of clinical trials with this drug suggest that it slows, but does not prevent, disease progression in these patients. Dogs diagnosed in earlier stages of the disease can often be managed more successfully than those that have progressed significantly by the time the diagnosis is made. Dogs with longstanding disease may be at risk for developing heart problems and these, too, will need to be identified and managed.

Current Research About Canine Idiopathic Pulmonary Fibrosis

Because idiopathic pulmonary fibrosis occurs primarily in Westies, a genetic basis for the disease is strongly suspected. As a result, several research studies have been performed in an effort to determine whether or not this is true, and, if so, which genes might be associated with development of the disease. In this section, we summarize the results of five recent studies, one of which describes a test for evaluating exercise tolerance in affected dogs.

Roels E, Dourcy M, Holopainen S, et al. No evidence of herpesvirus infection in West Highland White Terriers with canine idiopathic pulmonary fibrosis. Vet Pathol 2016, April 22 Epub ahead of print.

This study was performed to determine if there is an association between idiopathic pulmonary fibrosis in Westies and the presence of herpesvirus infection. The rationale for this study was that Epstein Barr virus infection has been associated with a similar disease in people and equine herpesevirus has been consistently isolated from lung tissue of horses with pulmonary fibrosis. To see if a similar association exists in Westies with idiopathic pulmonary fibrosis, blood and lung samples from Westies with the disease and age-matched controls without the disease were studied to determine if they contained different amounts of a specific gene associated with herpesvirus. The herpesvirus gene could not be amplified by PCR from any of the blood or lung samples from either population of dogs. Therefore, it is highly unlikely that an association exists between the disease and herpesvirus infection.

L. Lilja-Maula, P. Syrja, H.P. Laurila, E. Sutinen, M. Palviainen, O. Ritvos, K. Koli, M.M. Rajamaki and M. Myllarniemi. Upregulation of alveolar levels of activin B, but not activin A, in lungs of West Highland White Terriers with idiopathic pulmonary fibrosis and diffuse alveolar damage. J Comp Path 2015; 152: 192-200.

Activins are cellular products that play important roles in inflammation and fibrosis, and have been implicated in the development of idiopathic pulmonary fibrosis in people. Westies with canine idiopathic pulmonary fibrosis often have acute exacerbations of the disease that are characterized by diffuse damage to the alveoli. This study was performed to compare the concentrations of two activins, A and B, in lung tissue of Westies with idiopathic pulmonary fibrosis, Westies with other severe pulmonary diseases, and healthy Westies. Activin B, but not activin A, was strongly increased in the pulmonary alveoli of Westies with idiopathic pulmonary fibrosis and in dogs with other severe pulmonary diseases. Activin B was detected in the fluid from Westies with the disease, particularly during acute exacerbations. It was not detected in fluid from healthy Westies. These findings suggest that activin B may be important in the development of idiopathic pulmonary fibrosis and could be used as an indicator of alveolar damage. Additional studies will be needed to further characterize the role of activin B in this disease.

L. Lilja-Maula, H.P. Laurila, P. Syrja, A.K. Lappalainen, E. Krafft, C. Clercx, and M.M. Rajamaki. Long-term outcome and use of 6-minute walk test in West Highland White Terriers with idiopathic pulmonary fibrosis. J Vet Intern Med 2014; 28:379–385.

In this 5-year study, survival time, prognostic factors, and use of a standardized 6-minute walk test were compared for two groups of West Highland White Terriers, 15 with idiopathic pulmonary fibrosis and 11 without the disease. Although dogs with the disease had a significantly increased risk of death than the control dogs, the survival time for affected dogs was 32 months from the onset of clinical signs. Because the effects of a very similar diseases in humans is monitored using a standardized 6-minute walk test that determines how far a patient can walk in 6 minutes, the investigators used this test to compare the exercise tolerance of Westies with idiopathic pulmonary fibrosis to Westies without the disease. The investigators also examined a large number of laboratory assay results and severity of changes on thoracic radiographs to see if any of these could be used as factors to evaluate prognosis. However, there were no significant prognostic factors identified in this study. The investigators determined that Westies with idiopathic pulmonary fibrosis walked a significantly shorter distance (~435 yards) than control dogs (~540 yards) in 6 minutes, making this a good, non-invasive test to evaluate lung function and exercise tolerance in affected dogs.

Krafft E, Laurila HP, Peters IR, Bureau F, Peeters D, Day MJ, Rajamäki MM, Clercx C. Analysis of gene expression in canine idiopathic pulmonary fibrosis. Vet J. 2013 Nov;198(2):479-86.

This study was performed to characterize the expression of different genes in pulmonary tissues from dogs with idiopathic pulmonary fibrosis and dogs without the disease, with the aim of learning more about the development of the disease and to identify possible biomarkers. More than 700 genes were identified as having greater than two-fold difference in expression between affected and non-affected dogs. The biological functions associated with these genes were related to cellular growth and proliferation, developmental processes, cellular movement, cell-to-cell interactions, and antigen presentation. Genes whose expression levels were of particular interest encoded specific mediators of inflammation and fibrosis (various chemokines and fibroblast activation protein). Serum concentrations of one of the chemokines (CCL2) were significantly higher in Westies with idiopathic pulmonary fibrosis than in unaffected Westies, suggesting that this chemokine might serve as a candidate biomarker for the disease.

Norris AJ, Naydan DK, Wilson DW. Interstitial lung disease in West Highland White Terriers. Vet Pathol. 2005 Jan;42(1):35-41.

This study compared the microscopic findings in lung tissue from six Westies diagnosed with idiopathic pulmonary fibrosis to those typically seen in humans with the similar disease. The primary feature of the canine form of the disease was the deposition of extracellular matrix (connective tissue) around the capillaries that surround the alveoli in the lungs. This excessive amount of connective tissue impairs the normal diffusion of oxygen between the air in the alveoli and the blood in the alveolar capillaries, making it more difficult to properly oxygenate blood in the lungs. The authors reported seeing evidence of mild inflammation, which suggests that the fibrosis does not occur as the result of an overly aggressive inflammatory response to infection. Given these findings, it was suggested that additional research must be performed about the mechanisms that regulate collagen formation and degradation, as alterations in these processes may be important in the development of the disease.

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Mr. Matthew Crotts, a medical illustrator in Educational Resources in the College of Veterinary Medicine at the University of Georgia, created the illustration used in this chapter.

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Krafft E, Laurila HP, Peters IR, Bureau F, Peeters D, Day MJ, Rajamäki MM, Clercx C. Analysis of gene expression in canine idiopathic pulmonary fibrosis. Vet J. 2013 Nov;198(2):479-86.

Lilja-Maula L, Syrjä P, Laurila HP, Sutinen E, Palviainen M, Ritvos O, Koli K, Rajamäki MM, Myllärniemi M. Upregulation of alveolar levels of activin B, but not activin A, in lungs of west highland white terriers with idiopathic pulmonary fibrosis and diffuse alveolar damage. J Comp Pathol. 2015 Feb-Apr;152(2-3):192-200.

Lilja-Maula L, Syrjä P, Laurila HP, Sutinen E, Rönty M, Koli K, Rajamäki MM, Myllärniemi M. Comparative study of transforming growth factor-β signaling and regulatory molecules in human and canine idiopathic pulmonary fibrosis. J Comp Pathol. 2014 May;150(4):399-407.

Lilja-Maula LI, Laurila HP, Syrjä P, Lappalainen AK, Krafft E, Clercx C, Rajamäki MM. Long-term outcome and use of 6-minute walk test in West Highland White Terriers with idiopathic pulmonary fibrosis. J Vet Intern Med. 2014 Mar-Apr;28(2):379-85.

Lilja-Maula LI, Palviainen MJ, Heikkilä HP, Raekallio MR, Rajamäki MM. Proteomic analysis of bronchoalveolar lavage fluid samples obtained from West Highland White Terriers with idiopathic pulmonary fibrosis, dogs with chronic bronchitis, and healthy dogs. Am J Vet Res. 2013 Jan;74(1):148-54.

Norris AJ, Naydan DK, Wilson DW. Interstitial lung disease in West Highland White Terriers. Vet Pathol. 2005 Jan;42(1):35-41.

Roels E, Dourcy M, Holopainen S, et al. No evidence of herpesvirus infection in West Highland White Terriers with canine idiopathic pulmonary fibrosis. Vet Pathol 2016, April 22 Epub ahead of print.

Syrjä P, Heikkilä HP, Lilja-Maula L, Krafft E, Clercx C, Day MJ, Rönty M, Myllärniemi M, Rajamäki MM. The histopathology of idiopathic pulmonary fibrosis in West Highland white terriers shares features of both non-specific interstitial pneumonia and usual interstitial pneumonia in man. J Comp Pathol. 2013 Aug-Oct;149(2-3):303-13.

Legg-Calvé-Perthes Disease

Legg-Calvé-Perthes disease is a debilitating condition that occurs in young children and purebred dogs, including Westies. The condition develops as the result of death of the cells that comprise the head of the thigh bone (femur) that inserts into the hip joint. Because this process occurs without any evidence of infection, the condition also is called aseptic femoral head necrosis. This condition was first identified in children more than a century ago by three orthopedic surgeons, and is named after them.

Bone Growth and Skeletal Maturation

Dogs, like other mammals, are born with an immature skeletal system. When an animal is developing in utero, their bones are made entirely of cartilage. Normally, the cartilaginous bones in the dog's legs grow and mature using a process known as "endochondral ossification." During this process, the cartilage becomes calcified from the center of the bone outward. As this occurs, a thin layer of bone is laid around the the shaft of the bone (also known as the diaphysis). Bone marrow, which contains blood vessels, stem cells and maturing blood cells, develops inside the forming bone. Eventually, immature bone is formed as a lacey, woven matrix. The ends of the bones, or epiphyses, remain as cartilage and continue to grow until the animal matures. The area where the cartilaginous epiphysis meets the boney diaphysis meet is known as the growth plate. The bone increases in length from the growth plate, and eventually replaces the cartilage with bone both at the growth plate and within the epiphysis. In fact, the epiphysis has its own center of bone development, or ossification. Eventually, immature woven bone is remodeled into mature regular bone.

As the dog matures, the growth plates slow down and eventually cease activity. At this point, the bones stop growing. Depending on the breed, this maturation of the skeleton and bones generally occurs between 1 and 2 years of age. It is important to realize that all bone, in animals of any age, is "alive" – made up of cells, using nutrients and oxygen from the circulation, responding to demands for support and strength, constantly renewing itself, and capable of repairing injuries.

Bone growth is a very complex and well regulated activity. The genome of each dog contains instructions that direct the function of bone and cartilage cells, that regulate the organization of these cells into bones, and for the orderly growth of the skeleton to support the dog's activities. The proper formation of bone is heavily dependent on an adequate supply of nutrients such as protein, calcium and several other minerals, as well as the activity of a few vitamins and hormones. Bone formation is also controlled by the growth of blood vessels in and around the bone and in the covering of bone, the periosteum.

The Pathogenesis of Legg-Calvé-Perthes Disease

Because bone is a living tissue, it is vulnerable to a variety of diseases, ranging from developmental and congenital problems to cancer, infection, metabolic, or biochemical problems. Legg-Calvé-Perthes is classified as a developmental orthopedic (bone-related) disease.

Each stage of bone development requires healthy blood vessels to bring nutrients, including oxygen, to the working cells and carry waste from those cells. In Legg-Calvé-Perthes disease, blood flow to the developing bone in the head of the femur is disrupted. As a result, the cartilage and bone cells that rely on

Common Clinical Findings
Small Breed Dogs
4-11 Months of Age
Lameness and Pain
Abnormal Femoral Head on Radiographs

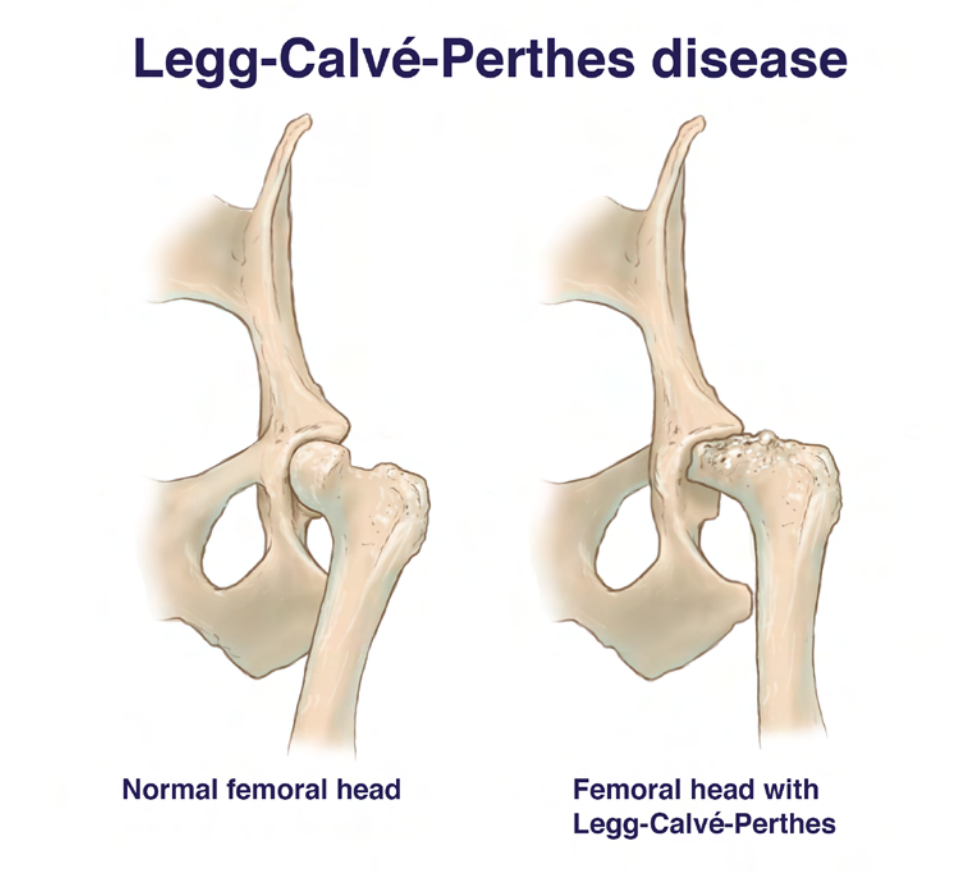

Figure 1 - In this illustration, the normal well-rounded head of the femur (left) fits well in the hip joint, whereas this is not the case with the abnormal femoral head of a dog with Legg-Calve-Perthese disease (right).

that blood fail to get the nutrients they need, and consequently they die (also known as "necrosis"). Consequently, the head(s) of the femurs do not properly develop and are weak. As a result of this boney weakness, the heads of the femurs in dogs with Legg-Calvé-Perthes may fracture, even with normal activity. The interruption in blood flow that appears to be the inciting cause of Legg-Calvé-Perthes is temporary, because the bone will eventually heal itself and remodel. However, this remodeling leaves the femoral head deformed and leads to arthritis and pain for the patient.

The exact cause for the disruption in blood flow to the femoral head is not known, even though this disease has been observed in people and in animals for more than a century. Theories include destruction of the growth plate, repeated blockage of blood flow, compression of the veins in the area, effects of sex hormones (in people, boys are more affected than girls), infection of the hip joint or increased pressure in the joint. A genetic component is suspected because several breeds are overrepresented in presentation, including Westies.

Clinical Signs

Legg-Calvé-Perthes disease typically affects smallbreed dogs, with clinical signs becoming apparent between four and eleven months of age; males and females are at equal risk. Only 12 to 16% of dogs have both legs affected. Patients experiencing these bony changes will be irritable, may limp and may be in pain. As the disease progresses, the gluteal and quadriceps muscles may atrophy, making them appear smaller. In 6 to 8 weeks, the dog may not put weight on the affected limb at all.

Diagnosis

The principal diagnostic tool for Legg-Calvé-Perthes disease is an xray or radiograph. Veterinarians look for increased space in the hip joint of the affected leg, decreased density of the bone (giving a grey appearance instead of a strong white), subtle or overt fracture of the head of the femur, and possible dislocation of the hip joint (subluxation). In early stages, affected dogs will experience pain when a veterinarian

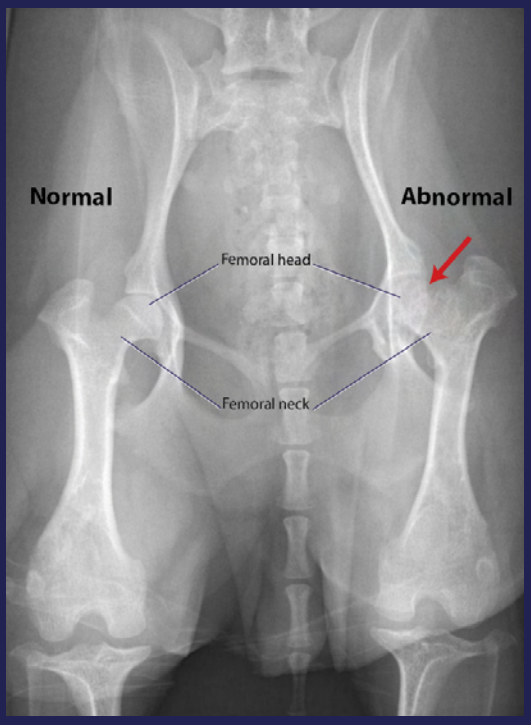

Figure 2 - A radiograph of the rear legs and hip joints of a dog with Legg-Calvé-Perthes disease. The head and neck of the femur are normal on one leg, but abnormal on the affected leg.

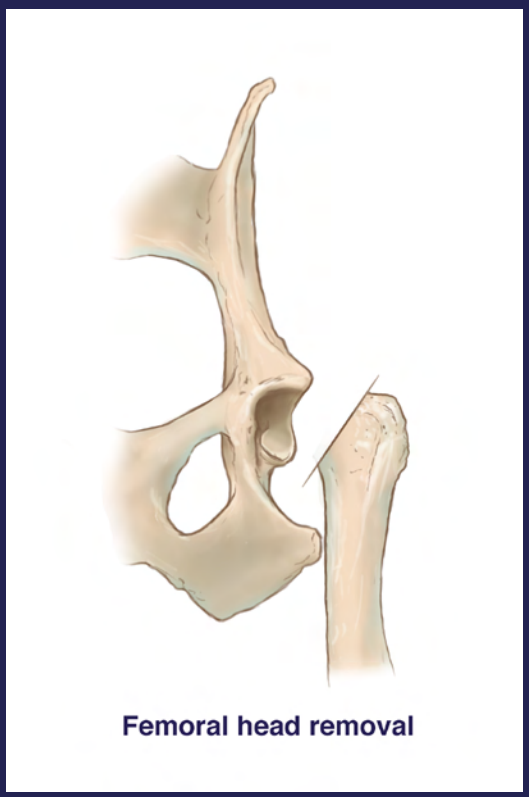

Figure 3 - This illustration depicts the angle at which the affected femoral neck is transected as part of the treatment of Legg-Calve-Perthese disease in a dog.

> In Legg-Calvé-Perthes disease, blood flow to the developing bone in the head of the femur is dirupted.

manipulates the limb outward away from the body. There also will be restricted limb motion, and possibly a grating feeling or sound in the hip joint (crepitus).

Figure 2, a radiographic image of an affected 10 month old dog (not a Westie), is a very good example of aseptic necrosis of the femoral head. At the arrow, there is degeneration of the top of the femur and detachment (subluxation) from the hip socket.

Treatment/Prognosis/Prevention

Treatment for Legg-Calvé-Perthes is surgical removal of the femoral head and neck, the section of bone right under the head. Once the surgery is completed, aftercare involves gently exercising the dog's legs by walking, and then running and swimming. The exercise encourages the growth of a fibrous false joint. The scar tissue that forms replaces the head of the femur and fits into the hip bone. While this procedure may seem dramatic, dogs undergoing the procedure often have full use of the leg in as little as four weeks.

This is dependent, however, on the degree of bony changes in the femur and hip joint before surgery, and may vary by individuals. Surgery relieves the pain and lameness in more than 80% of dogs with Legg-Calvé-Perthes disease, regardless of the progression of the condition or age of the patient. Proper surgical technique is critical; many veterinarians are very experienced with removing the affected femoral head.

Without surgery, dogs with Legg-Calvé-Perthes disease can be kept comfortable with rest, the judicious use of antiinflammatory drugs and medication to control pain, and attention proper nutrition (to promote natural healing). However, lameness resolves with this course of treatment in less than 25% of animals.

Curremt Research About Legg-Calvé-Perthes Disease

Unfortunately, there has not been much research on canine Legg-Calvé-Perthes disease in recent years. Although the disease was identified in dogs more than 50 years ago, only a handful of studies have been done to explore the causes and treatments for the condition in recent years. In this section, we review four recent studies about the disease.

Starr-Moss AN, Nowend KL, Alling KM, Zepp EJ and Murphy KE. Exclusion of COL2A1 in canine Legg-Calvé-Perthes disease. Animal Genetics. 1365-2052.2011.

Given that Legg-Calvé-Perthes disease in dogs of small stature is very similar to the same condition in people, in this study the investigators hypothesized that a mutation in the COL2A1 that is associated with the disease in people might exist in West Highland White Terriers. To test this hypothesis, genomic DNA was extracted from blood from dogs with and without the disease. To the investigators' surprise, there was no co-segregation of a mutation (i.e., single nucleotide polymorphism) with the presence of the disease. This finding suggests that a mutation in this gene is not responsible for Legg-Calvé-Perthes disease in West Highland White Terriers.

Isola, M, Zotti, A, Carnier, E, Baroni, E, Busetto, R, "Dualenergy xray absorptiometry in canine Legg-Calvé-Perthes Disease" Journal of Veterinary Medicine 52:40710, 2005

In this study, the investigators used a new diagnostic tool that has been used in human hospitals to quantify bone density to compare the density of affected and non-affected bones in dogs with Legg-Calvé-Perthes disease. This technique, called dualenergy xray absorptiometry, is used to provide precise data about mineral density in bones. The researchers hypothesized that differences would be apparent using this technique and that it might be a way to track the progress of boneweakening diseases and potentially diagnose such problems earlier than currently is possible. However, there were no significant differences in mineral density between the dogs' affected with the disease and non-affected legs. The researchers attributed this lack of difference to bone remodeling in the affected leg.

LeFond, E, Breur, G, Austin, C. Breed susceptibility of developmental orthopedic diseases in dogs. Journal of the American Animal Hospital Association 38: 467-477, 2002

In this study, veterinary teaching hospital medical records from 1986 to 1995 were reviewed, and the susceptibilites of different breeds to different developmental orthopedic disorders were ranked. The results of that study determined that West Highland White Terriers are 33.2 times more likely to have Legg-Calvé-Perthes than mixed breed dogs. Furthermore, of the breeds that were diagnosed with the condition, Westies were the seventh most represented breed. While breed susceptibility suggests a genetic component to the disease, the researchers pointed out that "the ultimate method to characterize genetic etiology for a disease is the determination of its heritability and mode of inheritance. Consequently, the best way to determine which mutations are associated with the disease would be to map the genome of Westies.

Brenig B, Leeb T, Jansen S, Kopp T. Analysis of blood clotting factor activities in canine Legg-Calvé-Perthes' disease. J Vet Intern Med. 1999 Nov-Dec;13(6):570-3.

Legg-Calvé-Perthes has been linked to overactive blood clotting in humans, with the end result being clots that block the blood vessels that normally supply the head of the femur, causing the death of cells in that part of the bone. In an effort to determine the potential role of blood clotting in dogs with Legg-Calvé-Perthes disease, the investigators in this study measured clotting factors in 18 dogs with the disease. Because all results were within normal limits, it appears that factors other than clotting contribute to the development of the condition in dogs.

Acknowledgements

Mr. Matthew Crotts, a medical illustrator in Educational Resources, created the illustrations used in this chapter, and Dr. Sam Franklin in the Department of Small Animal Medicine & Surgery provided input and guidance for the illustrations. Both Mr. Crotts and Dr. Franklin are in the College of Veterinary Medicine at the University of Georgia.

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Craniomandibular Osteopathy in Westies and other Scottish Terrier Breeds

Craniomandibular osteopathy is a non-neoplastic disease that primarily affects the mandible and tympanic bullae in terriers, particularly Scottish, West Highland White and Cairn terriers. In one study, 66 of affected dogs were either West Highland White or Scottish Terriers. The disease also has been reported to occur in other breeds, including Irish Setters, English Bulldogs, Shetland Sheepdogs, Great Danes, Boxers, Labrador Retrievers, Doberman Pinschers, Pit Bull Terriers, Bullmastiffs and Akitas. It is important to recognize that the incidence of the disease is low; in one study, LaFond et al identified 35 cases of craniomandibular osteopathy in a study of more than 300,000 case records from 10 veterinary teaching hospitals, an incidence of 0.01%. Nineteen of the 35 cases occurred in Westies.

Craniomandibular osteopathy is known by several synonyms, such as 'mandibular periostitis', 'Westie jaw', 'Scottie jaw' and 'lion's jaw'. Thickening of the mandible and the bullae results in pain, particularly when the dog chews its food. In many cases, enlargement of the angular processes of the mandible and the bullae prevents the dog from fully opening its mouth. Typically, signs of pain first become evident when the dog is between 4 and 7 months of age, and may be associated with intermittent episodes of fever. The pain associated with the disease adversely affects the dog's ability to eat, gain weight and grow. In some cases, the disease may become self-limiting when the dog reaches 12 to 18 months of age. At this time, abnormal bone growth slows or even may cease, coinciding with completion of regular endochondral bone growth and ossification.

The severity of the disease, time of onset, and rate of progression vary considerably among affected dogs. A lack of a gender predisposition has been documented in two studies (Watson et al, 1995; LaFond et al, 2002). It also has been reported that the disease can affect several dogs in the same litter (Tronwald-Wigh et al, 2000). Although an early study of the genetics of this disease, using retrospective pedigree analysis (Padgett et al, 1986), indicated that the disease is inherited as a simple autosomal recessive characteristic, this has recently been proven to be false. A more recent study at the University of Bern determined that a mutation in chromosome 5 causes the disease. In that study, approximately 85% of affected dogs had two copies of the mutation, 10% had one copy, and the remainder did not carry it. Thus, while the presence of the mutation strongly influences the presence of the disease, other genetic and/or environmental factors must be involved. The investigators also reported that incomplete penetrance can occur, meaning that dogs with one copy of the mutation might develop clinical signs, while others will not. The Westie Foundation coordinated the gathering of frozen samples for that research project, which were shipped to Switzerland. A genetic test now is available through OptiGen (www.optigen.com). The results of a study comparing three canine models of human rare bone diseases included craniomandibular osteopathy in Westies were published recently and are available online at the following site: http://journals.plos.org/plosgenetics/article?id=10.1371/journal.pgen.1006037

Diagnosis of Craniomandibular Osteopathy

The signs of craniomandibular osteopathy first identified by owners of affected dogs are difficulty grasping, holding and chewing food, drooling, and swelling of the face around the jaw. Some affected dogs may appear to be painful when the mouth is opened, and it may not be possible to open the dog's mouth fully. It has been reported that a painful reaction may be elicited when the dog's jaw and the joint between the jaw and skull (temporomandibular joint) are palpated (Padgett et al, 1986). Some affected dogs may be febrile, and some appear swollen over the jaw, temporomandibular joint, and at the base of the skull. This swelling is due to excessive growth of disorganized bone. Common laboratory tests typically are not useful in diagnosing this disease, and inconsistent results are obtained when indicators of bone remodeling or proliferation (e.g., serum inorganic phosphorus or alkaline phosphatase) are evaluated.

Common Clinical Findings
4 – 7 Months of Age
Mandible and Tympanic Bullae
Pain When Eating

> Affected dogs have difficulty grasping, holding and chewing food, drooling, and swelling of the face around the jaw.

A definitive diagnosis of craniomandibular osteopathy is usually made by identifying the characteristic changes seen on radiographs (x-ray images) of the temporal bone of the skull and the mandible of affected dogs (Schwarz et al, 2002). These changes include a disorderly proliferation of bone on the surfaces of the affected bones (mandible and temporal bone) that limits the function of the temporomandibular joint between these bones (***Figures 1-3***). In most affected dogs, the changes occur bilaterally and in about one-third of dogs the changes are limited to the mandible. It is important to know that this proliferation of bone is not a tumor (neoplasm).

The rate at which proliferation of bone occurs differs among dogs. In some dogs, the degree of proliferation is minimal and this results in minimal loss of function. In other dogs, however, the proliferating bone restricts movement of the temporomandibular joint, the dog's ability to open its mouth, grasp and chew food is reduced. In very severe cases, affected dogs can only open their mouth to a limited degree and experience very significant pain when trying to grasp food and chew. These severely affected dogs cease using the muscles that control these functions, and the muscles atrophy (shrink in size). This loss of muscle in the head and jaw may further compromise the dog's ability to eat. In the most severe cases, the proliferating bone may fuse the bones of the jaw to those of the skull. These severely affected dogs rarely show improvement clinically.

The changes that occur in this disease include bony proliferation, bone remodeling, increased connective tissue within and surrounding bone, and variable degrees of inflammation in and around bone (Riser et al, 1967). It is possible that the inflammation may play a role in the development of the condition, perhaps by supplying specific growth factors that stimulate bone growth. Consequently, affected dogs are often administered antiinflammatory drugs in an effort to control pain, reduce the fever, and perhaps slow progression of disease.

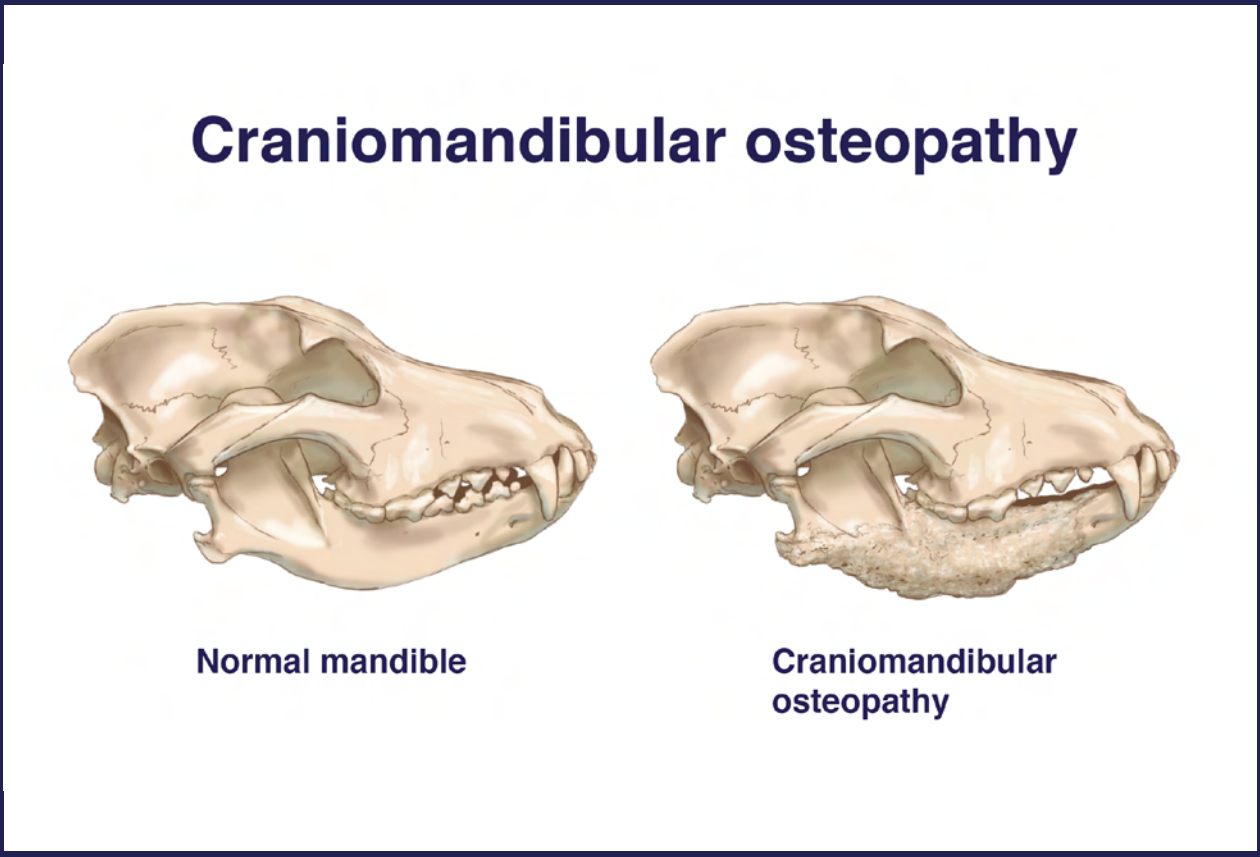

Figure 1 - An illustration depicting the abnormal thickening of the bones in a dog with craniomandibular osteopathy.

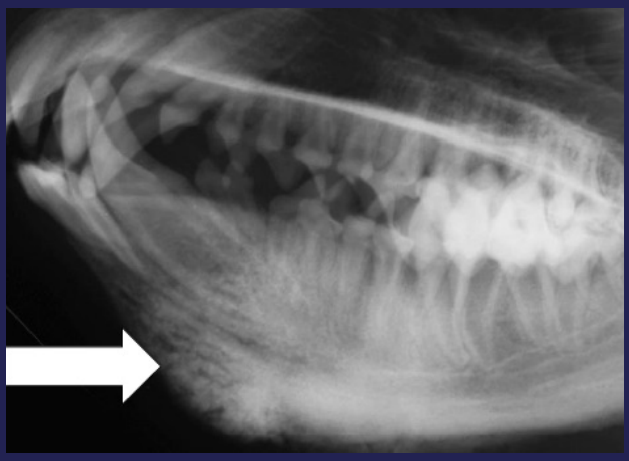

Figure 2 - Lateral radiographic view of the disorderly bony proliferation (white arrow) on the mandible (lower jaw) of a dog with CMO. The top of the skull is at the top of the figure, and the teeth/tooth roots clearly visible for reference. (Figure courtesy of Dr. Greg Daniel, VMRCVM; all rights reserved)

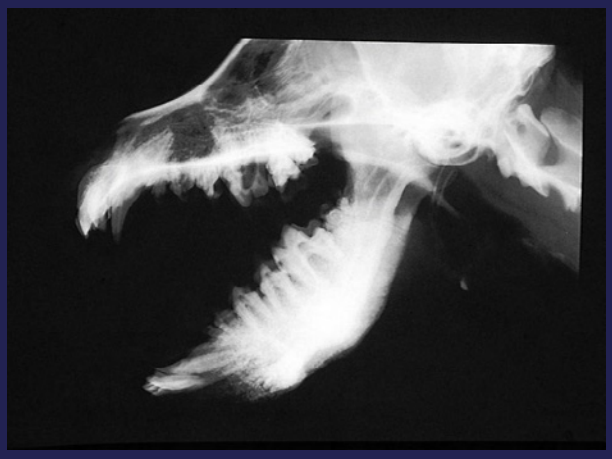

Figure 3 - Radiograph of anesthetized dog with CMO, with mouth open and view taken from the nose toward the back of the mouth. An endotracheal tube can be seen in the mouth (center, lower). Bilateral (both sides) disorderly bone growth on the mandibles and temporomandibular joints (white arrows) can be seen. The growth of this bone limits opening and closing of the mouth, ability to eat, is associated with pain and can be irreversible. (Figure courtesy of Dr. Martha Moon Larson, VMRCVM; all rights reserved)

In rare cases, dogs may have radiographic evidence of bone proliferation on the mandible and skull, but not have trouble eating. Equally uncommon, some dogs may have disorderly proliferation of bone on other bones in the body, including the bones of the legs (Padgett et al, 1986).

Other Things to Consider

Although Westies as a breed are more likely to develop craniomandibular osteopathy, the condition is relatively rare and there are several other reasons why a Westie might be having difficulty eating or a painful mouth. A good saying to remember is "Common things happen commonly", and the following possible causes for these clinical signs should be considered first (listed in no particular order):

- Abnormalities of the teeth and gums
- Mouth, nose and throat infections
- Oral ulcers or ulcers elsewhere in the digestive tract
- Strains, sprains and fractures
- Tumors of soft tissues and bones of the skull and jaw
- Inflammation of the muscles of the head and neck
- Palatability of food items offered
- Exposure to toxins in the diet or environment

It is very important to see your veterinarian if your Westie is failing to gain weight, has trouble eating, appears to be painful or is drooling.

Treatment of Craniomandibular Osteopathy

There is some controversy regarding the progression of craniomandibular osteopathy. Most veterinarians indicate that the disease is selflimiting, often regresses (slows and stops with age) and at times completely resolves (Riser et al, 1967; Alexander, 1983), although there is variability in the progression of the disease. In their review, Watson and colleagues (1995) noted that bony proliferations may show smoothing and remodeling in some bones of some dogs.

Many veterinarians advocate the use of antiinflammatory drugs to help control pain, fever and swelling in dogs with the disease. The judicious use of these drugs (both corticosteroids and nonsteroidal drugs, such as aspirin, carprofen and meloxicam) allows affected dogs to eat and drink. While attempts have been made to surgically eliminate the bony fusions in the temporomandibular joint of severely affected dogs, this approach has not been successful. It is clear that the best approach is to prevent the development of the condition by selective breeding.

Current Research About Craniomandibular Osteopathy

Due to its rare nature, there has not been a lot of research on craniomandibular osteopathy in dogs in recent years. There are, however, some recent reports that we believe deserve being reviewed and some information about a non-neoplastic proliferative bone disease in humans that might be of interest.

In 2002, LaFond and colleagues performed a large-scale epidemiological study designed to identify breeds of dogs at risk for 12 different developmental orthopedic diseases, including craniomandibular osteopathy. This study involved examination of data from medical records of dogs presented to 10 veterinary teaching hospitals. The frequency of different developmental orthopedic diseases ranged from a high of more than 10,000 cases of hip dysplasia to the low of 35 cases of craniomandibular osteopathy, more than half of which were in Westies. This study underscored the fact that the disease occurs in Westies, but that its incidence is low.

LaFond, E, Breur, GJ, Austin, CC, "Breed susceptibility for developmental orthopedic diseases in dogs," Journal American Animal Hosp Assoc 38:467-477, 2002.

In this recent clinical case study, an 8-month old Airedale Terrier was examined because she was head shy, was painful when the left side of her face and head were palpated, and her appetite had decreased. MRI was used to assess the bony and soft tissues structures of her head. The abnormalities identified involved the mandibles, frontal bones and calvarium, and included both bony proliferation and resorption that are characteristic of craniomandibular osteopathy. Based on these findings, a bone marrow biopsy sample was obtained and examined microscopically. The findings of that examination also were consistent with a diagnosis of craniomandibular osteopathy. Treatment included administration of non-steroidal anti-inflammatory drugs. The clinical signs of pain, shyness, and swelling had resolved when the dog was re-evaluated 3 months later.

Matiasovic M, Caine A, Scarpante E, Cherubini GB. Imaging diagnosis: Magnetic resonance imaging features of craniomandibular osteopathy in an Airedale Terrier. Vet Radiol Ultrasound. 2015 Oct 15. doi: 10.1111/vru.12304. [Epub ahead of print] PubMed PMID: 26466748.

This 4-month old Westie was presented for examination and treatment of a deformity involving both forelegs. The bones were thickened, as were the dog's mandible and skull. The dog also appeared to be painful when the mandibles were palpated. Radiographic findings were consistent with craniomandibular osteopathy and microscopic examination of samples of the affected bones in the legs revealed findings also consistent with this disease. The deformities were corrected surgically and the dog's behavior and appetite resolved over time.

Pettitt R, Fox R, Comerford EJ, Newitt A. Bilateral angular carpal deformity in a dog with craniomandibular osteopathy. Vet Comp Orthop Traumatol. 2012; 25(2):149-54.

Some aspects of the development of craniomandibular osteopathy in Westies are consistent with a disease in people called Paget disease of bone. In that condition, there is evidence of excessive bone resorption and new bone formation. Like craniomandibular osteopathy, this disease affects the skull, but it rarely affects the mandibles. It often affects the spine, causing clinical symptoms related to nerve compression. Unlike craniomandibular osteopathy, however, Paget disease of bone is caused by a mutation in a single gene and is an autosomal dominant disease. Therefore, only one parent must have the mutation in order for the disease to appear in offspring.

Acknowledgements

Mr. Matthew Crotts, a medical illustrator in Educational Resources, created the illustrations used in this chapter, and Dr. Scott Secrest in the Department of Veterinary Biosciences & Diagnostic Imaging provided the radiographs. Both Mr. Crotts and Dr. Secrest are in the College of Veterinary Medicine at the University of Georgia.

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Luxation of the Patella

The patella or 'knee cap' is the small bone that connects the thigh muscles to the bones that comprise the shin, namely the tibia and fibula. The term 'luxation' refers to the dislocation of a bone from its normal position. When this happens, it causes pain and lameness, and occurs commonly in small breed dogs, including Westies. In most cases, the patella becomes displaced medially, towards the inside of the leg, rather than laterally (towards the outside of the leg).

While one could easily envision how a traumatic event, like a fall or being hit by a car, could cause dislocation of the patella, in most cases the condition is caused by muscle and skeletal abnormalities present at birth. While the condition can be painful and a cause of lameness, it can be diagnosed and treated effectively in most dogs.

How does patellar luxation happen?

The bones of the knee joint include the thigh bone (femur), the shin bones (tibia and fibula), and the knee cap (patella), which sits in a groove in the femur called the trochlear groove. Ligaments connect these bones and serve to stabilize the joint. The quadriceps muscles are a set of four muscles on the front of the femur that come together near the patella to form the patellar ligament. This ligament can easily be felt between the patella and a prominence on the tibia (tibial tuberosity) over the front of the knee. The quadriceps muscles serve to extend, or straighten, the knee. During this process, the patella acts as a lever arm for the quadriceps and also exerts an even amount tension from the muscles on the patellar ligament.

Normally functioning knee joints work because all of the components of the knee joint (bones, ligaments, tendons, muscles) are lined up properly. In dogs with congenital patellar luxation, one or more of the components either is malformed, dysfunctional or becomes so as the dog begins to mature. Some dogs may develop this condition later in life, as a result of trauma or a combination of a congenital abnormality and subsequent wear.

Dogs with luxation of the patella typically have one or more of the following abnormalities: abnormal angulation between the head and shaft of the femur, medial displacement of the quadriceps, lateral twisting or bowing of the femur just above the joint, a shallow trochlear groove, or medial displacement of the tibial tuberosity where the patellar ligament attaches. ***Figure 1*** on the following page depicts the differences between a normal dog and one with luxation of the patella. In the normal dog, the patella is positioned under the quadriceps femoris muscle and is attached by the patellar ligament to the tibia. In contrast, in the dog with luxation of the patella, the patella and quadriceps are displaced medially.

There are several theories as to which deformity initiates the problem and results in luxation. The most widely accepted theory is that an abnormal angulation between the head and shaft of the femur causes the quadriceps muscle to move medially and pull the patella with it. There are three other theories for the development of the condition. These include 1) hormonal influences on bone formation and growth that result in development of a shallow trochlear groove in the femur, 2) hip diseases that cause dogs to walk abnormally, making the knee compensate inappropriately, and 3) abnormally positioned attachments of the muscles that cause the patella to be displaced medially. It is important to recognize that no single theory explains all cases. Regardless of the underlying cause for patellar luxation, there are several consequences if the condition is not treated. With the patella out of place, the cartilage on the surface of the patella, tibia and femur wears down, causing pain and restricting movement, eventually leading to arthritis. Other problems that may develop include rupture of the cranial cruciate ligament, one of the important

Common Clinical Findings
Small Breed Dogs
Wide Range of Clinical Signs
Abnormalities in Femur or Tibia
Joint Deformities on Radiographs

ligaments that attach the femur to the tibia. This ligament can be stretched too far and tear completely if the patella is displaced.

Patellar luxation can result in special consequences in dogs that are still growing. For example, a preexisting bone deformity that may be causing the luxation will worsen as the bones continue to grow unless it is corrected surgically. Similarly, without the normal pressure exerted by the patella on the trochlear groove of the femur, the groove does not deepen as it should. As a result, the groove will become too shallow to retain the patella in position, even if it is popped back into place. Consequently, is very important for an accurate diagnosis to be made and affected dogs receive treatment. This is particularly true for young, growing dogs.

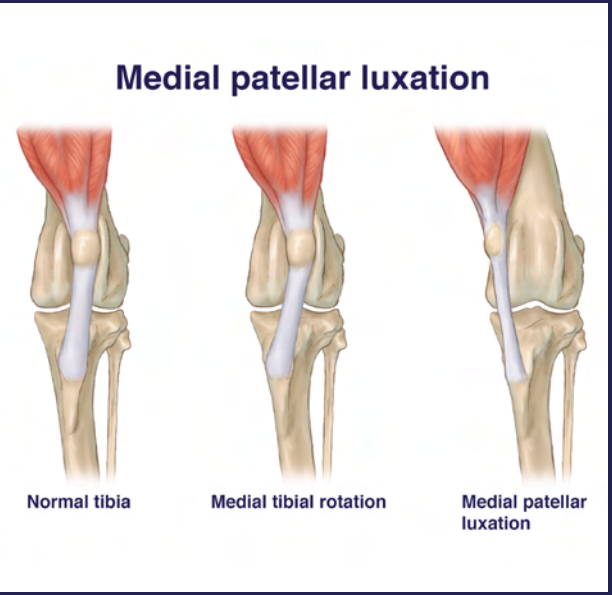

Figure 1 - An illustration depicting the normal alignment of the tissues comprising the joint (left), the effects of medial rotation of the tibia (middle), and medial lunation of the patella (right).

Signs and Severity of Patellar Luxation

Dogs with luxation of the patella may exhibit a variety of clinical signs, depending on the severity of the problem. To clarify and compare the severity of the condition in different dogs, four grades of severity are used. These range from the mildest, Grade I, to the most severe, Grade IV.

Grade I: Luxation of the patella in dogs with Grade I typically is discovered during a routine physical examination. In these cases, the patella can be forced out of place manually, but rarely luxates during the dog's regular daily activity. Because all of the components of the joint are normal, dogs with Grade I luxations will appear normal and are not lame.

Grade II: Dogs with a Grade II luxation have a mild underlying deformity of the femur. While the patella may be luxated manually, it occasionally may do so on its own. In some dogs, the patella returns to its normal position as the animal moves. In other dogs, the patella will need to be repositioned manually. Dogs with Grade II luxations will occasionally "skip" while walking or running, when the patella has become displaced. Their gait will return to normal when the patella returns to its normal position.

Grade III: Grade III luxations are more severe, causing the patella to remain out of position most of the time. The patella can, however, be repositioned manually. The quadriceps muscles in these dogs are displaced medially and bony deformities also are present. Dogs with Grade III luxations may 'skip' like dogs with Grade II luxations, although more frequently. If the patella is luxated more often than it is in its normal position, the dog will develop a 'weightbearing lameness'. This means that the dog will bear some weight on the affected leg, but will walk with a limp.

Grade IV: Grade IV luxations are the most severe form of the condition, as the patella is always luxated and cannot be replaced manually. Dogs with Grade IV patellar luxations have significant deformities of the bones and other components that comprise the stifle joint. Affected dogs walk with their hind legs crouched in a permanently flexed position, and are unable to extend their hind legs due to the permanent luxation of the patella.

Diagnosis

The diagnosis of a luxating patella alone is simple, as the patella can be felt or moved out of place during a physical examination. Radiographs will reveal joint deformities and help the veterinarian determine the grade of the luxation. Other orthopedic conditions that often coexist in dogs with luxation of the patella include hip dysplasia, cranial cruciate ligament rupture and Legg-Calvé-Perthes disease (see previous section on *Legg-Calvé-Perthes Disease*).

> Surgical treatment of patellar luxation has two goals: 1) to return the patella to its proper position, and 2) to realign the other components of the stifle joint to keep it in this position.

Treatment

The recommended treatment for a dog with patellar luxation depends on the grade of the luxation and the dog's age. Dogs that are not lame can simply be monitored for any changes that would indicate an increase in the severity of the luxation; surgery is not recommended for these animals. However, surgery is recommended for any dog that is lame and especially for those whose bones are still growing.

Surgical treatment of patellar luxation has two goals: 1) to return the patella to its proper position, and 2) to realign the other components of the stifle joint to keep it in this position. A veterinary surgeon may use a combination of techniques and procedures to achieve these goals. These include recentering the part of the tibia (shin) bone to which the patellar ligament attaches, cutting or reinforcing the ligaments on the sides of the joint, deepening the trochlear groove on the femur to increase the likelihood that the patella will remain within that groove, and shortening and realigning the tibia and or femur.

Dogs undergoing surgery should be walked only on a leash for up to six weeks after the procedure to give the joint sufficient time to recover. After that, the dog should be brought back up to his/her regular speed slowly, so as not to reinjure the area. Veterinarians may prescribe antiinflammatory drugs to help control pain following surgery.

Surgery is usually very successful in restoring normal activity in dogs with Grades III luxations. Because of their small size, Westies tend to have a higher success rate than large breed dogs. Dogs with Grade IV luxations may not return to normal activity, even after surgery. As many as 50% of all dogs undergoing surgery may have incidental Grade I luxations afterwards. Although arthritis cannot be avoided by surgery, it may not be as severe as if the patella had remained luxated.

Degenerative Joint Disease – A Consequence of Patellar Luxation

Degenerative joint disease, also called osteoarthritis, results from the breakdown of the bones and cartilage that make up a joint. During the development of degenerative joint disease, the cartilage that normally serves a cushioning function between bones, loses this ability. This often initiates inflammation of the cells that line the joint (synovium) and the surrounding joint capsule. The inflammatory mediators released by these tissues adversely affect the cartilage and any ligaments within the joint, resulting in loss of cartilage cells, thickening of ligaments, joint pain, stiffness and reduced range of motion. As the pain makes it difficult to move, the muscles may lose some of their size and strength.

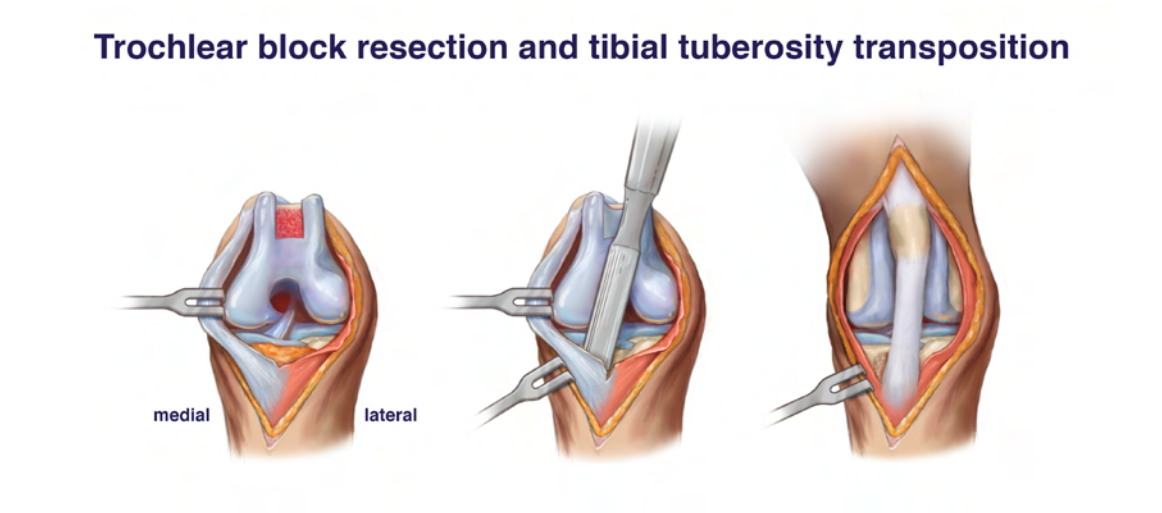

Figure 2 - An illustration depicting trochlear block resection and transposition of the tibial tuberosity in a dog with medial patellar luxation.

Current Research About Luxation of the Patella

Although there has not been a lot of research performed in the past decade on luxation of the patella in dogs, three recent studies would seem to be of most interest, as they concern a potential predisposition to develop the condition and the results of different types of treatments.

Wangdee C, Theyse LFH, Hazewinkel HAW. Proximo-distal patellar position in three small dog breeds with medial patellar luxation. Vet Comp Orthop Traumatol 28: 270-273, 2015.

It has been hypothesized that medial patellar luxation is associated with a high proximal position of the patella in the trochlear groove. In this study, the ratio of the length of the patellar ligament to the length of the patella was determined from radiographs of small breed dogs with and without medial patellar luxation. This ratio first was evaluated using radiographs obtained at five different stifle angles to determine the best angle to use to measure the ratio. Having done this, the ratio was then calculated for dogs with normal stifles as well as dogs with grades I, II and III medial patellar luxations. The ratio was the same for all three breeds of dog (Pomeranian, Chihuahua and Toy poodle), regardless of whether the stifle was normal or affected by medial patellar luxation. As a result, it appears that proximo-distal position of the patella is not associated with the condition, which means that length of the patellar ligament does not play a role in the development of the condition.

Clerfond P, Huneault L, Dupuis J, Moreau M, Auger J. Unilateral or single-session bilateral surgery for correction of medial patellar luxation in small dogs: Short and long-term outcomes. Vet Comp Orthop Traumatol 27: 484-490, 2014.

Because medial patellar luxation often occurs bilaterally in small breed dogs, veterinary surgeons have questioned whether it is better to perform the surgery on both legs in a single surgical session or to correct each leg in individual surgery sessions. This study was designed to answer that question by comparing overall, minor and major complication rates for dogs undergoing both surgeries in a single session with those for dogs have their condition treated in two separate surgery sessions. The authors concluded that there were no differences in complication rates, short-term or long-term outcomes between the two groups. Furthermore, while the anesthesia and surgical times were longer for the dogs undergoing bilateral corrective surgery, they were less than doubled. The results of this study suggest that bilateral single-session surgery can be recommended for dogs with bilateral medial patellar luxation.

Cashmore RG, Havlicek M, Perkins NR, James DR, Fearnside SM, Marchevsky AM, Black AP. Major complications and risk factors associated with surgical correction of congenital medial patellar luxation in 124 dogs. Vet Comp Orthop Traumatol 27: 263-270, 2014.

This study was performed to describe the major complications occurring after surgical correction of congenital medial patellar luxation in dogs and to identify the risk factors associated with the development of these complications. The authors determined that major complications occurred in 18.5% of the procedures, with failure of stabilization implants being the most common complication. Other major complications were patellar relaxation and avulsion of the tibial tuberosity. The likelihood of the latter complication was increase significantly when a single Kirshner wire was used in the procedure rather than a pair of wires. Furthermore, the risk of patellar relaxation increased substantially when trochleoplasty (deepening of the trochlear groove) was not performed in combination with surgically repositioning of the tibial tuberosity.

Acknowledgements

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Clerfond P, Huneault L, Dupuis J, Moreau M, Auger J. Unilateral or single-session bilateral surgery for correction of medial patellar luxation in small dogs: short and long-term outcomes. Vet Comp Orthop Traumatol. 2014;27(6):484-90.

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Addison's Disease (Adrenal Gland Insufficiency)

Addison's disease, also known as adrenal gland insufficiency or hypoadrenocorticism, is an uncommon condition in which the patient's adrenal glands no longer supply the body with two classes of hormones, called glucocorticoids and mineralocorticoids. These hormones help regulate cellular metabolism and electrolyte balance in the body. According to the most recent edition of the Merck Veterinary Manual (Merck, 2015), this disease is characterized by gastroenteritis (vomiting and diarrhea), loss of body condition, lethargy and weakness, and inability to respond to stress. Although this condition has been recognized in dogs for more than 60 years, it remains difficult to diagnose, primarily because the animal's symptoms mimic those associated with several other diseases. However, when the disease is identified, treatment is very effective, allowing affected dogs to lead normal healthy lives. In order to understand how Addison's disease develops, it is important to first understand something about the anatomy and physiology of the adrenal glands themselves.

Anatomy and Physiology of the Adrenal Glands

The adrenal glands are a pair, are complex, multifunctional organs that are located on top of the kidneys ('ad renal' – near the kidney). The outer layer of the gland (the cortex) produces three types of hormones: glucocorticoids, mineralocorticoids and small amounts of sex hormones.

In healthy animals, production of glucocorticoids is regulated by signals received from the brain. The hypothalamus is the region in the brain that produces a hormone called corticotrophin-releasing hormone (CRH), which stimulates another part of the brain, the pituitary gland, to release a hormone called adrenocorticotrophic hormone (ACTH). ACTH is released into the bloodstream and travels to the adrenal glands where it causes them to release glucocorticoids in the form of cortisol. When there is a healthy amount of cortisol circulating in the blood, this is sensed by the hypothalamus, which then reduces its production of CRH, and this causes the pituitary gland to stop releasing ACTH. The end result is a reduction in the production of cortisol by the adrenal glands. Because the healthy level of cortisol in the blood is exerting a negative influence on the production of CRH and ACTH by the brain, this is known as negative feedback. When the concentration of cortisol in the blood decreases, the hypothalamus and pituitary gland respond by releasing more CRH and ACTH, respectively, which stimulates the adrenal glands to produce more cortisol until circulating concentrations are restored.

Unlike the glucocorticoids, production of the mineralocorticoids is regulated by a system that starts with special cells in the kidneys, called the juxtaglomerular cells. These cells, which are located near the functional unit of the kidney called the glomerulus, sense the concentration of sodium in the blood, which is very important in the regulation of blood pressure. When the sodium concentration in the blood is low, the juxtaglomerular cells produce a chemical called renin, an enzyme that converts a substance in the blood called angiotensinogen to angiotensin I. Angiotensin I is then converted by another enzyme, which is located primarily in the blood vessels in the lungs, to angiotensin II. Angiotensin II has two effects: 1) stimulating the adrenal glands to produce aldosterone, the main mineralocorticoid, and 2) constricting small blood vessels to increase blood pressure.

Common Clinical Findings
Lethargic and Listless
Vomiting or Regurgitation
Weight Loss or Weakness
Abnormal Cortisol Response to ACTH Stimulaton

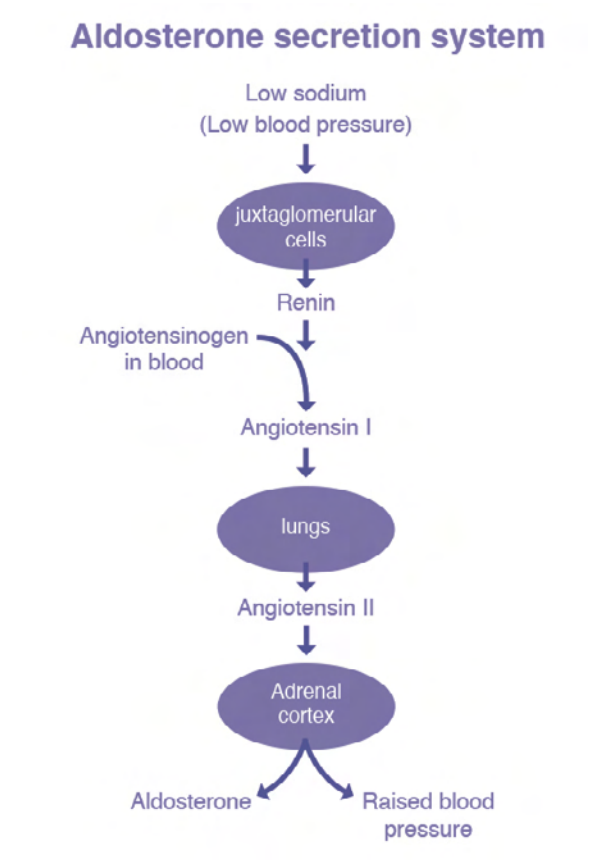

Figure 1 - A graphic representation of the production of aldosterone by the adrenal cortex. In response to low blood sodium concentration, the juxtaglomerular cells in the kidney release renin, which converts angiotensinogen to angiotensin I, which then is converted to angiotensin II. This latter compound stimulates the adrenal glands to secrete aldosterone, which returns blood sodium concentration to normal and increases blood pressure.

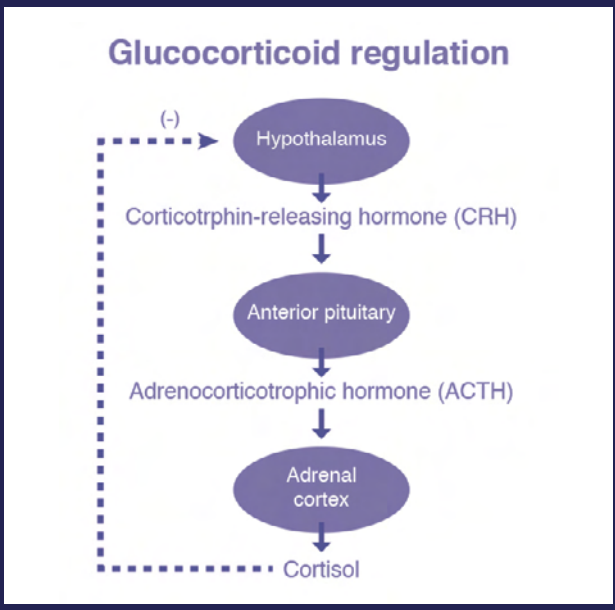

Figure 2 - A graphic representation of the negative feedback regulation of cortisol production by the adrenal cortex.

Aldosterone then causes the kidneys to absorb additional sodium and water from the fluid that it has filtered, which helps return blood sodium concentrations towards normal and increase blood pressure. At the same time, aldosterone causes the kidney to excrete potassium into the urine, which helps balance the electrolytes in the body.

How does this disease develop?

Addison's disease is characterized by the lack of production of glucocorticoids and mineralocorticoids. The disease can occur either as a result of an abnormality in the brain that then fails to stimulate the adrenal glands to perform their functions or in the adrenal glands themselves. When the problem originates in the brain, there is insufficient production of either CRH by the hypothalamus or ACTH by the pituitary gland. Lacking sufficient production of CRH or ACTH, the adrenal glands fail to function normally, production of cortisol and aldosterone is reduced, and the glands shrink in size (atrophy). This form of Addison's disease occurs infrequently.

Most cases of Addison's disease occur because the adrenal glands have been damaged and are no longer able to make cortisol and aldosterone, even when stimulated by ACTH and angiotensin II, respectively. In rare instances, special chronic inflammatory diseases (i.e., granulomatous diseases), hemorrhagic infarctions (blood clots forming and lodging in the adrenals and other tissues), cancer of the adrenals, and trauma can induce enough damage to the adrenal glands to cause Addison's disease. In the majority of cases of Addison's disease in dogs and people, an autoimmune process is responsible for destroying the adrenal glands. That means that the patient's own antibodies have destroyed the cells inthe adrenal glands, much like other antibodies destroy foreign invaders like bacteria or viruses. The underlying processes that stimulate this autoimmune attack on the adrenals are not known, but are the subject of active research. For some reason, females are twice as likely to develop Addison's disease as males.

Which clinical signs occur in dogs with Addison's disease?

Clinical signs of Addison's disease often are vague and nonspecific, with many affected dogs being lethargic, listless, anorexic, and reluctant to exercise or even do normal activities. Very often, these signs appear to wax and wane, making it even more difficult for owners to decide when to seek veterinary care. More than half of affected dogs have episode of vomiting or regurgitation of food, weakness, and weight loss. Diarrhea occurs in approximately one-third of dogs with the disease. The severity of the clinical signs may progress rapidly in some dogs and very slowly in others.

> Addison's disease is characterized by the lack of production of glucocorticoids and mineralocorticoids.

Acute exacerbation of the condition may occur when the dog's lifestyle is changed, for instance this may occur when the dog is moved, boarded or is examined by a veterinarian. Although dogs with Addison's disease may vary in age, the typical dog is 4-5 years old and female. These characteristics should not be surprising as many immune-mediated diseases occur more commonly in females than males.

All clinical signs of Addison's disease are due to the deficiencies of glucocorticoids (cortisol) and mineralocorticoids (aldosterone). For example, cortisol deficiency affects the body's metabolism, which results in a loss of appetite, vomiting, abdominal pain, weight loss and lethargy. Because aldosterone is critical for balancing electrolytes (reabsorbing sodium and excreting potassium) and maintaining blood pressure, a deficiency in aldosterone reduces serum sodium concentration, and lowers blood pressure as the result of reduced circulating blood volume. Dogs with low blood sodium concentration may lose weight, feel weak, have small hearts and produce dilute looking urine even though they may be dehydrated. High blood potassium concentrations can cause life-threatening problems with heart rhythm (called 'arrhythmias'). In fact, some affected dogs may develop such high blood concentrations of potassium that severe alterations occur in heart function and blood pressure, resulting in the development of shock. This clinical scenario is often referred to as an "Addisonian crisis". Unfortunately, Westies appear to be at a high risk for developing Addison's disease, as are Great Danes, Poodles, Portuguese Water Dogs, Soft-coated Wheaten Terriers, Nova Scotia Duck Tolling Retrievers and others. The results of recent studies suggest that there is a genetic predisposition for the disease in some breeds.

How is Addison's disease diagnosed?

Due to the wide variety of clinical signs that can occur and the fact that many of these are nonspecific (i.e., can occur in dogs with other diseases), Addison's disease is difficult to diagnose. As a result, many more dogs are suspected of having Addison's disease than end up being diagnosed with the condition. In one report, 15% of dogs tested for Addison's disease ended up having it (Lennon et al, 2007).

A reliable screening test for Addison's disease involves the measurement of cortisol in the blood. Most dogs with the disease have low resting levels of cortisol, whereas dogs with

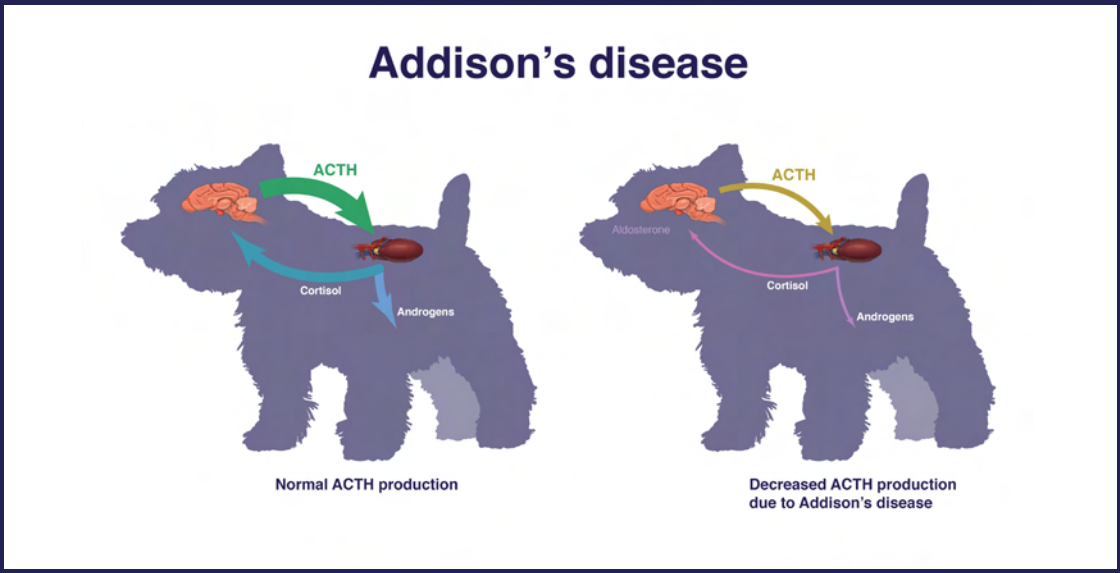

Figure 3 - This illustration depicts the normal interaction between the pituitary and adrenal glands. This results in stimulation of the adrenal glands by ACTH and production of cortisol and androgens, and the normal negative feedback effect of blood cortisol levels on the pituitary gland. In contrast, decreased production of ACTH in a dog with Addison's disease results in reduced synthesis of cortisol and androgens.

a high resting cortisol level are extremely unlikely to have the disease. When a low resting cortisol concentration is measured, the follow-up approach is to determine whether or not the adrenal glands will respond when stimulated. This is achieved by administering ACTH and measuring changes in cortisol concentration an hour later. If the dog's adrenal glands are normal, they should respond to the ACTH by increasing their production of cortisol. As a result, the blood concentration of cortisol will be significantly increased when measured an hour later. In contrast, the adrenal glands of a dog with Addison's disease will not respond to the ACTH, and the blood cortisol value measured after ACTH administration will be unchanged. It is important to know that any corticosteroids being given as a treatment as a result of the animal's clinical signs will interfere with this diagnostic approach. Consequently, it is important for these treatments to be stopped at least 24 hours before an ACTH stimulation test is performed.

While it is common to measure cortisol concentrations before and after an ACTH stimulation test, much less is known about circulating concentrations of aldosterone in dogs with Addison's disease. In a recent study, however, aldosterone concentrations were measured in healthy dogs, in dogs with clinical signs similar to those associated with Addison's disease, and in dogs with the disease. Concentrations of aldosterone were significantly lower in dogs with confirmed Addison's disease when compared with dogs in the other two groups. Furthermore, aldosterone concentrations were not increased after administration of ACTH in the dogs with Addison's disease. These findings confirm that damage to the adrenal cortex affects production of both glucocorticoids and mineralocorticoids similarly.

The ACTH stimulation test does not distinguish between hypoadrenocorticism due to abnormalities of the adrenals and the pituitary gland. In order to make this distinction, blood concentrations of ACTH must be measured. When the abnormality primarily affects the adrenal glands, ACTH concentrations will be high as the lack of cortisol production will not provide the normal negative feedback effect on the pituitary gland. As a result, it will continue to produce ACTH.

In contrast, if the abnormality primarily affects the pituitary gland, blood concentrations of ACTH will be low, due to the fact that it is not being produced by the pituitary gland. Dogs with the pituitary gland abnormalities may eventually respond to enough ACTH given by the veterinarian, whereas those with abnormal adrenal glands will not (i.e., their adrenal glands will continue to fail to produce cortisol).

In addition to the aforementioned blood tests, veterinarians may also use radiography (x-rays), ultrasonography, and electrocardiography (ECG; measurements of the heart's electrical output) to help make a definitive diagnosis of Addison's disease. Radiographic findings detected in many dogs with Addison's disease include reduced size of the heart, liver or specific blood vessels in the lung or abdomen. Ultrasound findings in affected dogs often include adrenal glands that appear smaller than normal, although this is not a consistent finding. The most commonly identified ECG abnormalities include those associated with excessively high blood concentrations of potassium.

Treatment

The key to treating dogs with Addison's disease is to address immediate life-threatening aspects of the disease first and then to consider what needs to be done long-term. Clearly, dogs with poorly functioning adrenal glands will need to be treated for the rest of their lives; owners should be made aware of this immediately and be willing to accept the responsibilities associated with the need for life-long therapy. Fortunately, the prognosis for a healthy, happy life is extremely good.

For dogs in a hypoadrenocortical crisis, the veterinarian's initial focus is to restore blood volume with IV fluids, correct electrolyte abnormalities by slowly, but consistently increasing the sodium concentration in the blood with sodium-containing fluids IV, restoring blood glucose and glucocorticoid levels to normal. The dog's responses to these initial treatments are monitored closely to ensure that tissue perfusion and blood pressure increase appropriately. Fluid therapy also is important to rehydrate the animal, reestablish normal kidney function and correct all serious electrolyte imbalances (e.g., reduce high blood potassium concentrations) that could adversely affect metabolism and heart function. Blood glucose concentrations are restored by administering IV fluids containing dextrose and closely monitoring changes in blood glucose levels.

Finally, a fast acting glucocorticoid is given to replace the glucocorticoids not being produced by the animal's adrenal glands. Typically this is done with an injectable glucocorticoid, such as dexamethasone, until the dog has recovered sufficiently to be treated with oral glucocorticoids. During the acute crisis, treatment with a mineralocorticoid is not critical, and many veterinarians prefer to incorporate this as part of the long-term care plan.

Current Research About Addison's Disease

Because there is a relatively high incidence of Addison's disease in Westies, a genetic basis for the disease is strongly suspected. Consequently, there is a great deal of interested in determining whether or not this is true, and, if so, which genes might be associated with development of the disease. There also is convincing evidence that the disease may have an autoimmune component to its development. In this section, we summarize two recent studies about the genetic basis for the disease and one about the autoimmune nature of the condition.

Boag AM, Catchpole B. A review of the genetics of hypoadrenocorticism. Top Companion Anim Med. 2014 Dec;29(4):96-101.

There is good evidence that hypoadrenocorticism in people has an autoimmune component to its pathogenesis, as several immune response genes have been implicated in increasing the susceptibility of humans to development of Addison's disease. There also is good evidence that a similar situation exists with regard to this disease in dogs. For example, specific breeds of dogs are over-represented in epidemiologic studies of the disease, and some recent molecular genetic studies have determined that some of the same genes and cellular signaling pathways that are involved in Addison's disease in people are associated with increased susceptibility of dogs to the disease. Examples of these include genes associated with immune responses, such as the dog leukocyte antigen and cytotoxic T-lymphocyte–associated protein 4 (CTLA4) genes. The authors of this review paper suggested that this increased understanding of the molecular mechanisms involved in the progression of Addison's disease may make it possible to establish genetic tests to identify dogs at risk of developing the disease and for the development of new treatments.

Short AD, Catchpole B, Boag AM, Kennedy LJ, Massey J, Rothwell S, Henthorn PS, Littman MP, Husebye E, Ollier B. Putative candidate genes for canine hypoadrenocorticism (Addison's disease) in multiple dog breeds. Vet Rec. 2014 Nov 1;175(17):430.

In this study, the authors performed candidate gene analyses for canine hypoadrenocorticism in several breeds in the UK: Bearded Collie, Border Collie, German Shepherd, Standard Poodle, Jack Russell Terrier, West Highland White Terrier and Softcoated Wheaten Terrier. They identified that some putative genetic loci for disease susceptibility form part of the T-cell receptor pathway, supporting the involvement of an autoimmune response. However, other genes that were identified are not involved in these responses, providing additional basis for the heterogeneity and complexity of the condition.

The authors cautioned that the animals involved were part of a laboratory-based collaboration, and thus may not be representative of all dogs in the UK. They also noted that a relatively small number of dogs were available for each breed, which meant that they may not have been able to detect small or moderate effects. Furthermore, the most aggressive forms of hypoadrenocorticism may be missing due to euthanasia or death before an accurate diagnosis was made. While the authors concluded that there is clinical heterogeneity between breeds, it is likely that the cause of hypoadrenocorticism within dogs of one breed is the same.

Boag AM, Christie MR, McLaughlin KA, Syme HM, Graham P, Catchpole B. Autoantibodies against cytochrome P450 side-chain cleavage enzyme in dogs affected with hypoadrenocorticism (Addison's Disease). PLoS One 2015; 10(11): e0143458

There is ample evidence that hypoadrenocorticism in dogs occurs as a result of immune-mediated destruction of portions of the adrenal glands and leads to deficiencies in glucocorticoid and mineralocorticoid production. In people with Addison's disease, circulating autoantibodies directed against some of the enzymes responsible for the synthesis of adrenal gland hormones have been identified. This study was performed to determine whether or not similar autoantibodies against enzymes of the corticosteroid synthesis pathway are present in dogs with hypoadrenocorticism, and whether a relationship exists between autoantibody status and clinical features of the disease. The results of this study indicated that autoantibodies directed against a key enzyme in this pathway exist in a proportion of dogs affected with hypoadrenocorticism, are more prevalent in affected female dogs, and appear to be related to breed and DLA-type. Further work is required to determine whether the presence of these autoantibodies is associated with reproductive dysfunction in affected female dogs and whether measurement of these autoantibodies is of use as part of the diagnostic approach for canine hypoadrenocorticism.

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Diabetes Mellitus

Stephanie Shrader, DVM and John Robertson, VMD, PhD

Introduction and Overview

Diabetes mellitus is a complex endocrine metabolic disorder that results in abnormally high blood glucose ("blood sugar") concentrations, a condition called hyperglycemia, and glucose in the urine (glycosuria). The disease was first named 'diabetes' almost 600 years ago in Greece, with the term referring to the excessive urination associated with the disease. In the 1600's the term 'mellitus', which means 'like honey' in Greek, was added to reflect the sweet smell and taste of the patient's urine. The primary cause of diabetes mellitus is a lack of activity of the hormone insulin, and two main forms of the disease are recognized in people and pets.

Type I diabetes is characterized by an inability of the beta cells of the pancreas to produce insulin. As a result, circulating concentrations of insulin are far too low to exert its effects on cells in the body. In people, Type I diabetes mellitus is also known as 'juvenile onset diabetes' as it tends to occur in young people. Type II diabetes is caused by an inability of insulin to exert its effect at the cellular level. Because the problem is not the lack of insulin, this form of the disease is called 'insulin resistant diabetes' to reflect the fact that the cells fail to respond to the insulin that is present. In people, this is the most common form of the disease. Although it previously was known as 'adult onset diabetes,' it is becoming more prevalent in children and is strongly associated with childhood obesity. The underlying causes of most cases diabetes mellitus are not known. However, some known factors can trigger the onset of diabetes including exposure to some drugs, abdominal tumors, pancreatitis and surgical procedures. According to a 2004 survey completed by the makers of Vetsulin (an FDA-approved veterinary product for the treatment of diabetes mellitus in both dogs and cats), approximately 1 in every 500 dogs suffers from diabetes mellitus. Survey results also showed that of the more than 200 veterinarians polled, 70% had between one and 10 diabetic canine patients, and 26% had 11 or more diabetic canine patients. Because West Highland White Terriers are one of the breeds predisposed to develop diabetes mellitus, it is important for owners to understand the signs and symptoms of the disease, the disease process, and treatments available.

The Pancreas

The pancreas, an elongated organ located near the beginning of the small intestine (i.e., adjacent to the duodenum), secretes substances into the intestine that are critical to normal digestion of food and into the bloodstream that are important in regulating blood glucose concentrations. The latter function of the pancreas is referred to as its endocrine role in the body. Consequently, we will focus our attention on the endocrine function of the pancreas.

The parts of the pancreas that have endocrine functions include clusters of cells called the "Islets of Langerhans" which can easily be recognized in microscopic examinations of the organ (***Figure 1***). The islets are made up of three major cell types (alpha, beta, and delta cells), each of which secretes specific hormones. The alpha cells secrete glucagon (which increases blood glucose levels), the beta cells secrete insulin (which lowers blood glucose levels), and the delta cells secrete somatostatin (which regulates secretion of other hormones).

Common Clinical Findings
Excessive Thirst
Frequent Urination
Weakness and Weight Loss
High Fasting Blood Glucose
Glucose in the Urine

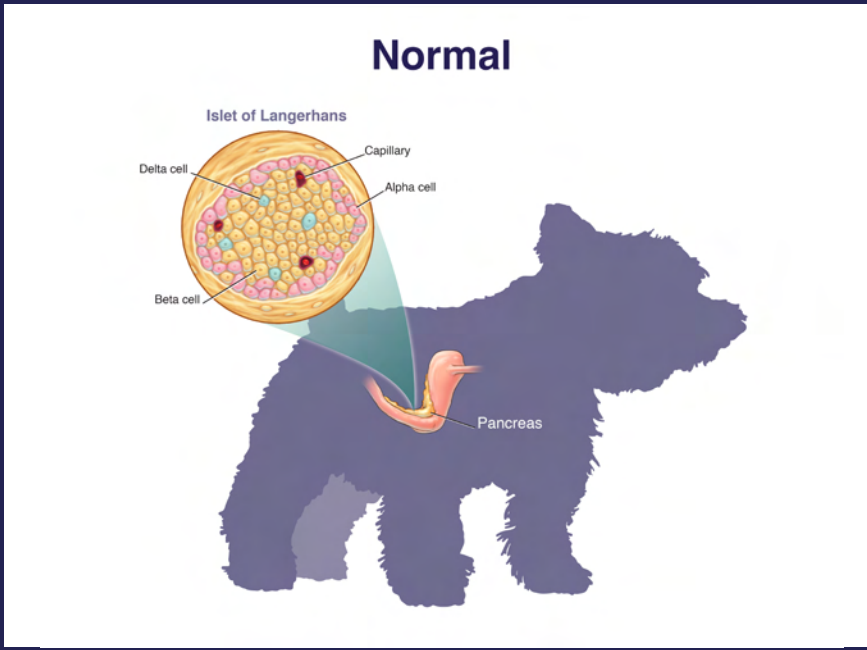

Figure 1 - In the normal dog, the pancreas contains specialized clusters of cells called Islets of Langerhans. These consist of alpha, delta and beta cells; beta cells are responsible for the synthesis of insulin.

Physiologic Role of Insulin

As you might have guessed, insulin and glucagon have opposing actions. To more easily understand these effects, let's consider what happens after a large meal, particularly one that is rich in carbohydrates. When a meal such as this is eaten, digestion of the food in the small interest releases glucose molecules. These glucose molecules are absorbed by the cells that line the intestine, after which they enter the blood stream. When the concentration of glucose in the blood increases, the beta cells in the pancreas secrete insulin into the blood. The insulin then interacts with specific receptor proteins on the surface of most cells in the body, like muscle and fat cells. As a result of insulin binding, these cells insert special glucose transporter ('channel') proteins in their membranes. These transporter proteins then allow glucose to enter the cells where it is metabolized to generate much of the energy the cell needs to function or, as occurs in muscle cells, to be stored in long chains as glycogen. Extra glucose molecules also can enter the cells in the liver where they can be stored as glycogen. The overall effect of the uptake, metabolism and storage of glucose from the blood is a decrease in the blood glucose concentration.

As the concentration of glucose in the blood decreases, the alpha cells in the pancreas respond by secreting glucagon. Glucagon exerts its effect on the liver to release the glucose that has been stored as glycogen or to synthesize new glucose molecules. As these glucose molecules enter the blood stream and increase the glucose concentration, the beta cells respond by increasing insulin secretion. In the normal person or animal, this interplay between insulin and glucagon result in blood glucose concentrations remaining within a fairly narrow normal range of values, typically between 70 and 110 mg/dl. As you know, the function of the kidneys is to remove wastes from the blood. To do this, the kidney acts as a filter. However, there are components of the blood that the body does not want to lose, and one of these is glucose. As a result, all of the glucose filtered from the blood is reabsorbed by cells in the kidney. When blood glucose concentrations are less than 180 mg/dl, essentially none of the glucose makes it into the urine. This is an extremely efficient way of maintaining blood glucose concentrations within the normal range.

What happens in diabetes mellitus?

In diabetes mellitus, there is either insufficient synthesis of insulin by the beta cells in the pancreas (Type I diabetes mellitus) or the insulin that is secreted cannot trigger the cells in the body to insert the transporter proteins into their membranes (Type II diabetes mellitus). In both cases, glucose molecules are unable to enter the cells to be metabolized or stored as glycogen. To compensate for the resulting low intracellular concentration of glucose, a metabolic process called glycogenolysis begins. As its name would suggest, glycogenolysis lyses the glycogen molecules, thereby making even more glucose available. The glucose molecules accumulate

“Type I diabetes mellitus is the most common form of the disease in dogs, and is caused by destruction of the pancreatic beta cells.”

in the circulation, resulting in blood concentrations much higher than 180 mg/dl (>400 mg/dl). This high blood level of glucose exceeds the amount the kidney can reabsorb, and glucose enters the urine. Consequently, in the absence of insulin, a paradox exists: glucose concentrations are high in the blood, low inside the cells, and lost into the urine.

When the glycogen stores are utilized, the body looks to other potential sources of energy. One of these involves lipolysis (lysis of fats). While this approach is initially beneficial, fat metabolism can result in the generation of substances called ketones, a decrease in the pH of the animal's blood (i.e., ketoacidosis), and eventually death. Diabetes mellitus, if unmanaged, can be life-threatening. It is another paradox of this disease – nutrients are available to cells in the circulation, but without insulin, the cells are starving. Starvation at the cellular level may be associated with increased appetite and eating (polyphagia). Consequently, dogs with long-term, poorly-controlled diabetes may actually waste away as body stores of calories are used up.

Type I Diabetes Mellitus

Type I diabetes mellitus is the most common form of the disease in dogs, and is caused by destruction of the pancreatic beta cells as the result of a combination of autoimmunity, genetics and environmental factors (***Figure 2***). Based on the evidence that dogs and people develop immune responses to pancreatic islet proteins and cells involved in immune reactions may destroy islet cells, many people have concluded that autoimmunity plays a key role in the development of diabetes. There also is evidence that pedigree dog breeds, including Australian Terriers, Samoyeds, Miniature Schnauzers, Westies and Cairn Terriers, have a higher risk of developing diabetes mellitus, whereas others (e.g., Boxer) appear to be far less likely to develop the disease. Consequently, genetic factors may be important in the development of the condition, much like the situation in human. As dogs and humans with this form of the disease require insulin injections to control their blood glucose concentrations, type I diabetes mellitus has been called “insulin-dependent diabetes.”

Although any dog can develop Type I diabetes mellitus, the disease typically affects dogs that are middle aged (6-9 years old) and intact bitches. The clinical signs commonly associated with Type I diabetes include polydypsia (increased thirst), polyuria (frequent urination), polyphagia (increased hunger), weakness, weight loss, increased susceptibility to infections (such as skin infections or urinary tract infections), depression and potentially loss of vision due to cataract formation.

Diagnosis of Type I Diabetes Mellitus

Although a veterinarian may presume that a dog with the clinical signs mentioned above (excess thirst, urination, appetite and weight loss) may have Type I diabetes mellitus, blood and

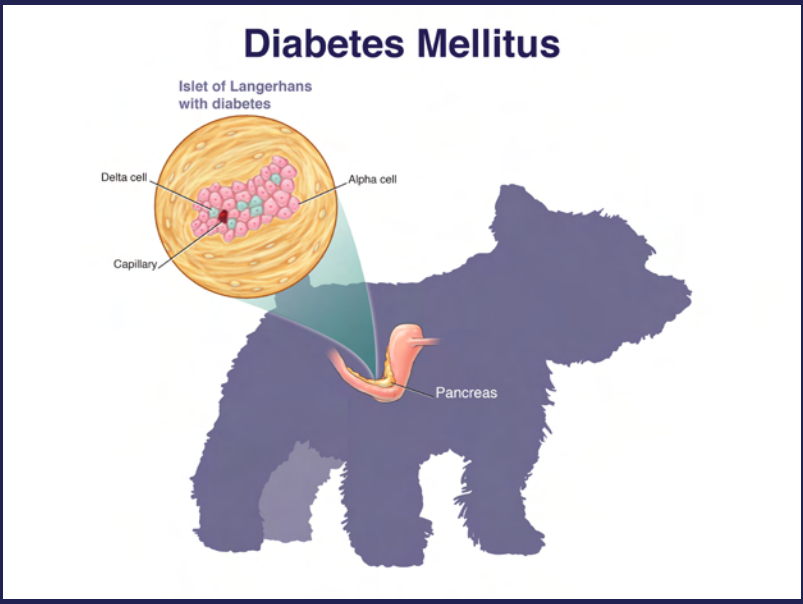

Figure 2 - In dogs with Type 1 diabetes, damage to the pancreas results in islets that are essentially devoid of functioning beta cells.

urine samples will need to be tested to make the diagnosis. It is critical that the correct diagnosis is made, as there are other diseases that could cause these same clinical signs. The laboratory tests that typically are performed are to detect hyperglycemia (high fasting blood glucose concentration) and glucosuria (glucose in the urine). Because blood glucose concentrations can increase substantially after a meal, the blood sample will need to be taken several hours after the dog's latest meal. There also may be other abnormalities identified in the blood, including some associated with high concentrations of ketones in the blood. Examples of these include high levels of cholesterol and serum enzymes leaking from cells in the liver. If the blood concentration of glucose is increased, the veterinarian will need to consider other possible conditions, most of which can be eliminated based on the dog's history and any current treatments. These include a recent history of administration of glucocorticoids or IV glucose, accidental exposure to ethylene glycol (anti-freeze), inflammation of the pancreas, or a pancreatic tumor that secretes glucagon.

Treatment of Type I Diabetes Mellitus

Treatment of dogs with Type I diabetes mellitus includes a few important goals, namely providing a sufficient amount of insulin (by injection) to adequately control blood glucose concentrations, preventing the development of glucosuria, minimizing the clinical signs of diabetes, and reducing the likelihood that long-term complications will develop. This requires tweaking the amount of insulin needed until the optimal results are obtain, a process that typically takes several weeks. During which time, the veterinarian will repeatedly monitor blood glucose concentrations, test the urine for the presence of glucose, and evaluate the dog's clinical signs. The goals will be to reduce the incidence of polydipsia, polyuria and ketonuria, maintain blood glucose concentrations between 60 and 160 mg/dl, and prevent the development of low blood glucose (hypoglycemia; <50 mg/dl).

Type II Diabetes Mellitus

This form of diabetes mellitus is much less common in dogs and will only be briefly discussed. In people, Type II diabetes is far more common, and is known as adult-onset or noninsulin-dependent diabetes. Rather than there being a lack of insulin, this form of diabetes occurs when the beta cells in the pancreas produce less than optimal amounts of insulin, these cells are slow in secreting it or the dog's tissues are resistant to its effects. Type II diabetes tends to occur in older obese dogs. While the exact cause is unknown, excess weight and inactivity appear to be important factors. While people with Type II diabetes can be treated with drugs that stimulate the remaining beta cells to increase their production of insulin, this therapy does not appear to work as well in dogs. As with Type I diabetes, if left undiagnosed, the results of Type II diabetes can be fatal. There is no current cure, although it can be prevented and managed by eating healthy, exercising, and maintaining a healthy weight.

Complications of Diabetes Mellitus

The two most commonly encountered complications of untreated or poorly treated diabetes in dogs involve the eye. One of these is the development of cataracts, a condition characterized by a cloudy appearance of the normally clear lens within the eye. Cataracts typically develop fairly rapidly as the excess glucose in the aqueous humor (fluid adjacent to the lens) diffuses into the lens where it is metabolized to two other sugar molecules that are then trapped within the lens. Because these two sugar molecules cannot leave the lens, they draw water from the aqueous humor into the lens, causing it to swell and become cloudy. In healthy dogs, the concentration of glucose in the aqueous humor never reaches the high concentrations that trigger this complication. This is yet another reason to administer insulin to dogs with Type I diabetes, as keeping glucose concentrations within normal limits will minimize the likelihood that cataracts will form.

The other complication of diabetes mellitus that affects the eye is glaucoma, a condition in which pressure within the eye increases. If the pressure becomes excessive, it will cause damage to the optic nerve that connects the retina to the area of the brain that is allocated to vision. Glaucoma can have many causes but it usually is caused by a narrowing or obstruction of an angle at the front of the eye beneath the cornea through which the aqueous humor normally flows out of the eye. Glaucoma can lead to intense ocular pain, decreased vision, and, in many cases, blindness.

Summary and Important Points

Diabetes mellitus is a relatively common metabolic disease in dogs, including West Highland White Terriers, but that fortunately is treatable with good success. The causes are unknown but include pancreatic disease, genetics and possible environmental factors. Common signs are increased thirst (polydipsia), increased urination (polyuria), and appetite (polyphagia). Blood and urine tests are used to identify the high concentrations of glucose in the blood and the presence of glucose in the urine. Treatment usually involves giving daily injections of insulin that are sufficient to meet daily metabolic needs and monitoring blood glucose concentrations. If left untreated, diabetes mellitus can cause ketoacidosis, coma, glaucoma, coma, and even death. Properly treated dogs can live relatively normal lives.

Current Research About Diabetes Mellitus

Due to the enormous impact that diabetes has in humans and animals, it is not surprising that there is a lot of research being performed in this area. We have chosen to feature three recent articles in this section that we believe cover topics of interest to dog owners. One of the articles summarizes the experiences of dog owners in treating their own animals with diabetes, one provides some interesting new data regarding the potential role of the immune system in the development of Type I diabetes in dogs, and the third indicates that dogs can be trained to help human diabetics avoid problems caused by hypoglycemia.

Aptekmann KP, Armstrong J, Coradini M, Rand J. Owner experiences in treating dogs and cats diagnosed with diabetes mellitus in the United States. J Am Anim Hosp Assoc. 2014 Jul-Aug;50(4):247-53.

A key factor in the success of treating animals with life-long disease conditions, such as diabetes mellitus, are the experiences of the people providing the treatments, in this case the dog owners themselves. This study was performed to summarize the experiences of a large number of owners of dogs with diabetes that were treated on a daily basis by the administration of insulin. In addition to other factors, the investigators were interested in the responses of the owners and their pets to the injections, how they monitored the success of treatment, how the owners' lifestyles were affected by this new responsibility, and how well their dogs' clinical signs were controlled. More than 800 dog owners participated in the study with nearly all of them administering insulin twice daily by injection. More than 60% of owners reported that their dog's clinical signs had improved or resolved entirely, that it was easy to give the injections, and that their daily schedule was affected very little by having to treat their dogs twice daily. Approximately half of the owners used more than one way to monitor the success of the treatment (e.g., measuring urine or blood glucose concentrations, and keeping track of water and food consumption). Approximately half of the owners reported that it was difficult to arrange care for their pets when they traveled. Finally, more than half of the owners reported that they felt more attached to their pet than they did before the diagnosis of diabetes was made.

Kim JH, Furrow E, Ritt MG, Utz PJ, Robinson WH, Yu L, Eckert A, Stuebner K, O'Brien TD, Steinman L, Modiano JF. Anti-Insulin Immune Responses Are Detectable in Dogs with Spontaneous Diabetes. PLoS One. 2016 Mar 31;11(3):e0152397.

Diabetes mellitus is a common disease in dogs worldwide, and is characterized by degeneration of the beta cells in the pancreas and dependence on exogenously administered insulin. At this time, the underlying causes of diabetes in dogs are incompletely understood. There are strong breed predispositions, suggesting that there may be genetic or heritable aspects of this disease that have been linked to alterations in various components of the dog's immune system, including the gene that encodes for insulin. Although autoantibodies directed against insulin and related proteins have been detected in dogs with diabetes, there is evidence that this disease is not exclusively an autoimmune condition. In this study, the investigators demonstrated that both cellular and humoral (i.e., antibody) responses directed against insulin were present in some diabetic dogs treated with exogenous insulin, suggesting that ways to induce tolerance to specific insulin-related antigens might be a way to improve the control of blood glucose levels in dogs with diabetes.

Hardin DS, Anderson W, Cattet J. Dogs can be successfully trained to alert to hypoglycemia samples from patients with Type 1 diabetes. Diabetes Ther. 2015. 6:509-517.

One of the most common and potentially devastating complications associated with insulin therapy is the development of hypoglycemia. This problem is particularly true in human patients with diabetes that inadvertently administer themselves an excessive amount of insulin. Episodes of hypoglycemia carry the risk of serious neurological and cardiovascular effects, and are of increased concern when the patient has lost the early warning symptoms of declining blood glucose levels. This study was performed to assess the ability of dogs trained to detect odors in human patients' perspiration associated with hypoglycemia. The results of this study indicate that properly trained dogs can successfully recognize and alert people to the presence of hypoglycemia using smell alone. This study provides a new avenue for future studies in which the optimal methods for training dogs for this important service to humans with diabetes.

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Cushing's Disease

Introduction and Overview

Cushing's disease is the term commonly used to identify a condition that results from the over-production of cortisol by the adrenal glands, two small glands located near the kidneys. Cortisol, a hormone that is important for regulating the metabolism of proteins, fats and carbohydrates, is produced by specialized cells comprising the outer or cortical portion of the adrenal glands. As a result, this condition also is called hypercortisolism (hyper = excessive, cortisolism = involving cortisol) or hyperadrenocorticism (hyper = excessive, adrenocorticism = involving the adrenal cortex). The term 'Cushing's Disease' often is used to describe this condition, which is named in honor of Harvey Cushing, an American neurosurgeon who first described the clinical syndrome in people in 1932. In his original publication, the underlying problem was a tumor in the pituitary gland in the brain that affected the adrenal glands and caused a variety of clinical signs and symptoms including high blood pressure, weight gain, fatigue, impaired immune function, and excessive deposition of fat on the sides of the face.

Cushing's disease typically occurs in middle-aged and older dogs of all breeds, with no predilection for either gender. The most common symptoms associated with the condition related to the urinary system include increased thirst (polydipsia) and urination (polyuria). Affected dogs also have changes in the musculoskeletal system, which include decreased muscle mass, muscle weakness, obesity, excessive fat on the neck and shoulders, a pot-bellied abdomen, and lack of energy. Skin manifestations of the condition include hair loss (alopecia), thin skin, bruising, hyperpigmentation, and white scaly patches on the elbows.

Pathogenesis of Cushing's Disease

Under normal conditions, cortisol production is indirectly controlled by a hormone, corticotropin-releasing hormone (CRH), released by a region of the brain called the hypothalamus. The hypothalamus releases this hormone under two circumstances. One is governed by the animal's diurnal rhythm, which is related to the normal sleep-wake cycle. Early in the morning, the hypothalamus releases CRH, which then stimulates the pituitary gland, which is located at the base of the brain, to release adrenocorticotropic hormone or ACTH into the blood, which then results in an increase in production of cortisol by the adrenal gland. As a result, blood levels of cortisol are highest in the morning, and these increased circulating concentrations of cortisol result in negative feedback on both the hypothalamus and the pituitary gland to reduce both CRH and ACTH. As a result, circulating concentrations of cortisol decrease and reach their lowest values at night. The other stimulus for increased cortisol secretion is stress, which again stimulates the hypothalamus to release CRH, which enhances ACTH production, and eventually increases cortisol production.

Cushing's disease occurs commonly in dogs, with more than 80% of cases being the result of a pituitary tumor called an adenoma that secretes ACTH. In dogs with pituitary adenomas, production of ACTH no longer responds to the negative feedback signal normally associated with cortisol production.

Common Clinical Findings
Middle-Aged and Older Dogs
Polydipsia
Polyuria
Obesity
Pot-Bellied Abdomen

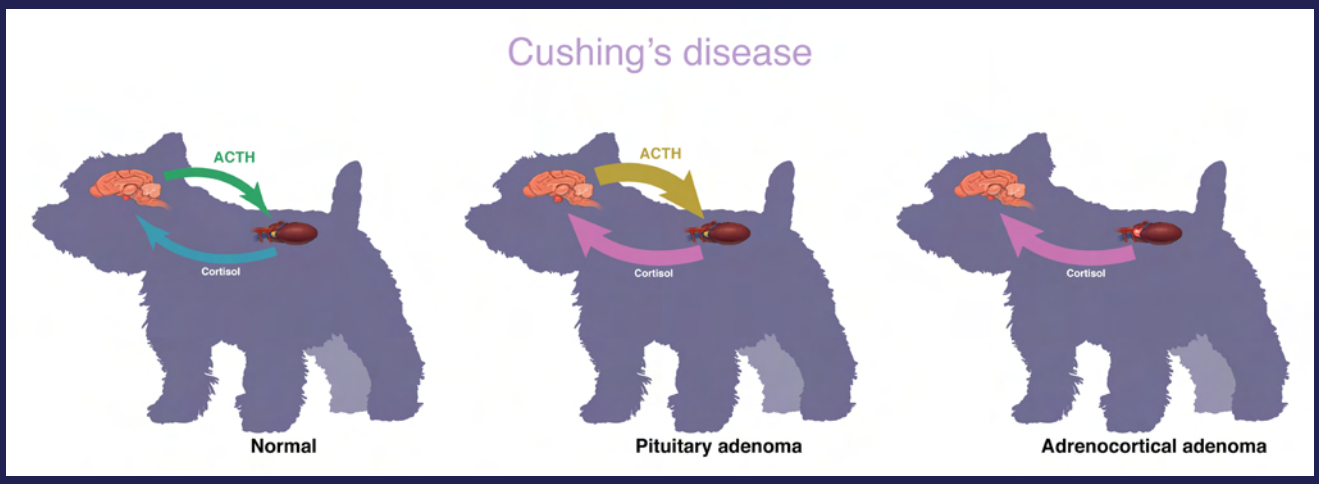

Figure 1 - This illustration depicts the normal interaction between the pituitary and adrenal glands, the effect of a pituitary adenoma on secretion of both ACTH and cortisol, and the effect of an adrenocortical adenoma on secretion of cortisol.

As a result, the cells in the adrenal cortex continue to secrete cortisol, resulting in hypercortisolism and Cushing's disease (***Figure 1***).

In a relatively small number of dogs, typically reported to be ~15% of cases, hypercortisolism occurs independent of ACTH secretion and is due to a cortisol-secreting tumor in the adrenal gland. In rare instances, the condition may occur secondary to chronic administration of corticosteroids used in the treatment of diseases caused by allergies, autoimmune or inflammatory responses, or neoplasia.

Clinical Signs and Symptoms of Cushing's Disease

Cortisol has important effects on metabolism of carbohydrates, proteins and fats. For example, it increases blood concentrations of glucose by inhibiting the uptake of glucose into cells and by stimulating the production of new glucose molecules by the liver. It also stimulates the degradation of protein and adipose tissue. When production of cortisol is excessive, as occurs in animals with Cushing's disease, the end result is very high blood concentrations of glucose, loss of glucose into the urine, which also occurs in dogs with diabetes mellitus, loss of structural proteins, muscle weakness and fatigue. For reasons that are unclear, some of the extra glucose is converted into fat and is deposited in the abdomen. Cortisol also interferes with kidney function, causing increased urination which in turn causes the animal to drink large amounts of water in order to replace what is lost in the urine.

Cushing's disease typically occurs in middle-aged and older dogs of all breeds, with no predilection for either gender. The most common symptoms associated with the condition related to the urinary system include increased thirst (polydipsia) and urination (polyuria). Affected dogs also have changes in the musculoskeletal system, which include decreased muscle mass, muscle weakness, obesity, excessive fat on the neck and shoulders, a pot-bellied abdomen, and lack of energy. Skin manifestations of the condition include hair loss (alopecia), thin skin, bruising, hyperpigmentation, and white scaly patches on the elbows.

Laboratory Diagnosis of Cushing's Disease

Based on the animal's history and physical examination findings, veterinarians suspecting that the underlying problem might be Cushing's disease measure cortisol concentrations in plasma or urine samples. It is important to note, however, that some dogs may have less obvious clinical signs and symptoms. Other findings that occur frequently in dogs with Cushing's disease include increased plasma activity of the alkaline phosphatase enzyme, high levels of lipids in the blood, and a reduced concentration of thyroxine (T4).

A diagnosis of hypercortisolism is based on a combination of the clinical signs, increased circulating concentrations of cortisol or the presence of cortisol in the urine, and a reduced sensitivity of the pituitary-adrenocortical system to the negative feedback effect that normally occurs in response to administration of a synthetic cortisol-like compound, referred to as a glucocorticoid. To perform this latter test, the veterinarian will measure blood concentrations of cortisol before, 4 and 8 hours after administering a synthetic glucocorticoid, such as dexamethasone. In healthy dogs, dexamethasone will exert a

negative feedback on the production of ACTH by the pituitary gland and significantly reduce blood concentrations of cortisol at the later time points. In contrast, an ACTH-producing pituitary tumor will not respond to the synthetic glucocorticoid and circulating cortisol concentrations will remain unchanged or be decreased only at the 4-hour time point. Because some dogs with illnesses unrelated to the adrenal glands may respond similarly, this test is not 100% reliable for making a diagnosis of hypercortisolism.

In many practices, additional emphasis is placed on the measurement of cortisol in the urine. This is because urine accumulates in the bladder before being voided, which minimizes the concern over potential fluctuations in concentrations of cortisol that may occur as the result of other stresses (e.g., a visit to the veterinarian's office). In most instances, urine concentrations of cortisol are related to those of creatinine and these measurements are made in urine samples collected on several consecutive days.

While it would appear logical that dogs with ACTH-producing pituitary tumors could easily be identified by measuring concentrations of ACTH in the circulation, this is not the case. This is because some dogs with hypercortisolism secondary to a pituitary tumor have normal circulating concentrations of ACTH. If, however, the hypercortisolism has developed as the result of a tumor in the adrenal cortex, this laboratory test is extremely important. Dogs with adrenocortical tumors will have extremely low circulating concentrations of ACTH, which makes it much easier to distinguish between hypercortisolism caused by a pituitary tumor or an adrenocortical tumor.

Treatment of Cushing's Disease

Many factors enter into the decision about how best to treat dogs with hypercortisolism. These include the underlying cause, other diseases that might exist (e.g., neoplasia), cost of treatment, and the client's preference. Fortunately, immediate treatment is not required in all dogs with hypercortisolism, particularly those exhibiting mild clinical signs.

When hypercortisolism is the result of a pituitary tumor, the condition can be treated either medically or surgically. Medical treatment of the condition involves administration of drugs that either reduce the production of ACTH by the pituitary tumor or the production of cortisol by the adrenal cortex. The most commonly used drug is trilostane, a synthetic steroid that inhibits one or more of the enzymes responsible for the synthesis of cortisol by cells in the adrenal cortex. The duration of effect (i.e., how long circulating concentrations of cortisol remain decreased) varies among dogs, which accounts for why once-daily administration is not effective in some dogs. As a result, the dosage may need to be increased or the drug administered more often to achieve the desired effect. Adjustments in the dose of trilostane are based on repeated assessments of clinical signs and the results of routine blood tests, such as determination of alkaline phosphatase concentrations. Typically improvements in the dog's status will be apparent in 7 to 10 days, but associated skin problems may require months to resolve.

The other drug that is commonly used to treat dogs with hypercortisolism is mitotane, a drug that causes destruction of the cells in the adrenal cortex that produce cortisol. To determine whether or not treatment with mitotane has achieved the desired results, the veterinarian will perform ACTH stimulation tests. The ultimate goal of treatment with mitotane is to reduce resting concentrations of cortisol and to see little, if any, increase after the administration of ACTH. When this has been achieved, it may be necessary to provide exogenous glucocorticoids during periods of high stress or illness.

Hypercortisolism in dogs with pituitary tumors also can be treated surgically or with radiation therapy. The surgical procedure is performed by cutting through the sphenoid bone beneath the pituitary gland and removing the tumor. Response to surgical treatment has been reported to be very good, and compares favorably with those reported for dogs treated medically as described above. The other approach involves the use of radiation therapy to reduce the size of the tumor. Outcomes with radiation therapy have been variable, with optimal responses occurring in dogs with small tumors.

When hypercortisolism is caused by a functional adrenocortical tumor, treatment is surgical removal of the tumor. If the entire tumor cannot be removed, mitotane can be administered to cause destruction of the tumor and associated adrenal cortical cells.

Current Research About Cushing's Disease

Cushing's disease affects about 100,000 dogs each year in the US. Because this condition also occurs in people, the approaches used to treat humans have been applied to dogs. While these approaches have markedly improved the prognosis in humans, questions remain about how best to treat the condition in dogs, how to improve the results obtained with surgical intervention, and how to more fully understand the effects of the disease. For these reasons, in this section we review three recent studies related to the most common form of the disease, namely pituitary-dependent hypercortisolism.

van Rijn SJ, Galac S, Tryfonidou MA, Hesselink JW, Penning LC, Kooistra HS, Meij BP. The Influence of Pituitary Size on Outcome After Transsphenoidal Hypophysectomy in a Large Cohort of Dogs with Pituitary-Dependent Hypercortisolism. J Vet Intern Med. 2016 Jul;30(4):989-95.

Surgical treatment of dogs with pituitary-dependent hypercortisolism consists of removal of the pituitary gland by a transsphenoidal approach, which is similar to the approach used in humans with the disease. Since the early 1990s, this surgery has been performed on dogs with this condition, with remission rates exceeding 80%. In earlier studies, one of the main prognostic factors for long-term remission in dogs was pituitary gland size. Consequently, the goal of this project was to further investigate the influence of pituitary gland size on outcome in a large number of dogs treated using this surgical approach over a 20-year period. To do this, the investigators determined survival times and recurrence rates for 306 dogs and related these variables to the pituitary gland size. Four weeks after surgery, 91% of dogs were alive and remission was confirmed in 92%. The median survival time was 781 days, median disease-free interval was 951 days. Over time, hypercortisolism recurred in 27% of dogs after a median period of 555 days. Dogs with recurrence had a significantly higher ratio of the area of the pituitary height to the area of the brain area. The survival time and disease-free interval of dogs with enlarged pituitary glands was significantly shorter than that of dogs with a nonenlarged pituitary gland. The size of the pituitary at the time of surgery significantly increased over the 20-year period. Although dogs with larger tumors have a less favorable prognosis, the outcome for dogs with larger tumors improved over time. These findings suggest that pituitary gland surgery remains an option for treatment of dogs with large tumors, and that success rates increase with increasing experience.

Fracassi F, Malerba E, Furlanello T, Caldin M. Urinary excretion of calcium and phosphate in dogs with pituitary-dependent hypercortisolism: case control study in 499 dogs. Vet Rec. 2015 Dec 19;177(24):625.

Pituitary-dependent hypercortisolism in dogs often is characterized by high circulating concentrations of phosphate. The goal of this study was to compare serum and urinary concentrations of phosphate and the degree to which phosphate and calcium are excreted into the urine in healthy dogs and 167 dogs with this disease. Serum concentrations of phosphate in dogs with pituitary-dependent hypercortisolism were significantly greater than those either in healthy dogs or in dogs with other diseases. Serum concentrations of calcium also were significantly higher in dogs with hypercortisolism than in dogs with other diseases. Dogs with hypercortisolism excreted less phosphate but more calcium than either healthy dogs or dogs with other diseases, whereas excretion of calcium was higher. These findings suggest that the high serum concentrations of phosphate in dogs with pituitary-dependent hypercortisolism are due, at least in part, to retention of phosphate by the kidneys.

Mamelak AN, Owen TJ, Bruyette D. Transsphenoidal surgery using a high definition video telescope for pituitary adenomas in dogs with pituitary dependent hypercortisolism: methods and results. Vet Surg. 2014 May;43(4):369-79.

Even though surgical removal of pituitary adenomas has been performed successfully in dogs for many years, it has not been used widely because it is both technically challenging and expensive. The two most commonly encountered difficulties are accurately defining the appropriate borders of the basisphenoid bone and illuminating the surgical site. To address these problems, these investigators used a new high definition video telescope to remove tumors from 26 dogs with pituitary dependent hypercortisolism. They modified the traditional surgical approach, observed the procedure using a high definition video telescope, and improved their ability to localize the site by drilling pilot holes in the basisphenoid bone followed by computed tomography. Overall, the mortality rate was 19%, with 0 deaths occurring in the last 16 dogs. The investigators reported sustained tumor remission and normalization of laboratory findings in 20/21 (95%) dogs at 1-year follow-up. They concluded that the modified trans-oral approach is a safe and effective strategy for long-term remission of hypercortisolism occurring secondary to pituitary adenomas.

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Fracassi F, Malerba E, Furlanello T, Caldin M. Urinary excretion of calcium and phosphate in dogs with pituitary-dependent hypercortisolism: case control study in 499 dogs. Vet Rec. 2015 Dec 19;177(24):625.

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Mamelak AN, Owen TJ, Bruyette D. Transsphenoidal surgery using a high definition video telescope for pituitary adenomas in dogs with pituitary dependent hypercortisolism: methods and results. Vet Surg. 2014 May;43(4):369-79.

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Inflammatory Bowel Disease (IBD)

Inflammatory bowel disease is an immunerelated disorder in which the intestines are chronically or intermittently inflamed. A synonym for inflammatory bowel disease that is abbreviated the same way is 'irritable bowel disease'. Affected dogs may be presented with a history of vomiting, diarrhea, weight loss or a combination of these signs. There is a great deal of variation in the severity, duration, response to therapy, and long-term effects of IBD among dogs.

While IBD exists in different forms, the most common is lymphocyticplasmacytic enteritis (***Figure 1***), which means that the inflammation of the small intestine (enteritis) is associated with increased numbers of two white blood types that are linked to the immune system (i.e., lymphocytes and plasma cells). These are the primary immune cell types that are identified in biopsies of the affected sections of the small intestine. Lymphocytes are the cells that detect and kill viruses, fungi, and even tumor cells. When they are exposed to infectious agents, including bacteria and some complex molecules like foreign proteins and complex carbohydrates, they can transform into cells that produce antibodies. These cells are called plasma cells. Lymphocytes also interact with other immune and inflammatory cells to create the body's active defense system that helps protect people, dogs, and other animals against disease.

IBD also can affect other parts of the dog's gastrointestinal tract. For example, the condition known as lymphocyticplasmacytic colitis (***Figure 2***) primarily affects the colon (a portion of the dog's large intestine). There also is a rare condition characterized by inflammation caused by a different type of white blood cell. This condition, called granulomatous enteritis/gastritis, affects the small intestines and/or stomach (***Figure 3***).

Canine IBD, especially granulomatous enteritis/gastritis, is similar in some respects to the human disorder, known as Crohn's disease. Humans with Crohn's disease experience many of the same symptoms as dogs with IBD and are often treated in the same manner. In fact, much of our veterinary knowledge of IBD comes from research on Crohn's disease using dogs and other animals with spontaneous and experimental disease as translational animal models. Because Crohn's disease is thought to have a genetic component, veterinary researchers are examining the same possibility in dogs.

How does a dog develop IBD?

Over the past few decades, several theories have been proposed regarding the cause of IBD. These include vascular abnormalities that disrupt the function of the intestines, overproduction of mucus, an overactive gut, an infectious agent, or a dog with the equivalent of 'hyperactivity disorder'. Currently, it is understood that IBD is an immune-related disorder, with strong evidence for a genetic predisposition in some breeds and alterations in the bacterial flora in the intestines, otherwise known as the microbiome. For example, single nucleotide polymorphisms have been identified in genes that encode for specific innate immune factors in German Shepherds (Allenspach et al, 2010). There also is evidence for a shift in the bacterial populations in dogs with intestinal inflammation from gram-positive to gram-negative organisms, although at this point it is unknown if these changes are the cause or the result of the inflammation.

In a healthy dog, the small and large intestines, which includes the colon, have their own local part of the immune system. This purpose of the immune system in the gastrointestinal tract is to protect the body against viruses, bacteria or other antigens (unwelcome outsider proteins and complex molecules) that may be consumed in the dog's food and water. The healthy

Common Clinical Findings
Vomiting
Diarrhea
Weight Loss
Reduced Serum Cobalamin

intestinal tract is inhabited by a wide range of bacteria, many of which are important for the health of the dog. These 'resident' bacteria, otherwise known as normal flora, help restrict the other microbes and antigens to the lumen of the intestine; in essence, the resident bacteria serve as a barrier against the unwanted microbes and antigens from gaining access to the circulation. Under normal circumstances, the intestinal immune system ignores the resident bacteria, allowing them to do their job.

However, in animals with IBD, a problem has developed in one of three areas: the local intestinal immune system or its regulation (the body may be attacking itself or the resident bacteria), the integrity of the intestines themselves (through some type of injury), or the balance of normal flora in the intestines has been disrupted. Any of these problems can trigger an unwanted immune response that becomes excessive and selfperpetuating.

What are the clinical signs associated with IBD?

The most prominent clinical signs in IBD are vomiting, diarrhea and weight loss. In general, dogs in which the small intestine is affected have large volume diarrhea, vomiting and weight loss, whereas those with involved of the large intestine are constipated, strain or frequently defecate small amounts of feces containing blood and mucus. Often the clinical signs seem to come and go randomly, particularly in the early stages of the disease. During that time, affected dogs may appear perfectly healthy except for a change in stool consistency and frequency. A common effect of gastrointestinal inflammation is failure to absorb cobalamin (vitamin B12), a vitamin that has an important role in many biochemical reactions. Consequently, serum concentrations of cobalamin often are used to characterize the severity of the disease process. As cobalamin is absorbed in a specific segment of the small intestine, abnormal serum concentrations of cobalamin also help to localize the disease.

If the disease is undiagnosed or left untreated, some dogs may lose weight, and develop vitamin and mineral deficiencies that manifest as malnutrition. Another long-term problem that can occur is lymphangiectasia (dilation of lymphatic vessels), which can eventually result significant protein loss and the development of tissue masses in the affected area.

How is IBD diagnosed?

The diagnosis of IBD is made by eliminating other possible causes for the dog's clinical problems. Because similar clinical signs (vomiting and diarrhea) occur with intestinal parasites, food allergies, dietary changes, stresses associated with

Figure 1 - The most common form of inflammatory bowel disease affects the small intestine (enteritis).

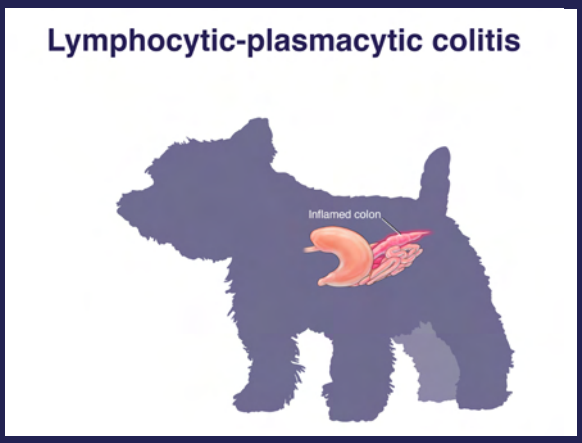

Figure 2 - This form of inflammatory bowel disease primarily affects the colon (colitis).

Figure 3 - This rare form of inflammatory bowel disease affects the small intestine and or stomach (enteritis and gastritis).

moving/traveling/boarding, and even changes in household occupants (like the arrival of new babies), these must be ruled out first using a battery of diagnostic tests. For example, a fecal test will be performed to help rule out the potential role of parasites, such as Giardia. Blood work will be performed, and may reveal an increased population of immunerelated cells, indicating inflammation. Abdominal ultrasound and xrays, taken either with or without a concurrent barium enema, may provide information about the status of the intestine. While both approaches may reveal other abnormalities, neither is very helpful in making a diagnosis of IBD, but may reveal other problems.

An important diagnostic test used to diagnose IBD is a thorough examination of the intestines with a flexible videoendoscope. A videoendoscope is a long cable with a camera on one end and a viewing port on the other. The camera-end of the videoendoscope is passed into the dog's gastrointestinal tract to allow the veterinarian to view the tissue lining the inside of the intestine and to take a biopsy, if necessary. In a 2015 study, Slovak and colleagues developed and prospectively validated an endoscopic scoring system for veterinarians to use to assess the severity of disease in dogs with IBD.

Having identified inflamed areas such as this, the veterinarian can obtain small samples of the tissue using a special biopsy instrument that is passed through the length of the videoendoscope and controlled from the outside. This procedure requires sedation, anesthesia, and is invasive, time-consuming and can be expensive. The biopsy samples are placed in a tissue fixative and prepared for microscopic examination by a veterinary pathologist, who will determine if they contain an excessive number of immune cells. It is important for the pathologist to have access to several biopsy specimens, as the inflammatory response either may be localized or diffuse. If the microscopic findings do not correlate with the dog's clinical signs and other findings, a full-thickness intestinal biopsy may be obtained during more invasive exploratory abdominal surgery. This approach allows the pathologist to more fully evaluate the intestine for changes in the small intestinal villi or mucus and goblet cells in the large intestine. For some affected dogs, this is the only way a definitive diagnosis of IBD can be made.

A major differential diagnosis in dogs with some of these signs is a specific cancer affecting the intestine called malignant lymphoma. Making this diagnosis requires collaboration between the clinical veterinarian and a skilled pathologist, as the most common features of this neoplastic disease is the presence of an increased number of abnormal lymphocytes in the biopsy tissue. A major differentiating feature of IBD is the presence of mixed populations of normal lymphocytes, plasma cells, and sometimes cells like neutrophils and eosinophils (Craven, et al, 2004). If there is any doubt about the diagnosis, it is an excellent idea to obtain a second opinion from another veterinary pathologist.

A veterinarian may also used the canine IBD activity index to "score" a patient's clinical signs and determine the severity of the disease (Jergens 2004; Jergens et al, 2003, 2010). Using this approach, the veterinarian assigns a number from 1 to 3 for each of six clinical signs: attitude/activity, appetite, vomiting, stool consistency, stool frequency and weight loss. The total score is used to determine if the disease is considered clinically insignificant, mild, moderate or severe. This index is based on similar approaches designed to quantify Crohn's disease in humans and can be used to assess a patient's progress with treatment.

Although routine blood tests typically are not very helpful in making a definitive diagnosis of IBD, the low serum protein and cholesterol concentrations that typically are measured in dogs with IBD provide evidence of a protein-losing intestinal abnormality. While this is not a way to definitively diagnose IBD, this is certainly one of the major reasons routine bloodwork is performed in patients with chronic gastrointestinal signs. Other abnormalities that may be identified in a small number of dogs with IBD are decreased numbers of circulating platelets; this abnormality was present in 2.5% of affected dogs in one study (Ridgway, et al, 2001). Treatment of these dogs for IBD resolved the low platelet count. In another case report, two dogs were identified with anemia, presumably due to blood loss through the gastrointestinal tract (Ristic, et al, 2002).

Treatment of IBD

Unfortunately, relatively little is known about the effectiveness of particular treatments for IBD. As a result, treatment is based on empirical evidence and the clinical experience of the veterinarian. Treatment of IBD is usually multifaceted and will likely include a combination of diet changes, antibiotics and immunosuppressive drugs, including the use of corticosteroids such as prednisone. Management of dogs with IBD using medications alone is not recommended and usually is of limited value.

Dietary changes: One of the most important components of treating a dog with IBD is to change the dog's diet. This can be done by switching to a completely different diet, to reduce exposure to certain antigens that might be present in the current feed. Similarly, commercial diets may be fed that contain hydrolyzed proteins that are smaller than typical proteins so as not to be recognized as antigens. Many veterinarians recommend feeding a highly digestible, rice-based diet that contains readily digestible fats and restricted amounts of fiber. Other dietary changes that can be made include altering the

relative levels of omega3 and omega6 fatty acids (to reduce inflammation), and feeding prebiotics, such as inulin, or probiotics, such as Lactobacillus. The positive results obtained in recent studies in which dietary modifications were made in dogs with lymphocyticplasmacytic enteritis underscores the importance of restricting exposure to antigens; in those studies, more than 60% of dogs responded positively and many did not require prolonged treatment with immunosuppressive drugs (Mandigers et al, 2010; Luckschander, et al, 2006).

Antibiotics: Antibiotics are administered to dogs with IBD in the hopes of reducing the amount of bacterial antigens present in the intestinal lumen and to control any bacterial overgrowth that might exist. Regardless, the aim is to reduce the intestinal immune response and local inflammation that are associated with IBD. The most commonly used antibiotics are tylosin or metronidazole, which in addition to its antibacterial effects also may help modulate the immune response. The beneficial responses that occur in some dogs with antibiotic therapy strongly suggest that these animals have what is called antibiotic-responsive enteropathy.

Immunosuppressive drugs: Based on the apparent role played by the immune system in the development of IBD, corticosteroids are given to suppress this response. Unfortunately, administration of these drugs is associated with a variety of ill effects, including gastric ulcers, increased appetite, increased urination, obesity, muscle weakness, and development of diabetes. Consequently, veterinarians are interested in pharmacologic agents that modulate the immune system, but cause fewer side effects. Because similar problems occur in human IBD patients administered corticosteroids, a relatively new drug called budesonide has been developed which is as effective as another commonly used corticosteroid, prednisone. In a recent clinical study comparing budesonide and prednisone in 40 client-owned dogs, Dye et al (2013) reported that both drugs resulted in similar remission rates (>75%) but the frequency of adverse effects also was similar between the groups.

If the response to corticosteroid therapy is poor, many veterinarians also use azathioprine, cyclosporine A, and/or mycophenolate mofetil, immunosuppressive drugs sometimes used to treat autoimmune diseases and cancer. The most common side effect of treatment with azathioprine is bone marrow suppression, whereas gastrointestinal side effects tend to occur with the use of cyclosporine A and mycophenolate mofetil. In one study, Allenspach and coworkers (2006) administered cyclosporine A to 14 dogs that had not responded well to corticosteroid therapy, and reported concurrent improvements in clinical signs in 12 dogs and a decrease in the number of lymphocytes in intestinal biopsies obtained from these animals.

Cobalamin supplementation: Human patients with chronic gastrointestinal diseases often require monthly injections of vitamin B12 to address the low circulating concentrations of this vitamin, and a similar situation exists in dogs with chronic enteritis, such as IBD. In a 2016 study, Toresson and colleagues studied 51 dogs with chronic enteritis and low serum cobalamin concentrations, and reported that oral administration of cobalamin effectively normalized the concentrations. While these results are promising, the authors suggested that more in-depth studies need to be performed before oral supplementation can be recommended as part of the routine treatment for affected dogs.

It is critical for owners of dogs with IBD to realize that managing this disease requires a lifelong commitment. The prognosis for a dog with IBD depends on the severity of the disease and the progression at the time of diagnosis. While a change in diet and close monitoring of the dog may be all that's needed to manage many affected dogs, for others the situation may be quite different. Therefore, it is important for owners to be aware that this is a disease that is unable to be cured, instead it can be managed long-term, with the goal of achieving remission.

Current Research About Inflammatory Bowel Disease

Because IBD occurs in a variety of breeds, including Yorkshire and Soft-coated Wheaten Terriers, the disease may be of increased interest to Westie owners. In this section, we summarize the results of two recent studies about this important disease.

Pérez-Merino EM, Usón-Casaús, JM, Zaragoza-Bayle C, et al. Safety and efficacy of allogeneic adipose tissue-derived mesenchymal stem cells for treatment of dogs with inflammatory bowel disease: Clinical and laboratory outcomes. The Vet J 2015. 206:385-390.

There is a lot of interest in using stem cells in the treatment of different diseases. One of the reasons for considering them as a possible treatment for IBD is that stem cells have been shown to exert anti-inflammatory and immune system modulatory effects in different studies. In this study, adult stem cells called derived from adipose tissue were tested for their safety and feasibility of use in 11 dogs with IBD. The dogs were administered the stem cells IV and their responses were summarized 6 weeks later. None of the dogs reacted adversely to the stem cells, and there was evidence of clinical improvement in 9 of the 11 dogs, including an increase in serum cobalamin. The investigators concluded that the stem cells were well tolerated and appeared to produce clinical benefits with severe IBD.

Rossi G, Pengo G, Caldin M, et al. Comparison of microbiological, histological, and immunomodulatory parameters in response to treatment with either combination therapy with prednisone and metronidazole or probiotic VSL#3 strains in dogs with idiopathic inflammatory bowel disease. PLoS One 9(4): 1-13, 2014.

Based on the alterations in the bacterial populations that exist in the gastrointestinal tracts of dogs with IBD, there is a lot of interest in the potential use of probiotics in the treatment of dogs affected with this disease. This study was performed to compare the responses of dogs with IBD to treatment with either a commonly used combination therapy (prednisone and metronidazole) or probiotic strains (VSL#3). In this study, 20 dogs with IBD were randomly assigned to each treatment group and then monitored for 2 months during treatment and 1 month later. The dogs receiving the probiotic had improved clinical scores and reduced evidence of lymphocyte infiltration into the intestine when compared to the dogs receiving the combination therapy. This initial study provides the bases for larger clinical trials to evaluate the effectiveness of VSL#3 in dogs with IBD.

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Copper Toxicity in the Canine Liver

Stephanie Shrader, DVM and John Robertson, VMD, PhD

Introduction

The 19th century American philosopher, William James, once said, "Is life worth living? It all depends on the liver." And he was right. The liver is a vital organ that performs more than 1000 biological functions, the most important of which include: protein synthesis, detoxification, glycogen storage, hormone production, red blood cell decomposition and the production of bile. The liver is a major organ involved in digestion of food and distribution of nutrients (carbohydrates, fats, and proteins) to the cells in the body. Consequently, liver disease can reduce or eliminate one or more of these functions – most of which are critical to life. While there are many disease processes that can affect the liver, this chapter will focus on copper toxicity and its effect on hepatic function. First, we will review how copper is involved in daily biological functions and the dog's dietary needs, and then will discuss the pathophysiology, clinical signs and treatment of copper toxicity.

Copper's Role in the Body

Copper is an important trace mineral that plays a role in a variety of metabolic processes. Its main function is to act as a cofactor for enzymes, meaning that by binding to an enzyme, copper makes it possible for the enzyme to properly carry out its intended biological activities. Below are some of the processes in which copper is a key player:

Energy Production (ATP Synthesis): To understand how copper is involved in the synthesis of energy by cells, it first is important to recognize where energy is produced in the cell and in what form. Cells contain small structures called mitochondria that serve as powerhouses for the cell. The mitochondria contain enzymes that convert specific breakdown products of sugars, fats and proteins into high-energy compounds called ATP. ATP then is used to power a variety of cellular functions. One of the enzymes involved in this process, cytochrome c, is present in one of the membranes that comprise the mitochondria. This enzyme is part of a series of proteins whose function is to pump hydrogen ions across the membrane. When the hydrogen ions flow back across the membrane, they drive a special enzyme that synthesizes ATP. Because copper is a critical component of cytochrome c, acute copper deficiency (usually due to a lack of copper in the diet) decreases the ability of cytochrome c to carry out its function, thereby reducing ATP production. As you might expect, a reduction in ATP would result acutely in fatigue and impaired brain function, and long-standing copper deficiency can be life-threatening. ***Figure 1*** depicts cytochrome c oxidase and its role within the processes that produce energy for cells.

Elimination of Free Radicals: To appreciate the role that copper plays in preventing cellular membrane damage by 'free radicals', it is important to understand what they are and where they arise. During the cell's normal metabolic processes, compounds are derived from oxygen molecules that are used by the cell during the production of energy. These compounds, called either reactive oxygen molecules, peroxide free radicals are simply free radicals, have the ability to damage cellular membranes. To prevent these potentially damaging effects of the free radicals, cells make an enzyme called superoxide dismutase (SOD) that removes the free radicals and turns them into compounds that have no damaging capabilities. This is often referred to as the 'antioxidant' effect of SOD. The enzyme SOD depends on copper being present in order to function as an antioxidant. In fact, copper (along with zinc) serves as a critical cofactor for SOD, allowing it to prevent the effects of the free radicals. ***Figure 2*** depicts how the copper-dependent enzyme SOD functions to prevent oxidative damage in the body.

Common Clinical Findings
Loss of Appetite
Abdominal Pain and Vomiting
Jaundice
Increased Liver Enzymes in Blood

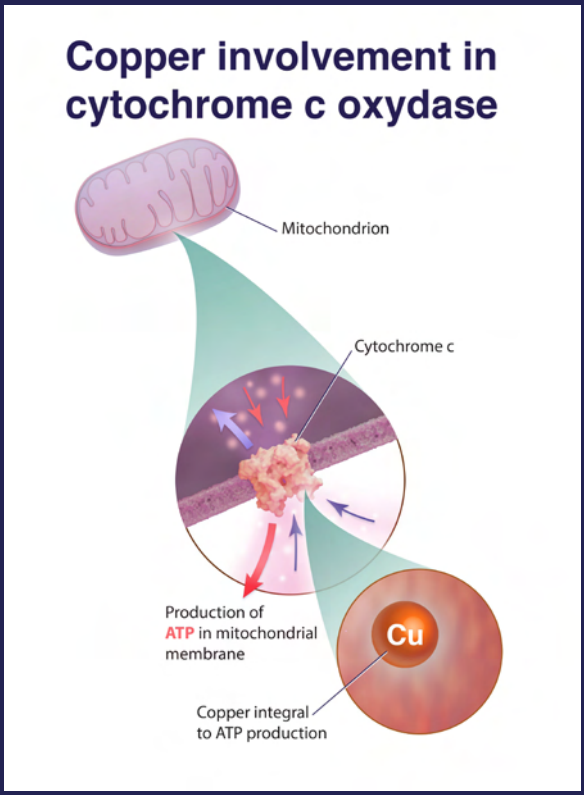

Figure 1 - An illustration depicting the central role of copper in the production of ATP by cytochrome c in mitochondria.

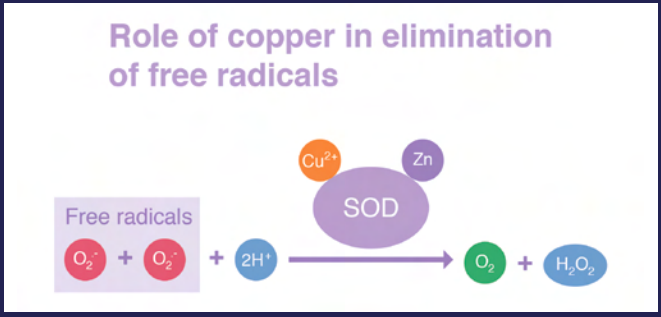

Figure 2 - A graphical representation of the elimination of free radicals by the enzyme superoxide dismutase (SOD).

The Role of Copper in Facilitating the Uptake of Iron

One of the most important chemical elements in the body is iron. For example, iron is a key component of the heme group that allows hemoglobin in the blood to bind and carry oxygen from the lungs to the tissues. Iron also is a component of myoglobin, a protein in skeletal muscle that binds oxygen and makes it available to the muscle cells when needed. Iron also participates in DNA synthesis and cell division, maintaining the immune system, and in the function of neurotransmitters. Copper plays an important role in the uptake of iron by the body, by serving as a component of ceruloplasmin, a transport protein in blood serum, that also functions as an enzyme for catalyzing the oxidation of minerals such as iron. This oxidation process allows iron to bind to its transport protein (transferrin) and to be distributed to tissues in the body. Both copper deficiency and hepatic disease can lead to the same outcome – iron deficiency. Without copper, ceruloplasmin cannot be synthesized by the liver, and without a healthy liver, synthesis of plasma proteins will be decreased.

Copper Plays a Key Role in Pigmentation

Copper is a cofactor for another enzyme called tyrosinase, the enzyme that catalyzes the synthesis of melanin, the primary protective pigment in skin. Tyrosinase in melanocytes converts the amino acid tyrosine to melanin. Consequently, if the tyrosinase enzyme is lacking or nonfunctional, the end result is albinism, an inherited recessive genetic condition. There is a rare genetic disorder in people called Menkes Disease in which copper is poorly distributed to the body's cells; one of the findings in this disease is sparse, kinky hair, although the effects on the nervous system are far more critical.

In summary, copper directly or indirectly controls many important functions in the body. Too little copper may lead to a loss of key activities such as the control of free radical damage, loss of immune functions, and impairment of iron transport and function. However, too much copper is also bad and is described more fully below.

Copper in the Diet

The National Research Council provides recommendations to the pet food nutrient industry about the dog's daily requirements for different elements, including copper. The major dog food companies have spent millions of dollars formulating foods that contain the correct ratios of nutrients for growth, maintenance, or even for dogs suffering from disease. Therefore, if your Westie is fed one of these commercial diets, it is getting the proper amount of nutrition. With that said, we have read some conflicting reports stating that many dog foods provide excess copper. A quick perusal down the dog food aisle and examination of the

nutrition labels was fruitless; the copper content is often not listed. We were also unable to determine the copper content of some commercially available dog foods by searching company websites. If you are interested in how much copper is in your dog food and the information is not provided on the label, do not hesitate to contact the company. They are usually more than happy to provide nutritional information. Dogs that are fed home-made rations run the risk of developing nutrient imbalances and associated disease processes. Some owners who formulate these homemade diets may not properly balance nutrients. It is important to discuss diet and dietary change with your veterinarian, whether you are using a commercial diet or one you make at home.

Dietary sources of copper include fish, some mollusks, cashews, sesame seeds, liver, legumes (beans), raisins (not especially good for dogs), cocoa (definitely a no-no for dogs), olives, and avocados (another no-no). Copper absorption occurs throughout the intestinal tract, but as with most other nutrients, the majority of the absorption occurs in the small intestine. Once absorbed, copper is stored mainly in the liver, with lesser amounts being stored in muscle, kidneys, brain, and heart. Hepatic concentrations of copper reflect an animal's intake and copper status. In healthy dogs, if amounts of copper are excessive, it is normally excreted in the bile.

Copper Toxicity – Pathology and Clinical Signs

Accumulation of toxic levels of copper in the liver is a heritable trait that can be present in many animals, including dogs. The inherited problem is either an inability to properly metabolize copper or the result of a copper storage disease. The end result is the same - chronic liver failure. Most research studies list the Bedlington Terrier as the most susceptible dog breed, but other breeds predisposed to copper toxicity include the West Highland White Terrier, Skye Terrier, Doberman Pinscher, Labrador Retriever, Keeshond, and American Cocker Spaniel (Dodds, 2011). Healthy dogs have a mean copper concentration in the liver of 200-400 ppm on a dry weight basis. In contrast, concentrations exceeding 2000 ppm are considered toxic; dogs with copper toxicosis can have copper concentrations as high as 10,000 ppm.

Dogs with this heritable trait start to accumulate copper early in life and show no clinical signs at first. During this early stage, the copper concentration in the liver can quickly reach a concentration of 1500 ppm, a level bordering on toxicity. If the veterinarian suspects copper toxicosis due to clinical signs of liver failure, it may be advisable to obtain a surgical biopsy of the liver. A histological preparation of biopsied tissue (stained with rhodanine and hematoxylin) would to show copper deposition. ***Figures 3 and 4*** show copper granules stained red-brown by the rhodanine stain in the liver from two dogs with copper toxicosis.

In the second stage of the disease, copper levels will continue to increase to values approaching 2000 ppm and there will be obvious microscopic evidence of hepatitis (liver inflammation, scarring and cell loss). Blood work often reveals increased circulating activities to two liver enzymes, alanine

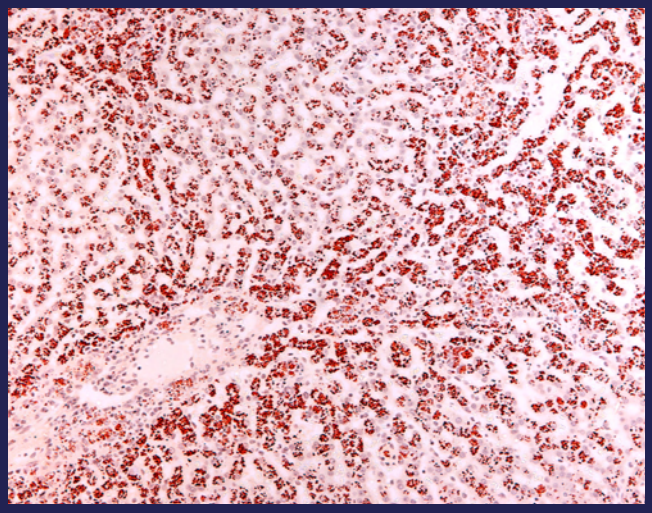

Figure 3 - A low power magnification of the liver of a dog with copper toxicity. The red pigmented granules are evidence of copper deposition. (Image courtesy of Dr. Susan Haywood, School of Veterinary Science, University of Liverpool)

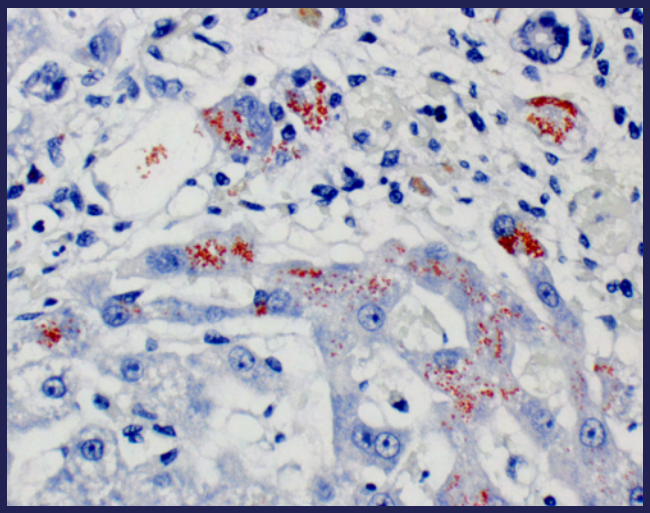

Figure 4 - A high power magnification of the liver of a dog with copper toxicity. The red pigmented granules within the cells are evidence of copper deposition. (Image courtesy of Dr. Cathy Brown, College of Veterinary Medicine, University of Georgia)

aminotransferase (ALT) and alkaline phosphatase (ALKP), as well as alterations in bilirubin, albumin and the number of red blood cells; all of these changes are due to decreased liver function. As copper concentrations exceed 2000 ppm, the liver is no longer able to function and portions become necrotic (dead). An animal at this stage may present with loss of appetite, depression, abdominal pain, vomiting, increased thirst and urination, jaundice, and weight loss. Unfortunately, these clinical signs may be seen with many other diseases as well, so your veterinarian will have to take a thorough history and run some laboratory tests to properly diagnose copper toxicosis. As noted above, it may be necessary to do a surgical biopsy of the liver to make a definitive diagnosis of copper toxicity.

Treatment Options

The goals of treatment for copper toxicity in dogs are:

- To reduce further absorption of copper from the gastrointestinal tract
- To promote copper excretion
- To preserve liver function and encourage liver healing

This can be achieved by feeding a diet low in copper, combined with supplements and medications that reduce copper absorption and enhance its secretion (Filippich, 2009). The first step is a dietary change. Your veterinarian will either prescribe or help you formulate a diet that is low in copper. Do not do this yourself as it can lead to other nutrient deficiencies/toxicities!

Simultaneously, the veterinarian may decide to decrease intestinal absorption of copper by the oral administration of zinc, an element that competes with copper and similar elements in the diet. The daily dosage of zinc must be controlled very closely as providing excessive amounts of zinc can cause serious gastrointestinal upset and hemolytic anemia if zinc toxicosis occurs. Your veterinarian will prescribe an appropriate zinc supplement for you to use.

In addition to changes in the diet and supplementation with minerals, your veterinarian may also prescribe a chelating drug, such as d-penicillamine, a substance that forms complex molecules with certain metal ions, thereby inactivating the ions so that they cannot react detrimentally with other chemicals to produce precipitates. Once the chelating drug binds to copper, the complex that is formed can be excreted in the urine. Dogs being treated for copper toxicosis should be examined on a regular basis by the veterinarian. These examinations will include performing the appropriate blood work, to be sure that hepatic function is returning to normal and that there are no adverse reactions to the medications.

The liver, as an organ, has a lot of 'reserve capacity" and the ability to heal by regeneration of tissue. In response to a reasonable amount of damage, cells may be quickly replaced (within hours to days). However, if there is a lot of damage to the blood supply or bile channels, and/or a lot of scar formation, healing does not proceed well. Chronic copper toxicity is a disease that can cause a lot of liver scarring and severely affected dogs are unlikely to regain normal liver function. These dogs may have continued problems with digestion, maintaining body condition, susceptibility to infections and decreased immunity. Because the liver synthesizes blood clotting proteins, some affected dogs may develop clotting abnormalities. It is very important to get an accurate diagnosis of copper toxicity in early stages of the disease to prevent significant (and often permanent) liver damage.

One final note: It is currently thought that most cases of copper toxicity are due to inherited defects in copper metabolism. Affected dogs should not be bred so that this defect is not passed to future generations.

Current Research About Copper Toxicity in the Canine Liver

There has been a lot of interest in copper-associated liver disease since it was first reported to occur in 1975. Because of its linkage to inherited alterations in copper metabolism, there has been recent work on the genetics of the condition and the potential to use this disease as a model for similar disorders in people, most notably neurological conditions known as Menkes and Wilson diseases. Of equal importance, however, has been some recent work on the use of D-penicillamine to bind (chelate) copper and remove it from the body. For these reasons, in this section we review two recent studies related to the genetics of copper metabolism disorders in dogs and one study about D-penicillamine.

Langlois DK, Lehner AF, Buchweitz JP, et al. Pharmacokinetics and relative bioavailability of D-penicillamine in fasted and nonfasted dogs. J Vet Intern Med 2013. 27: 1071-1076.

D-Penicillamine is the copper-chelating agent used most often to treat dogs with copper-associated hepatitis. The response to treatment can be variable, and potentially influenced by administering the drug with food, a practice commonly recommended to dog owners. In this study, the investigators administered D-penicillamine orally to dogs either alone (fasted) or with food and blood samples were collected over a 24-hour period to measure circulating concentrations of the drug. Administering the drug with food significantly reduced blood concentrations of the drug, which could decrease its ability to chelate copper. The investigators expressed concerns that this approach could prolong therapy, increase cost to the owner, and result in greater disease morbidity. As a result, they strongly recommended that D-penicillamine not be given with food.

Haywood S, Boursnell M, Loughran MJ, Trafford J, Isherwood D, Liu X, Olohan L, Carter SD. Copper toxicosis in non-COMMD1 Bedlington terriers is associated with metal transport gene ABCA12. J Trace Elem Med Biol. 2016 May;35:83-9.

An inherited condition in people called Wilson's disease is manifested by accumulation of copper in the liver and brain, and is due to an inhibition of copper excretion. A similar condition occurs in Bedlington terriers, although the damage only occurs in the liver. Classically, this condition has been associated with a defect in a specific gene (COMMD1), but also has been recognized in some Bedlington terriers that lack that specific mutation. This study was performed to study the genomes of terriers with copper toxicosis and compare the findings with those of unaffected dogs. The aim of the study was to screen and sequence the dogs' DNA to target the putative mutant gene. The study has identified a significant disease association with a region on one of the chromosomes that contains a gene that has a close functional relationship to the gene responsible for causing Wilson's disease in people, suggesting that the disease in dogs may be due to impairment of the liver's ability to excrete copper into the bile.

Fieten H, Gill Y, Martin AJ, Concilli M, Dirksen K, et al. The Menkes and Wilson disease genes counteract in copper toxicosis in Labrador retrievers: a new canine model for copper-metabolism disorders. Dis Model Mech. 2016 Jan;9(1):25-38.

Menkes and Wilson diseases are neurodegenerative conditions in people that are caused by mutations in the genes encoding for proteins that transport copper into and out of cells, with the ultimate aim being to provide the cell with the copper needed to function appropriately as a cofactor while at the same time preventing the accumulation of toxic amounts of the metal. Working together, these proteins participate in the absorption of copper from the intestine and the excretion of copper from the cells. Because copper toxicosis associated with these genetic mutations occurs rarely in the human population, it is difficult to identify the specific genes causing the disease or to study the effects of modifying these genes on the development of the disease. Recently, the Labrador retriever was characterized as a new model for copper toxicosis, primarily because these purebred dogs have far less genetic variability. The investigators identified the involvement of a specific copper transporter in copper toxicosis in these dogs, and determined that new functional mutations of one or more of the genes that regulate copper transport help reduce the accumulation of copper. These findings not only contribute to our general understanding of the handling of copper by the body, but also may provide the basis for a new way to treat this condition in the future.

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White Shaker Disease Syndrome

Lindsey Buracker, DVM and John Robertson, VMD, PhD

Introduction and Overview

White Shaker Disease Syndrome is a neurologic disease seen primarily in dogs with white coats, particularly in West Highland White Terriers, Maltese Terriers (Bagley et al., 1993), and Samoyeds (Cummings et al., 1986). Affected dogs have a very unique generalized tremor (unintentional, rhythmic muscle movements) and typically are 5 months to 3 years old when the disease is first recognized (Yamaya et al., 2004). There is no gender predilection for this disease. Because this disease has been identified in breeds of dogs lacking a white coat (Dachshund, among others; Yamaya et al., 2004), and in the adult years of their life, the terms "shaker dog syndrome", "white shaker disease" and "little white shaker dog" commonly are used (Yamaya et al., 2004). The cause of the disease is not known and there is little research being done on this condition in any breed.

Because there are several neurologic and neuromuscular diseases that can produce similar clinical signs, it is essential that Westie owners immediately get a thorough evaluation of their dog and that an accurate diagnosis is made.

Symptoms and Diagnosis

Affected dogs have a history of a relatively sudden onset of constant tremors over the entire body, including the head and eyes. These tremors occur when opposing muscle groups alternately contract and relax in a repetitive manner (Smith and Thacker, 2004). Uncontrolled eye movements, referred to as opsoclonus, consist of rapid, involuntary, multidirectional (horizontal and vertical) movements of the eyes.

The tremors are exaggerated by excitement, handling, forced locomotion, and high levels of stress (Summers et al., 1995). Although some affected dogs may have constant tremors, they remain alert and responsive to their owners and environment. These dogs generally retain normal sensory and muscle functions, which are controlled by the cranial nerves. Consequently, they are able to sense when their faces are touched, and their pupils dilate and constrict appropriately in response to changes in light. In some instances, tremors may be severe enough to cause a wobbly, uncoordinated gait, or overreaching with the legs when walking forward (Smith and Thacker, 2004). This latter change in gait is called hypermetria.

Because other diseases can manifest as tremors, they must be ruled out before an appropriate treatment can be administered (Smith and Thacker, 2004). Examples of these diseases include various inflammatory or infectious diseases of the nervous system, epilepsy, and exposure to toxic substances such as moldy food, lead or organophosphates. These possibilities are ruled out by performing an electrophysiological evaluation of nerve function and microscopic examination of a portion of a nerve obtained by biopsy. After a variety of diagnostic tests are performed to eliminate the aforementioned possibilities, dogs with typical clinical signs that lack evidence of other diseases are diagnosed with White Shaker Disease Syndrome.

Occasionally, affected dogs may have a head tilt. Because head tilts also can occur other central nervous system disease, peripheral neurologic disorders and even with ear problems, these other causes must first be ruled out before a diagnosis of White Shaker Disease Syndrome is made (Smith and Thacker, 2004).

The diagnosis of White Shaker Disease Syndrome is generally made based on the dog's history, age at onset, and symptoms. Blood cytology, chemistry and x-rays, as well as physical

Common Clinical Findings
Terriers at Increased Risk
5 Months - 3 Years Old
Tremors

examination findings, are usually normal and have not proven valuable to aid in a diagnosis. A sample of cerebrospinal fluid may be collected for analysis, as an increase in the number of lymphocytes has been noted in some cases (Smith and Thacker, 2004). Fortunately, White Shaker Disease Syndrome is rarely a fatal disease.

> "The tremors are exaggerated by excitement, handling, forced locomotion, and high levels of stress."

Krabbe Disease (Globoid Cell Leucodystrophy)

Young Westies also can develop tremors as a result of another neurologic disease that does not appear to be related to White Shaker Disease Syndrome. This disease, which is known as Krabbe disease or globoid cell leucodystrophy (GCL), is a neurologic disease in which a substance that is toxic to the myelin-forming cells in the nervous system accumulates inside nerve cells. Myelin, which makes up most of the white matter in the central nervous system and is present in the peripheral nervous system, is essential for normal nerve function. The accumulation of this substance results in the breakdown of myelin, which leads to severe neurological symptoms such as progressive blindness, seizures, and eventually death.

This disease, which occurs as the result of a deficiency in a specific enzyme called galactocerebrosidase (GALC) that is critical for cellular metabolism, is called a "storage disease." Deficiency of GALC has been demonstrated not only in the brain but also the liver and kidneys of affected dogs (Fletcher et al., 1972; Yunis et al., 1976, Wenger et al., 1999).

West Highland White and Cairn terriers are the two breeds most affected by GCL, which is inherited as an autosomal recessive trait (Parker et al., 1995; Wenger et al., 1999). Clinical signs typically become evident beginning around 3 months of age, and include ataxia of the hindlimbs, muscle wasting, head and body tremors, and even blindness. In many dogs, there are substantial degenerative changes in the peripheral and autonomic nervous systems (Summers et al., 1995), and affected dogs may die from the disease in less than a year or may be euthanized due to poor quality of life (Parker et al., 1995). Pathologists have identified gray discolored areas of the brain in affected dogs, firmness of the cerebral cortex, and dilation of the ventricles, reflecting tissue loss (Summers et al., 1995). The brains of affected dogs appear smaller than normal, with a notable decrease in the amount of white matter (Summers et al., 1995).

To determine if a dog is affected with GCL, a blood sample is analyzed by polymerase chain reaction (PCR) to identify the enzyme deficiency underlying the condition (Cifti et al., 2000). Although not done commonly, examination of a sample of a nerve obtained by biopsy using electron microscopy may aid in reaching a diagnosis and MRI can also be useful (Cozzi et al., 1998; Wenger et al., 1999).

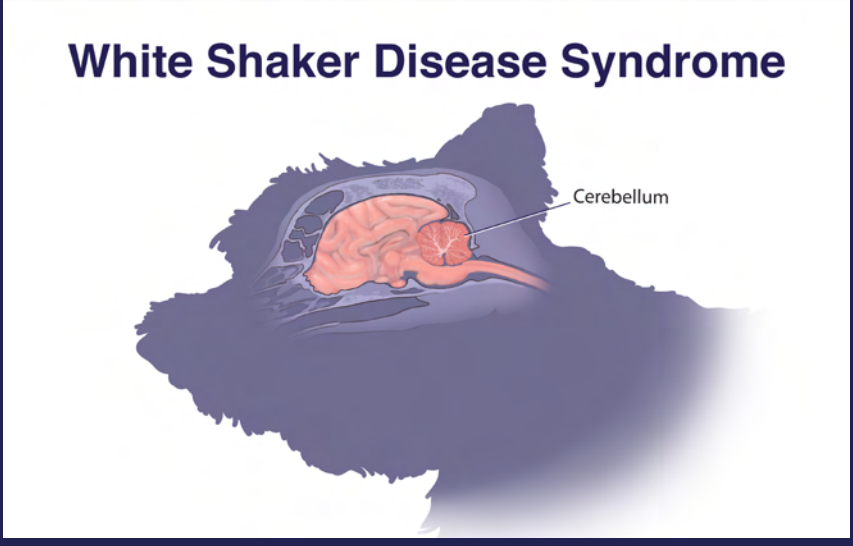

Figure 1 - One of the most commonly affected areas of the brain in dogs with White Shaker Disease Syndrome is the cerebellum, which is responsible for 'fine control' of movements.

Krabbe disease has been reported in humans, dogs, mice, monkeys, and sheep (Fletcher et al., 1972). Although death usually occurs before affected infants reach 2 years of age, the disease also has been identified in older people. Canine GCL most closely resembles the late-onset, ultimately fatal form of Krabbe disease occurring in human patients.

Causes

Though the cause remains unknown, White Shaker Disease Syndrome is most often associated with mild inflammation of the central nervous system (non-suppurative encephalomyelitis) (Smith and Thacker, 2004). The cerebellum, which is the part of the central nervous system responsible for 'fine control' of movements, is commonly affected. As a result, dysfunction of this part of the brain could be one of the initiators for the tremor. It is not known if the inflammation is the true underlying cause or if there is an associated neurotransmitter abnormality in affected dogs. Further research should be done to rule out that possibility as well as any virus that might serve as the cause of the disease. There has also been some speculation that White Shaker Disease Syndrome can be congenital in some breeds (West Highland White Terriers, Maltese Terriers, and Samoyeds).

Treatment and Prevention

Early diagnosis of the disease is beneficial in treating affected dogs, as many will respond in a few days to immunosuppressive levels of corticosteroids that have anti-inflammatory effects (Yamaya et al., 2004). The tremors can be reduced with diazepam (Valium), which is used to diminish anxiety or modify behavior, as a muscle relaxant, or an anticonvulsant (Smith and Thacker, 2004). In some cases, dogs will have to remain on a low dose of corticosteroids for the duration of their life in order to remain free of signs of the disorder.

There are a few adverse affects that can occur from taking high doses of corticosteroids. Some of these include vomiting, gastrointestinal bleeding, ulcers, and diarrhea (Smith and Thacker, 2004). Even though these complications can be serious, most can be managed with appropriate care. Unfortunately, there is no known way to prevent the disease.

Some dogs experiencing tremors may have convulsions, and may refuse to eat or seem to be disconnected from their environment just before onset of the seizures. Affected dogs may need to be encouraged to eat and drink. Some owners have noted that hand feeding and raising food and water bowls off the floor is helpful (Swingle C, 2008), and that symptoms can lessen or resolve when the dog is relaxed or sleeping (Summers et al., 1995). Some dogs respond well to being crated in a minimally dark room that is quiet during times of high stress.

In summary, White Shaker Disease Syndrome is a disease that affects primarily white-coated dog breeds, including Westies. Clinical signs, including involuntary tremor, are seen in young dogs. An accurate diagnosis is essential in order to appropriately manage affected dogs, which can be sustained with treatment. Further research is needed to determine the cause(s) of the disease.

Current Research About White Shaker Disease Syndrome

As a result of its low prevalence, there has not been a lot of research on White Shaker Disease Syndrome osteopathy in dogs in recent years. However, there have been a few recent reports regarding the disease and Krabbe disease in people that deserve specific mention.

Cantuti-Castelvetri L, Maravilla E, Marshall M, Tamayo T, D'auria L, Monge J, Jeffries J, Sural-Fehr T, Lopez-Rosas A, Li G, Garcia K, van Breemen R, Vite C, Garcia J, Bongarzone ER. Mechanism of neuromuscular dysfunction in Krabbe disease. J Neurosci. 2015 Jan 28;35(4):1606-16.

Krabbe disease in people results in the loss of skeletal muscle mass and function, the cause of which remains unknown. This study was performed to study skeletal muscle cells and the junctions between nerves and muscles (i.e., neuromuscular junctions) from mice and dogs with GLD. The investigators determined that muscular dysfunction in Krabbe disease is compounded by dysfunction of the neuromuscular junctions, and low levels of a specific cellular pathway that is involved in growth of muscle fibers under normal conditions. The investigators propose that in the future it may be possible to either activate this pathway or replace missing proteins with gene therapy to improve the lives of people with this disease. As it is likely that studies such as this will initially be performed in affected dogs, findings from those studies may be important in veterinary practice as well.

Fletcher JL, Williamson P, Horan D, Taylor RM. Clinical signs and neuropathologic abnormalities in working Australian Kelpies with globoid cell leukodystrophy (Krabbe disease). J Am Vet Med Assoc. 2010 Sep 15;237(6):682-8.

In 2010, Fletcher and colleagues studied globoid cell leucodystrophy in a group of Australian Kelpies that were deficient in the enzyme that underlies the condition. Their primary goal in this study was to determine whether or not the degree of demyelination and inflammation in the affected dogs' central nervous system correlated with the clinical signs exhibited by the dogs (i.e., tremors and abnormal gait). They reported that the age of onset and rapid progression of the disease, and the clinical signs were corresponded with those seen in West Highland White and Cairn Terriers, and that the clinical signs reflected abnormalities of the cerebellum. Because Australian Kelpies originated from Collie breeds, the investigators concluded that the disease in these dogs may not be due to the same mutations that cause the disease in West Highland White Terriers, Cairn Terriers or Irish Setters.

Acknowledgements

Mr. Matthew Crotts, a medical illustrator in Educational Resources in the College of Veterinary Medicine at the University of Georgia, created the illustration used in this chapter.

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Juvenile Cataracts in West Highland White Terriers

Lindsey Buracker, DVM and John Robertson, VMD, PhD

Introduction

Dogs have a very keen sense of vision, with an ability to see in extreme conditions of light and darkness, and to be highly perceptive of movement. Although we generally don't think of them as primal predators, Westies are born with these instincts and need excellent vision. To make sense of what happens when cataracts develop, it is important to first have a solid understanding of the anatomy and physiology of the eye.

The Anatomy of the Eye and the Phenomenon of Vision

The eye is comprised primarily of two connected chambers. The smaller of the two chambers, called the anterior chamber, is bounded by the transparent cornea at the front of the eye and the lens posteriorly. The larger posterior chamber, which is bounded externally by the tough outer layer called the sclera, contains the lens, the gelatinous vitreous humor, and the retina. The retina is a membrane comprised primarily of neural receptors that respond to light and initiate the visual pathway. The eye also contains blood vessels in the uveal tract and connective tissue.

The lens is an amazing tissue. It is a tight clustering of specialized cells, enclosed in a capsule, located behind the iris and in front of the vitreous body, held in place by fibers, the anterior vitreous face, and the iris (Magrane, 1972). The lens is normally quite flexible, and its shape is controlled by small muscles and fibers that either tense or relax its edges. By changing its shape, the lens alters its refractive power to bring objects into focus, depending on whether they are near or far away. The lens grows in size with age, and requires nutrients that reach it by diffusion through the aqueous and vitreous humors. It also can be damaged by injury and disease, and has a limited ability to heal. Consequently, the shape of the lens changes during life.

There are three main components of the lens, namely the capsule, surface layer or epithelium, and fibers. The capsule is a thickened smooth membrane made of collagen and produced by the lens epithelium and fibers. It completely surrounds the lens and has elastic properties, so when not under tension, the lens assumes a rounded shape. The epithelium is comprised of cells that elongate over time and are eventually transformed into lens fibers, which contain high concentrations of the protein crystalline. It is this protein that helps the lens refract and transmit light. The fibers are tightly packed and extend the full length of the lens. Continual growth of the lens adds more elongated cells and fibers and produces an arrangement similar to the layers of an onion (Magrane, 1972). Damage to any of the components of the lens can result in a cataract.

The formation of the lens helps orchestrate the overall development of the eye, as it forms relatively early and helps induce the formation of both chambers and other parts of the eye. This pivotal role of the lens in controlling development of the eye is important for several reasons. First, if the lens does not properly form, this can affect the development of other parts of the eye. Second, disease or defective gene expression that occurs during pregnancy can significantly affect formation of the lens and, by extension, the development of healthy eyes. Third, the presence of cataracts at birth not only is indicative

Common Clinical Findings
Age When Recognized Varies
Autosomal Recessive Trait
Common Ancestors or Selective Breeding
Examination by Veterinary Ophthalmologist

of abnormalities in lens development, but also may signal the potential for problems elsewhere in the eye. Finally, it is important to remember that puppies are born with incompletely matured eyes and some of the process of development takes place after birth. A good rule of thumb is that formation of the eye is complete by about 12 weeks of age, in most breeds of dog. Dogs should have good visual acuity by this age.

Vision is an interesting phenomenon. In essence, light energy from the surroundings produces electrochemical changes in specialized nerve cells called rods and cones in the retina. These changes result in the generation of signals called 'nerve action potentials' that are relayed to the brain, where they are processed and consciously appreciated as a vision (Magrane, 1972). The lens is a key part of the system that focuses and transmits light to the retina so that signals that eventually produce vision are received on the retina.

An Introduction to Cataracts

Simply defined, a cataract is an irregularity and opacity in the lens. In most cases, the cataract appears as a cloudy white discoloration in the lens. It is important to know, that cataracts can affect only one or both eyes. When cataracts develop in the center of the lens, they will interfere with the path of light energy to the retina at the back of the eye, thereby impairing visual acuity. Cataracts often are classified as either 'immature' or 'mature,' terms that refer to the developmental stage of the cataract. Immature cataracts are newly formed and may occupy only a portion of the lens, whereas mature cataracts have been present longer and may involve the entire lens. In some mature cataracts, the cells in the lens have degenerated and liquefied. This debris persists within the lens capsule.

Many cataracts are more common in older dogs than young dogs, and develop in older dogs as a result of ocular disease (e.g., glaucoma, panophthalmitis and uveitis), systemic disease (e.g., diabetes mellitus), exposure to certain chemicals, as a side effect of radiation therapy of the head and neck, or direct penetrating trauma to the eye that damages the lens capsule and lens cells. These cataracts are considered to be "acquired" as a result of the initiating process.

Two specific ocular diseases associated with cataracts deserve specific mention: uveitis and glaucoma. Uveitis, an inflammation of the vascular ('uveal') layer of the eye, can be caused directly by degeneration of the lens, in some cases. With the formation and disruption of mature and hypermature cataracts, lens protein can leak from inside the lens capsule into the anterior chamber, spontaneously or as a result of trauma, and induce severe inflammation.

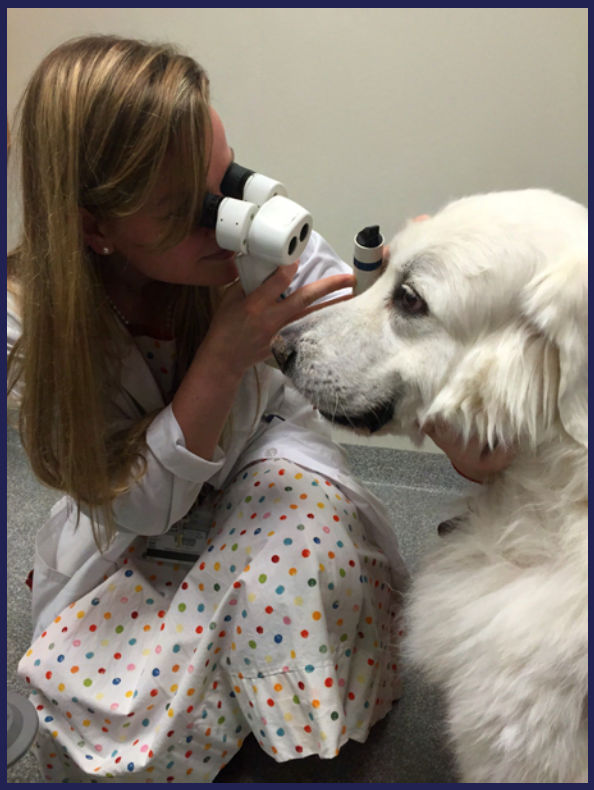


Figure 1 - Examination of a dog's eyes using a specialized slit lamp ophthalmoscope.

The relationship between glaucoma and cataract formation is complex. Glaucoma is a disease condition characterized by elevated intraocular pressure. In some cases of glaucoma, interference with the production and drainage of fluids within the eye is the primary disease process that increases intraocular pressure. The increased pressure within the eye may damage the lens, resulting in the formation of cataracts. In other cases, cataracts and other lens diseases may be a cause of glaucoma. For example, lenses with cataracts may become dislodged from their normal fibrous connections and migrate into the pupil, where they occlude the normal flow of fluid from the posterior chamber to the anterior chamber. This essentially blocks the drainage of fluid and pressure increases within the eye, resulting in glaucoma.

Juvenile Cataracts

Cataracts also may form as the result of a defect during development of the eye. These cataracts, which are known as juvenile cataracts, either may form before birth or develop shortly after birth as the dog's eyes mature. Juvenile cataracts may be caused by the expression of defective genes and/or viral infections that occur during gestation or in newborns. In some breeds of dogs, the incidence of cataracts increases with age; these cataracts are considered to be hereditary in

> Juvenile cataracts may form before birth or develop shortly after birth as the dog's eyes mature.

origin. Regardless of the cause, the outcome is the same – a decrease in visual acuity for the dog. Some inherited cataracts that appear early in the dog's life may result in blindness by the time the dog is 3 years of age. Other late onset inherited cataracts often do not interfere with vision and are identified before the dog reaches 8 years of age.

Most inherited cataracts in dogs are inherited as autosomal recessive traits, such as the mutation in heat shock transcription factor gene, HSF4, which is responsible for recessively inherited cataracts in Boston Terriers, Staffordshire Bull Terriers and French Bulldogs (Mellersh et. al., 2006). Typically, dogs are affected bilaterally, the cataracts are located in the posterior region of the lens, and the rate at which they grow is highly variable. Interestingly, Muller and coworkers (2008) were not able to identify mutations in HSF4 in Dachshunds or Enttlebucher Mountain Dogs with hereditary cataracts.

Another mutation of the HSF4 gene affects Australian Shepherds, but is different from the mutation in Boston Terriers, French Bulldogs and Staffordshire Bull Terriers (Mellersh et. al., 2009). This mutation is dominant, meaning that only a single copy is needed to predispose a dog to the disease. Fortunately, not all dogs with this mutation develop cataracts, suggesting that one or more other gene interactions are involved in the process.

Many breeds of dogs appear to be predisposed to developing juvenile cataracts, including the West Highland White Terrier. To examine this concept, Oberbauer and colleagues recently compared the prevalence of ten inherited disorders, including early onset cataracts, in purebred and mixed breed dogs in a study of more than 88,000 dogs. They determined that the prevalence of early onset cataracts in most purebred groups was not different from that in mixed breed populations. They concluded that groups with higher specific disorders may have common ancestors or this could be an effect of selecting for specific structural features (e.g., shape or size).

Many puppies appear normal at birth, many do not show signs until six months to two years of age, and some may have the cataracts appear after five years. Consequently, there is no way to know if the puppy you are buying is going to develop juvenile cataracts. Fortunately, juvenile cataracts do not always lead to blindness. In many cases, the puppy or young dog still sees basic shapes, but they may be blurry. In some cases, the disease leads to the development of glaucoma.

The only way to eradicate juvenile cataracts in dogs is for breeders to have both parents evaluated fully by a licensed veterinary ophthalmologist no more than a year before breeding. Because not all breeders do this, it is advisable to ask for eye registry papers for both parents before agreeing to purchase a puppy.

Noticing Your Dog's Eyes and Behavior

Owners and breeders are often the first to detect a problem with a dog's eyes and vision. Some common signs that something is not right include:

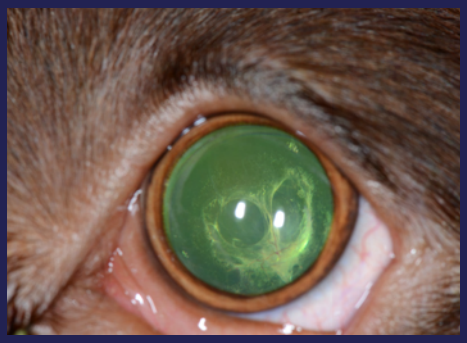
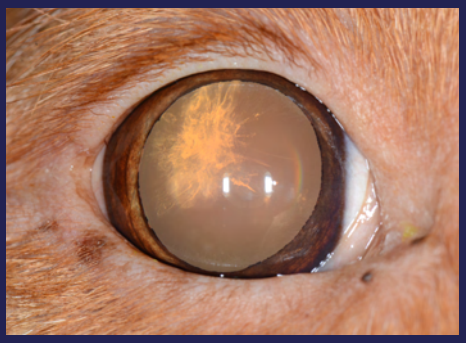
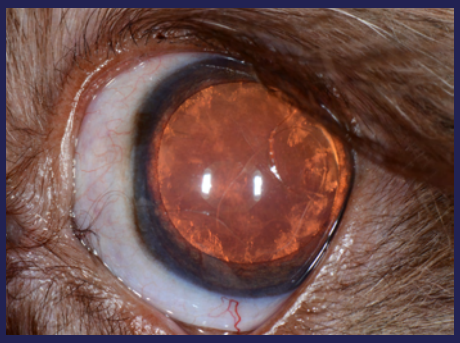
- The eyes, lids, and membranes of the eye just don't look right; there may be milky white/opaque discoloration, irregularities in shape and size, or perhaps the eyes are inappropriately proportioned to the dog's head.
- Puppies may bump into things in their path, and observations that must be differentiated from just clumsiness or poor coordination).
- Puppies appear reluctant to move about or are overly shy; most Westie puppies are pretty affable and playful.
- Puppies are reluctant to explore darkened areas.
- Puppies appear to cue interactions based on hearing rather than on both hearing and seeing.

If a problem with vision is suspected, your dog's eyes should be examined by your veterinarian.

Eye Examination by a Veterinarian

All thorough physical examinations of dogs include an evaluation of the eyes. Most evaluations by veterinarians include common elements, and some of the routine evaluation is done with simple tests:

- Evaluation of the gross appearance of both eyes, comparison of one eye with the other and with the head in terms of size, shape, coloration, tone, and integration with facial shape,
- Visual signal processing, based on the pupillary responses (constriction) to light shined in one eye. This is actually a simple test of a complex process, as it tests whether light focused on the retina then creates a visual 'signal' that is then transmitted via nerve fibers to the brain. At that point, the signal is interpreted as vision.
- The ability to track movement in a lighted area is assessed by the dog's responses to hand movements near the eyes. The veterinarian will determine if the dog will blink in response to movement near the eyes – assessing both visual perception and the automatic blink response.
- Tone (palpable firmness) of the eyes can be first evaluated by gently applying pressure through the lids. Most dogs

Figures 2 - 4 - Example of the different ways that cataracts can appear in dogs.

do not mind this part of the examination and it helps determine if the eyes are firm, but not too firm, and if there are irregularities or pain,

- Ophthalmic evaluation of the anterior chamber, posterior chamber, and intraocular structures (lens, iris, pupil, retina).

The value to Westie owners in seeking regular evaluations of their dogs should be evident. Health problems can be detected, diagnosed and most are treated effectively. Many eye problems can be detected with the above approach. When more complex treatments, such as surgery, are needed to treat problems and to correct defects, it makes sense to seek the services of a specialist, such as a veterinary ophthalmologist. These specialists have the facilities and equipment needed for more extensive diagnostic approaches and for treatment (***Figure1***). Because they concentrate exclusively on treating diseases of the eye, they have seen more cases, many of which are the more difficult ones, and will be more familiar with the variety of abnormalities affecting the lens (***Figures 2 – 4***). Veterinary opthalmologists are certified by examination boards after years of advanced training and experience treating diseases of the eye.

Prevention of Cataracts

Since we know that some types of cataracts have a hereditary basis (Table 1), it is essential for dog breeders to keep thorough records of litters and diseases affecting each pup. Breeders should keep in regular contact with the owners of pups from their litters throughout the lives of these dogs. The presence of cataracts in young dogs (less than 6 months old) and in multiple dogs from the same breeding is very suggestive of an underlying genetic problem. One caveat – if, during gestation, there is evidence of ill-health in the dam, cataracts may be the result of damage to the developing puppies. Most experienced breeders are very aware of the need to keep pregnant dams well-nourished and free from exposure to potentially damaging viruses and chemicals in the environment.

In the event that a litter is delivered and one or more pups develop cataracts, the breeder has a responsibility to 1) seek veterinary diagnosis and discuss treatment options for affected pups, 2) examine the breeding and pedigree of both dam and sire for similar problems (or the presence of other congenital defects from this paired breeding), and 3) refrain from breeding either sire or dam until the relationship between breeding and cataract development can be clearly determined. Hereditary cataracts were first identified as a significant problem in the Miniature Schnauzer breed in the 1970s and 1980s. Following the leadership provided by breed associations, veterinarians and research scientists, this autosomal recessive trait was identified and bred against, resulting in a substantial decrease in the incidence of the disease in Miniature Schnauzers today. By identifying those dogs that are carriers of the disease and not breeding them, juvenile cataracts can be controlled and eventually eliminated. The importance of keeping accurate breeding records and long-term follow-up information on litters cannot be overstated.

Potential owners need to do an extensive "background check" before purchasing a Westie from a breeder. These potential Westie owners need to be sure there are accurate records for each dam and sire, a solid bloodline, and no overt problems or diseases noted in each litter from the time of whelping. If Westie owners and breeders work together, this disease will eventually be eliminated from breeding stock.

Treatment

Before dogs with cataracts undergo surgical treatment, it is important to determine whether or not the dog is experiencing any vision problems. In other words, if the cataracts are relatively small and the dog is able to see sufficiently or can compensate for the impairment in vision, treatment isn't needed. In some dogs, juvenile cataracts do not become more severe or do so very slowly. In other dogs, the severity of the cataracts may change and other problems, such as glaucoma and inflammation of the eye, may develop. Consequently, it

Table 1. Inherited cataracts in the dog (Gelatt, 2008).

Breed	Age of Onset
Afghan Hound	6-12 Months
American Cocker Spaniel	6+ Months
Boston Terrier	Congenital
Chesapeake Bay Retriever	1+ Years
German Shepherd	8+ Weeks
Golden Retriever	6+ Months
Labrador Retriever	6+ Months
Miniature Schnauzer	Congenital or 6+ Months
Old English Sheepdog	Congenital
Siberian Husky	6+ Months
Staffordshire Bull Terrier	6+ Months
Standard Poodle	1+ Years
Welsh Springer Spaniel	Congenital
West Highland White Terrier	Congenital

is advisable to have the dog's eyes checked on a regular basis. When cataracts interfere with vision, the dogs may have trouble finding their way in their environment, locating food or water, and be reluctant to walk or run. In these cases, a visit to the veterinarian is warranted.

If cataracts are interfering with the dog's vision, the treatment requires surgical intervention by a veterinary ophthalmologist. Before this is done, however, specialized tests including an ERG and ocular ultrasound will be performed to ensure that the dog's retina is functioning normally. If the retina is not normal, the end result of surgery is not likely to be an improvement in visual acuity.

The most commonly used surgical technique involves using ultrasonic waves to transform the lens to a liquid, which then can be removed through a small incision. This technique, which is performed with the dog under general anesthesia, also is referred to as phacoemulsification. In many cases, an acrylic implant will be inserted to replace the lens that has been removed.

Prognosis and Follow-up Care

Although there is a risk of complications with any surgery, the short-term prognosis for the return of visual acuity after surgery exceeds 90%. The long-term outcome regarding restored or improved vision ultimately depends on the stage of the cataract at the time surgery is performed and other co-existing conditions. A protective collar will be applied to prevent the dog from scratching the eye and initially frequent eye drops or lubricants will need to be administered. Typically, dogs that undergo surgery are examined 1 week after surgery, at which time additional long term follow-up examinations will be scheduled, since there remains a risk for complications.

Current Research About Juvenile Cataracts in West Highland White Terriers

There has been a considerable amount of new information in the veterinary scientific literature in the past decade regarding the pathogenesis, diagnosis and treatment of cataracts in dogs. The following three recent studies would seem to be of most interest, as one concerns the clinical manifestations of the condition in small breeds of dogs examined in Korea, one reviews the clinical presentation of dogs with the disease in France, and the third compares the prevalence of another important eye disease of dogs covered in this eBook, keratoconjunctivitis sicca, in two populations of dogs after surgical treatment for cataracts.

Park SA, Yi NY, Jeong MB, Kim WT, Kim SE, Chae JM, Seo KM. Clinical manifestations of cataracts in small breed dogs. Vet Ophthalmol. 2009 Jul-Aug;12(4):205-10.

Because the majority of earlier clinical studies of cataracts in dogs had involved middle and large breed dogs, this study was performed to characterize the condition in small breed dogs presented to a veterinary teaching hospital in Korea. More than 560 small breed dogs were included in this study, with the most frequently presented breeds being the Miniature/Toy Poodle (n = 112, 20.0%), Yorkshire Terrier (n = 110, 19.6%), and Shih Tzu (n = 95, 16.9%). The investigators noted that significantly more female dogs were presented with cataracts than male dogs. The average age of affected dogs was 8.3 years, with Miniature/Toy Poodles and Yorkshire Terriers being significantly older and Miniature Schnauzers being significantly younger. While this study focused primarily on the incidence of cataracts and their clinical features, additional studies will need to be performed to determine the prognosis associated with different types of treatments.

Donzel E, Arti L, Chahory S. Epidemiology and clinical presentation of canine cataracts in France: a retrospective study of 404 cases. Vet Ophthalmol. 2016 Apr7. 1-9.

Although the prevalence of cataracts in dogs has been reported previously in North and South America and Korea, little was known about the disease in Europe. Consequently, the investigators undertook this study of more than 2,700 dogs presented for evaluation at a veterinary school in France. Of these dogs, 404 had cataracts; 54% were males and 46% females. The mean age of all dogs with cataracts was 9 years, and 54 breeds were represented. Of these, the Yorkshire Terrier was the only breed significantly overrepresented. The major causes of cataracts in this population were breed predisposition, aging, and progressive retinal atrophy.

Gemensky-Metzler AJ, Sheahan JE, Rajala-Schultz PJ, Wilkie DA, Harrington J. Retrospective study of the prevalence of keratoconjunctivitis sicca in diabetic and nondiabetic dogs after phacoemulsification. Vet Ophthalmol. 2015 Nov;18(6):472-80.

Diabetes mellitus occurs commonly in dogs, and often is complicated by the formation of cataracts. In fact, 50% of diabetic dogs have been reported to develop cataracts within 6 months of being diagnosed with cataracts. When cataracts interfere with visual acuity, phacoemulsification is used to help improve vision. It has recently been determined that tear production, as measured using the Schirmer tear test, is significantly lower in diabetic dogs with cataracts than in nondiabetic dogs with cataracts. Therefore, the investigators hypothesized that keratoconjunctivitis sicca would be more common in diabetic dogs after phacoemulsification. This study, which involved 117 nondiabetic dogs and 118 diabetic dogs, determined that the greatest risk for the development of keratoconjunctivitis sicca for all dogs is during the first 2 weeks after surgery, and that the populations at greatest risk are small dogs, small diabetic dogs, and large dogs with preoperative Schirmer tear test results <22 mm/min.

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Keratoconjunctivitis sicca ("Dry Eye")

Stephanie Shrader, DVM and John Robertson, VMD, PhD

Introduction and Overview

Keratoconjunctivitis sicca (KCS) is a disease of the eyes, characterized by inflammation of the cornea and conjunctiva. This condition occurs secondary to a deficiency in formation of the tear film that normally protects the cornea (Best et al, 2014), which leads to dry, irritated eyes. As a result, KCS is commonly known as "dry eye" or in veterinary terminology, xerophthalmia. This disease occurs often in West Highland White Terriers, but is also common in many other breeds, including Lhasa Apso, English Bulldog, American Cocker Spaniel, English Springer Spaniel, Pekingese, Pug, Chinese Shar Pei, Yorkshire Terrier, Shih Tzu, Miniature Schnauzer, German Shepherd, Doberman Pinscher, and Boston Terrier. While the reported incidence of KCS across all dog breeds ranges from 1% to 2%, there appears to be an increased predisposition reported for both neutered male and female dogs, and for female West Highland White Terriers, in particular.

Relevant Anatomy of the Eye

To understand how KCS develops and ultimately how it is treated, if is important to have a good appreciation of the relevant anatomy of the eye and the glands that produce tears. The relevant components of the eye are the clear outer cornea, the conjunctiva, the eyelids, and the Meibomian and lacrimal glands (***Figure 1A, 1B***). The Meibomian glands are located along the edge of the eyelid. There are two lacrimal glands associated with each eye. One lacrimal gland is located slightly above and lateral to the eye, and the other is located medially by the third eyelid (also called the nictitating membrane.

How Tears Are Produced

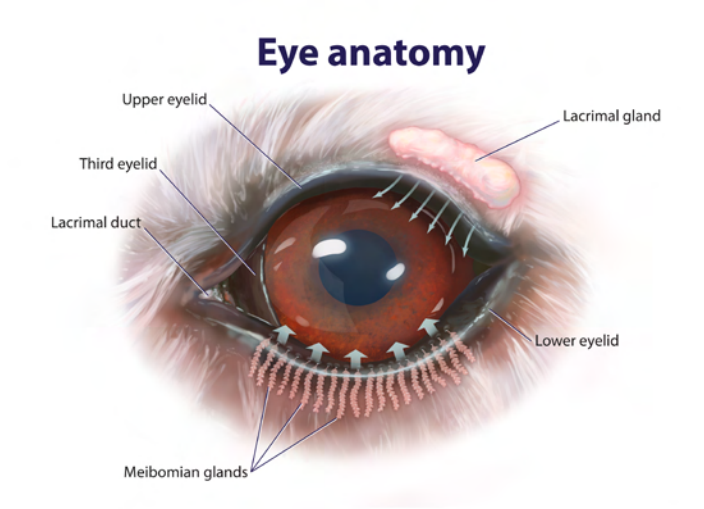
The tear film that covers the eyes is made up of three distinct layers. The outermost layer is made up of oils, which are secreted by the Meibomian glands. This lipid layer provides protection against evaporation, binds the tear film to the cornea, and prevents tears from simply pouring out over the lower eyelid onto the face. The middle layer of the tear film is the aqueous layer, which is produced by the lacrimal glands. As its name would suggest, the aqueous layer consists primarily of water, along with important proteins and enzymes that help remove bacteria and cellular waste material, and lubricate the surface of the cornea. The innermost layer of the tear film is the mucin layer, which is is produced by tiny secretory cells in the conjunctiva known as goblet cells. The mucin layer facilitates the spread of the tear film over the cornea.

What causes Keratoconjunctivitis sicca?

There are several potential causes of KCS in dogs, which include immune disorders that destroy the lacrimal tissue, diseases that affect the conjunctiva and lacrimal tissue, congenital conditions in which the lacrimal tissue fails to develop, medications, traumatic incidents and treatments. The common feature among these causes is that they impair the ability of the tear-secreting tissues in the eye to perform their basic functions, with the end result being the development of "dry eye".

Immune-Mediated Adenitis: The most common cause of KCS is immune-mediated lacrimal adenitis, which means that the body's own immune system is causing abnormal inflammation of the lacrimal glands. The underlying reason why the immune

Common Clinical Findings
West Highland White Terriers at Risk
Red, Irritated Eyes
Pawing at Eyes
Ocular Discharge



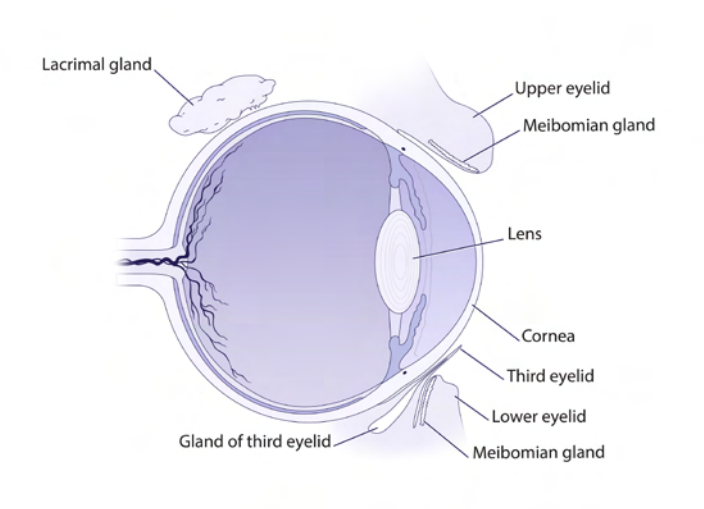


Figure 1A and B - Two illustrations depicting the important anatomical features of the dog, particularly the locations of the lacrimal and Meibomian glands that are critical to the secretion of the tear film.

system targets the lacrimal glands for destruction is unknown, but the end result is infiltration of the glands with lymphocytes and the inability to produce the aqueous layer of the term film. There does not appear to be a specific breed predisposition to this condition.

Congenital Acinar Hypoplasia (Congenital Alacrima): As its name implies, this condition is genetic in origin and the term 'alacrima' literally means "no tears." This is an autosomal recessive trait in which the responsible allele is carried on the non-sex determining chromosomes. Thus, if two animals having the recessive trait for alacrima mate, there is a 25% chance that the offspring will inherit the disorder. Breeding dogs that have congenital disorders is problematic, as this practice continues the disease in future offspring. Most breeders monitor the health of litters they have sold, in order to detect the emergence of congenital disorders such as this in litters or breeding stock. Therefore, it is critical that the history and health records of potential breeding pairs are obtained and examined before a puppy at risk of conditions such as this are purchased. There is evidence that Yorkshire Terriers and Bedlington Terriers are overrepresented when compared to reference populations of dogs (Westermeyer et al, 2009).

Drug and anesthesia induced decreases in tear production: Certain drugs/anesthetics can produce either temporary or permanent KCS. A decrease in tear production for up to 24 hours is sometimes noted to occur after anesthesia and surgery, but the inciting cause is unknown. Consequently, it is important for all veterinarians to use a lubricating ointment or fluid to protect eyes during surgery to prevent this temporary decrease in tear production.

There are other drugs whose use have been associated with the development of KCS. These include some of the sulfonamide antibiotics and etodolac, an orally administered nonsteroidal anti-inflammatory drugs that has been used to help relieve pain and inflammation in dogs with osteoarthritis (Klauss et al, 2007). In the latter study, dogs that had received the drug for less than 6 months had a much better chance to complete remission of clinical signs. The investigators advised veterinarians to monitor tear production before and during administration of this drug to ensure that problems can be identified early and drug administration discontinued, if necessary.

Iatrogenic KCS: The term 'iatrogenic' refers to a problem that develops as a result of or associated with a treatment. Consider, for example, a dog that has an abnormal growth involving the gland of the third eyelid (nictitans gland). If this abnormal growth were removed, it could increase the risk that the dog will develop KCS, because that gland is responsible for production of part of the tear film. In fact, this is what happened years ago when a condition caused by inflammation and proliferation of lymphoid tissue near the third eyelid (i.e., "Cherry Eye") was treated by removal the gland. Today, this condition is treated using a combination of medical and surgical treatments instead of removal.

Infectious Diseases: A common viral disease in dogs, canine distemper, is often associated with KCS. Canine distemper is a highly contagious disease that is typically spread via aerosolized respiratory secretions. In most cases, the virus first attacks the respiratory system, and then spreads to the gastrointestinal and nervous systems. When the virus colonizes components of the eye, including the cornea, conjunctiva and the lacrimal

> The common feature among these causes is that they impair the ability of the tear-secreting tissues in the eye to perform their basic functions.

glands, KCS can develop (Gilger, 2009). Consequently, it is extremely important to have all dogs vaccinated against the canine distemper virus.

Metabolic Diseases/Disorders: Tear production has been reported to be reduced in a small number of patients being evaluated for endocrine abnormalities commonly encountered in dogs (Williams et al, 2007). These three conditions were hypothyroidism, diabetes mellitus and hyperadrenocorticism (Cushing's disease). Although the underlying cause or causes for the reduction in tear production were not identified in that clinical study, the investigators suggested that tear production should be measured in dogs with any of these conditions to reduce the chances the damage to the cornea could occur.

Neurologic: Parasympathetic innervation to the lacrimal glands is provided by one of the 12 cranial nerves, namely the facial nerve. Damage to this nerve, either due to disease or trauma, can result in KCS by decreasing the amount of tear film produced. Similarly, damage to the ophthalmic branch of the trigeminal nerve could result in loss of innervation to the lacrimal gland, conjunctiva, and upper eyelids, with the end result being the development of KCS.

How is Keratoconjunctivitis sicca diagnosed?

Dogs with KCS are often presented to the veterinarian because they have red/irritated eyes, are pawing at their eyes because they itch and/or hurt, and may have a thick ocular discharge that can range from off-white to green in color. The veterinarian also may notice that the third eyelid is protruded, and that the cornea no longer has its normal shiny appearance (***Figures 2 and 3***). This latter finding is due to inflammation of the cornea. In advanced cases of disease, there may be evidence of corneal ulceration and pigmentation; corneal scarring may lead to vision loss.

To differentiate KCS from other ocular disorders, the veterinarian will do a comprehensive eye exam that will include a Schirmer tear test, staining of the cornea with fluorescein dye, and evaluation of pressures within the eye for evidence of glaucoma.

Schirmer Tear Test: The Schirmer tear test is a painless diagnostic procedure designed to quantify the amount of tear film produced by the eye. To perform this test, the veterinarian places a thin strip of paper (about an inch long and quarter of an inch wide) just under the dog's eyelid for one minute. This piece of paper has a small scale on it (***Figure 4***). During the minute, the tear film "wicks" up the paper. At the end of one minute, tear production is quantified by measuring the distance the tear film travelled in the paper. The result is reported in mm/min, with values for normal dogs being >15 mm/min.

Application of Fluorescein Stain: Fluorescein is a bright yellow/orange stain that is used to detect corneal ulceration. The veterinarian will place a few drops of the stain in the eye,

Figure 2 - Examination of a dog's eye using a specialized ophthalmoscope.

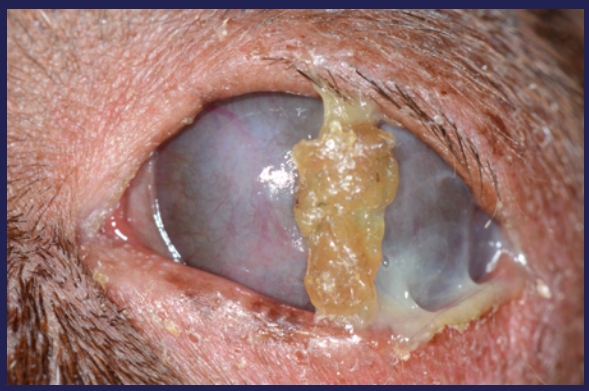


Figure 3 - An affected eye in a dog with keratoconjunctivitis sicca, characterized by a cloudy cornea and thick ocular discharge.

Figure 4 - A packet of standardized Shirmer Tear Test strips that are used to measure tear production.

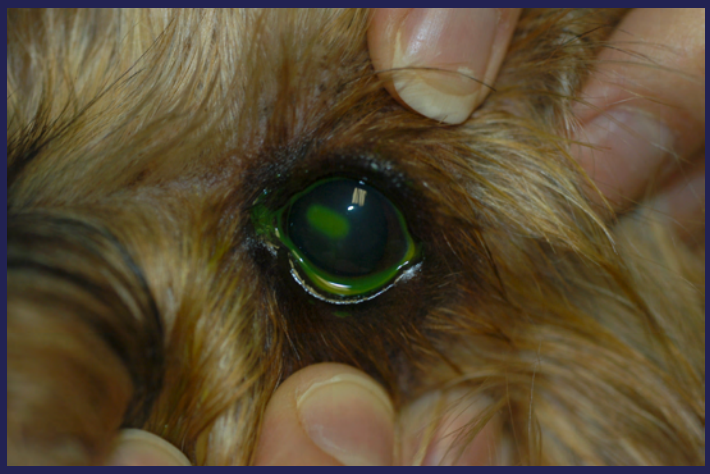


Figure 5 - The eye of a dog with keratoconjunctivitis sicca in which the green fluorescein stain identifies a damaged area of the cornea.

turn off the exam room lights, and use the ophthalmoscope to determine if corneal ulcers are present (***Figure 5***). In dogs with KCS, it is not uncommon to also find corneal ulceration because of the chronic irritation.

Examination of Intraocular Pressure: Although changes in intraocular pressure generally do not occur in dogs with KCS, most veterinarians will measure intraocular pressure to rule out another relatively common eye disease, namely glaucoma. Measurement of intraocular pressure is performed in a quick, painless manner using a special handheld device known as a tonometer. Normal intraocular pressure in dogs ranges from 15 to 25 mmHg.

Treatment of Keratoconjunctivitis sicca

There are a variety of treatments for KCS that can be used. These include stimulating the production of tears, replacing the tears, reducing inflammation and controlling bacterial infections. For most dogs with KCS, topical treatments will be required for the life of the animal. Initially, application of topical medications to the eye can be challenging, as some dogs with KCS are painful. Fortunately, with effective management, the level of pain decreases and putting medications in the eyes becomes a routine practice for both dog and owner. Providing rewards as positive reinforcement may help. The following guidelines for deciding when to initiate therapy appear to be reasonable (Best, 2014):

1. Initiate therapy for KCS in all dogs presented with clinical signs of the disease and Schirmer tear test results <5 mm/min.
2. Either initiate therapy for KCS or repeat the Schirmer tear test in one month in breeds predisposed to the disease that have clinical signs of the disease and Schirmer tear test results of 10-15 mm/min.
3. Consider other causes for reduced tear production in dogs presented with clinical signs of the disease and normal Schirmer tear test results.

Stimulating Tear Production: Three drugs are commonly used in an effort to restore tear production in dogs with KCS. Two of these compounds, cyclosporine A and tacrolimus, modulate the immune response that appears to be responsible for the condition in a large number of dogs. They also reduce inflammation, restore production of mucin by goblet cells, and stimulate tear production. These drugs appear to be very effective, positive responses being reported for more than 80% of affected animals (Kaswan et al, 1990; Hendrix et al, 2011). The third compound, pilocarpine, stimulates tear production by interacting with receptors in the lacrimal system. This drug is used when the cause of the condition is determined to be neurogenic in origin (i.e., damage to the nerves involved in tear production).

Replacing Tears: Tear replacement solutions are typically a combination of ingredients that replace one or more components of the tear film. There are three types of solutions, gels and ointments that are used for this purpose. These include artificial tear solutions that help remove debris and mucus from the surface of the eye. Artificial tear solutions have a relatively short duration of activity, must be reapplied several times a day and are not effective as the sole treatment. Another approach is to use cellulose-based solution and gels that are thicker, last longer and can be applied less often. The most viscous formations, which include lanolin, mineral oil or

petrolatum, are used most often for dogs that produce tear film deficient in lipids.

Topical Anti-Bacterial and Anti-Inflammatory Drugs: In some affected animals, there may be a secondary bacterial infection causing the thick, mucopurulent discharge. In these cases, topical ophthalmic anti-bacterial drugs will need to be applied to the eyes 3-4 times daily. These drugs typically include a combination of bacitracin, neomycin and polymyxin. If the conjunctiva are inflamed, many veterinarians also will use topic corticosteroids, such as prednisolone or dexamethasone, to reduce the inflammation. These medications are manufactured as ointments and solutions; your veterinarian will determine which medication is best for your dog.

Surgical Intervention (Parotid Duct Transposition): Some dogs with severe KCS that is unresponsive to medical therapy, may require surgery. To understand the rationale for the surgical procedure used, it first is important to know a bit about the parotid salivary gland that is located behind the jaw and just below the base of the ear. This is the largest salivary gland in the body and produces secretions that aid in chewing and lubricating food and swallowing. Because tears and saliva share similar properties, saliva can be used successfully to treat dogs with severe KCS. The surgical procedure that is performed moves the duct that normally connects the gland with the mouth to a position near the conjunctiva (***Figure 6***). When this is done, the lubricating and antibacterial secretions from the salivary gland flow onto the surface of the eye. This flow of saliva is intermittent, and increases in response to eating. Veterinarians with experience performing this procedure routinely are most likely to have a successful outcome.

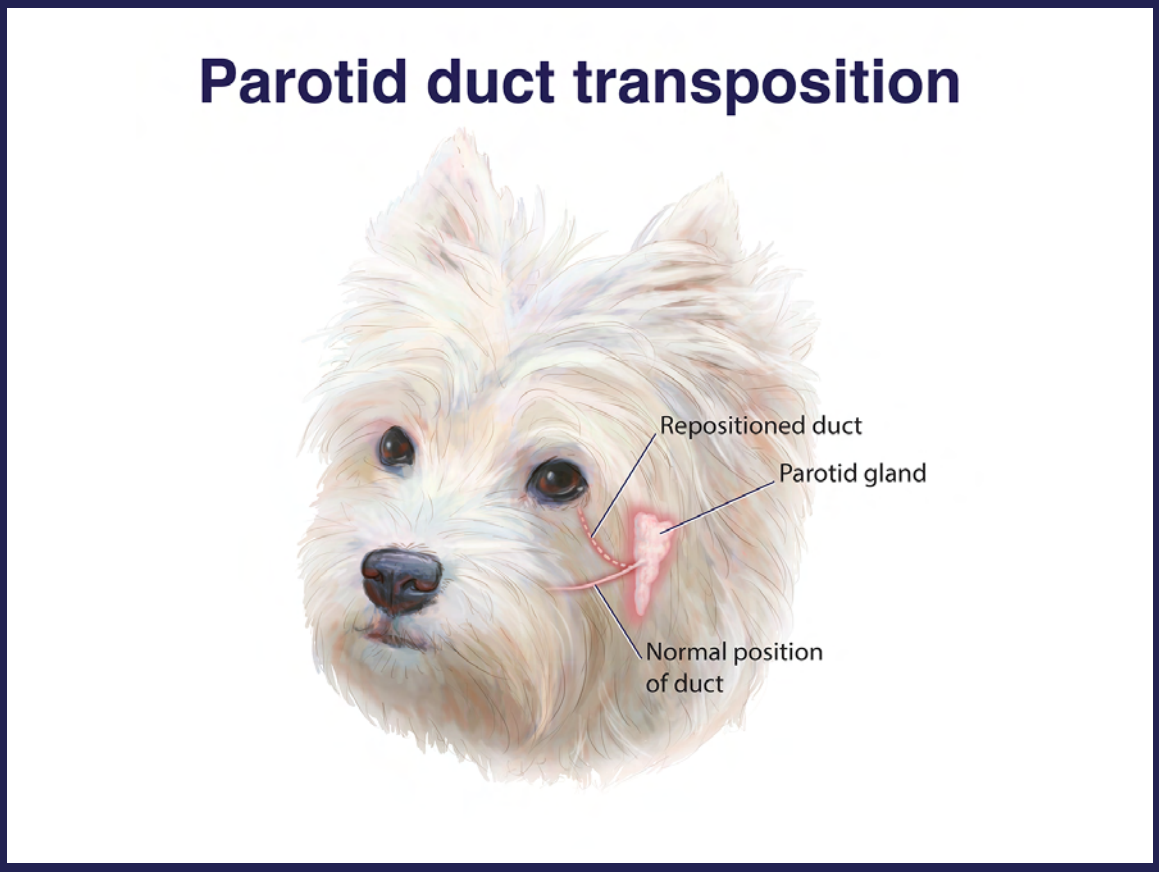


Figure 6 - An illustration depicting the normal position of the parotid duct where it enters the mouth and its new location adjacent to the eye after the parotid duct transposition surgery has been performed.

Current Research About Keratoconjunctivitis sicca

The majority of the published studies regarding KCS have centered on its association with other concurrent diseases and on the effectiveness of different treatments. With the increased interest in the effects of diabetes in dogs, the results of a recent study comparing the prevalence of KCS in dogs after treatment of cataracts in dogs with and without diabetes are summarized below. The other two studies selected for review compare the effectiveness of different treatments for the KCS.

Gemensky-Metzler AJ, Sheahan JE, Rajala-Schultz PJ, Wilkie DA, Harrington J. Retrospective study of the prevalence of keratoconjunctivitis sicca in diabetic and nondiabetic dogs after phacoemulsification. Vet Ophthalmol. 2015 Nov;18(6):472-80.

In this study, the occurrence of KCS was compared for 118 diabetic dogs and 117 nondiabetic dogs undergoing a procedure called phacoemulsification for treatment of cataracts. The Schirmer tear test was performed before surgery and several times after surgery for up to one year; a diagnosis of KCS was based on the presence of clinical signs consistent with the disease and Schirmer tear test results < 15 mm/min. The investigators determined that the greatest risk for developing KCS was during the first 2 weeks after surgery, and the animals at greatest risk were small dogs, small diabetic dogs and large dogs with preoperative Schirmer tear test results <22 mm/min. Based on their findings, the investigators suggested that monitoring of tear production and the use of artificial tear supplements immediately after cataract surgery may be warranted for all dogs, but especially for small diabetic dogs.

Chen T, Powell CC. Effect of once daily topical 0.3% naltrexone on tear parameters and corneal sensitivity in dogs with uncontrolled keratoconjunctivitis sicca: a double-masked randomized placebo-controlled clinical trial. Vet Ophthalmol. 2015 Nov;18(6):497-501.

In this study, the investigators evaluated the effectiveness of naltrexone, a drug that normally is given to antagonize the effects of opioids, on tear production and corneal sensitivity in dogs with KCS. The study was based on a previous small study in which two animals had increases in their Schirmer tear test results after being treated with the drug. To eliminate the chance that people involved in the study might be biased if they knew whether or not the drug was being given, they performed this study as a double-masked placebo-controlled trial. This means that the animals either received naltrexone or a commercial saline solution eye wash once daily, without the people involved knowing which was being used until after the study had ended. Sixteen dogs with KCS were involved in the study, and corneal sensitivity and Schirmer tear test results were recorded over 5 weeks. They found no evidence of an increase in tear production or a change in corneal sensitivity, and speculated that this lack of effect may have been due to the chronic nature of the disease in the dogs or the relatively short duration of treatment.

Rhodes M, Heinrich C, Featherstone H, Braus B, Manning S, Cripps PJ, Renwick P. Parotid duct transposition in dogs: a retrospective review of 92 eyes from 1999 to 2009. Vet Ophthalmol. 2012 Jul;15(4):213-22.

Some dogs with KCS fail to respond to medical therapy and develop chronic ocular pain or blindness. In an effort to treat these severely affected dogs, fifty years ago veterinary surgeons began surgically moving the parotid duct to bathe the cornea in saliva. This procedure was widely used until it was determined that cyclosporine was effective in the treatment of KCS. Because relatively few veterinary ophthalmologists now have the training and experience needed to successfully perform the procedure. The investigators in this study consider transposition of the parotid duct a viable technique in the treatment of dogs with severe KCS. The aim of this study was to critically assess the success of this procedure in dogs over a 10-year period. Although there was a 50% complication rate, the overall surgical success rate was 92%, and 90% of owners were satisfied with the outcome.

Acknowledgements

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Tumors, Cancer, and Your Westie

John Robertson, VMD, PhD

Introduction and Overview

"Your dog has a tumor." This is one of the most stressful things a Westie owner can ever hear from their veterinarian. For most people, there is an immediate concern about what it is (what kind of tumor), what to do about it (if anything), and what is going to happen to their dog. This chapter discusses tumors (also called "neoplasms" – new cells), how they are detected and further diagnosed, types of therapy, and what to expect if your dog has a tumor. The chapter is not intended to provide comprehensive information about tumors and cancer. The best source of information about tumors in dogs and specifically in your dog is your veterinarian. Veterinarians are extensively trained to understand how tumors develop, the factors that foster their growth, and, most importantly.… what to do. Unfortunately, the author of this chapter knows personally about tumors and cancer in dogs and cats, and the toll it takes on owners. His best friend, Fluffer I the Westie succumbed to a tumor of the testis when he was a young boy. Experience is a terrible way to learn some things.

What are tumors ("neoplasms") and what causes them? All tissues in the body (of dogs and people alike) are made of many cells. Cells in different tissues, such as muscle cells in muscle and kidney cells in kidneys, have different architectures and functions. All of these cells started from a single cell – the fertilized egg - that gave rise to an embryo and eventually to all cells and tissues. Since every cell in every tissue came from one single cell, all cells have the same DNA, organized into genes and chromosomes in the cell nucleus. As a result, all cells are genetically identical.

During the processes of cell growth, duplication, and organization into tissues, the form and function of the cells and tissues evolves into their 'final' adult form. This process of cell evolution is called differentiation. Cell growth, replication (making more cells), and differentiation let tiny puppies grow into dynamic adult dogs.

The processes of cell growth, replication, and differentiation occur every day and throughout life. These processes are absolutely critical in repairing damage and replacing worn out tissue components. It is important to realize that the processes of growth and repair are very tightly controlled by genes in the nucleus of every cell. When these processes are working perfectly, cells that can replicate make exact copies of themselves, and other cells ensure that tissues continue to function properly.

Tumors (neoplasms) are groups of abnormal cells that have escaped from the normal controls of cell division, replication, and differentiation. The fundamental 'thing' that starts and fuels this out-of-control process is mutation of genes that program and control cells. Mutations (changes in gene structure and function) have an important normal role in evolution, as they provide the mechanisms needed for changes in genes to be incorporated into organisms (and eventually into species). Mutations that favor new characteristics and improve survival become permanent additions to the gene blueprint of cells ("the genome"). Mutations that damage the DNA in genes in the genome and that impair cell survival usually aren't preserved, as the cells with these profound defects die off before they make more cells.

Some mutations affect critical elements in genes that control cell growth, replication, differentiation, and survival. It is these mutations that give rise to tumors (neoplasms).

Mutations can be caused by many things. Surprisingly, some mutations (favoring abnormal gene control and function) can be inherited. We know that the selective breeding of dogs for the past 200+ years has facilitated the passage of mutations favoring tumor development in some breeds of dogs, including

> Tumors (neoplasms) are groups of abnormal cells that have escaped from the normal controls of cell division, replication, and differentiation.

Westies. An example of an inherited 'risk' for developing tumors is bladder cancer in Scottish and West Highland White Terriers (see *Bladder Cancer in Westies and Scotties*). At some point in the selective breeding of these purebreds, one or more mutations were incorporated into their genome and have been inherited ever since. Another example is lymphoma in Golden Retriever dogs. Based on breed and health club statistics, about 60% of Golden Retrievers will succumb to lymphoma or tumors of the spleen (hemangiosarcoma). As dog breeders and owners, we need to be aware of the presence of breed-associated inherited mutations linked to the development of tumors.

Many mutations are caused by exposure to excessive ionizing radiation (e.g., ultraviolet light, x-rays/gamma rays), chemicals that damage DNA (called chemical mutagens), and some very specialized viruses (called oncogenic viruses). These entities (radiation, chemicals, and viruses) are collectively referred to as carcinogenic agents. They damage DNA and genes, removing critical control elements that regulate cell replication, differentiation and survival. Dogs and people get exposed to these carcinogenic agents in the air, drinking water, in food, and by direct physical contact. Exposure is unavoidable; but our bodies and those of our dogs are very resistant to the effects of the agents, and very, very few exposures ever lead to mutations and even fewer lead to the uncontrolled growth of cells (tumors). Our bodies simply kill off nearly all mutated cells. Unfortunately, a few survive.

We now know that the formation of tumors begins in individual cells that acquire several mutations (either through inheritance or exposure to carcinogenic agents). These mutated cells make more mutated cells…and more mutated cells, creating a tumor. This process of evolving from one uncontrolled cell to a clinically important tumor takes months to years. So, by the time we owners see tumors in or on our dogs, they have been developing for a long time.

Benign tumors and malignant tumors ("cancer"): By examining small samples microscopically, tumors are classified by their growth patterns and cell architecture (see *Detecting and Diagnosing Tumors*) as being either benign or malignant. Benign tumors, such as warts (officially known as "cutaneous papillomas"), are characterized by excessive cell growth in a local area. Many benign neoplasms form discrete lumps and bumps. These are frequently treated by surgical removal, local chemotherapy, radiation, cryosurgery (freezing), or a combination of these treatments. Benign tumors usually respond very well to treatment, being well controlled for long periods of time or cured completely.

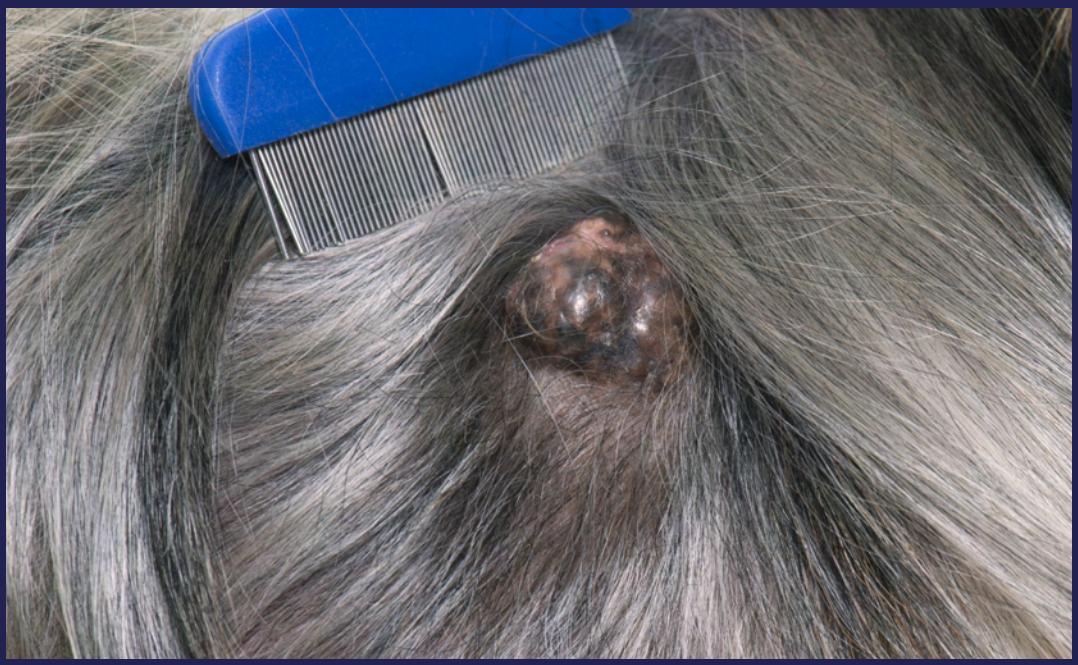

Figure 1 - Some skin tumors may be hidden beneath the dog's hair.

Malignant tumors are a different story. Malignant tumors are those types of neoplasms that are officially "cancer". Malignant tumors start as local uncontrolled cell clusters, but may spread (infiltrate) into the tissue around them. Malignant neoplasms may also spread to distant sites, a process called "metastasis", by way of the blood stream and lymphatic channels. Sometimes, veterinarians will use the terms "carcinoma" or "sarcoma" when discussing malignant neoplasms. These terms help define the type of tissue that the cancer originates from and relates to terminology that pathologists use when describing what they see in the tissue samples (see *Detecting and Diagnosing Tumors*).

Malignant neoplasms are difficult to control or eliminate in dogs and people. One reason for this is that malignant cells tend to infiltrate normal tissues around the site of tumor growth early in the life span of the tumor. Because malignant neoplasms infiltrate tissue, they are more difficult to remove with surgery or radiation therapy. As a result, malignant neoplasms frequently require extensive surgical resection, followed by additional radiation and chemotherapy to control tumor growth. Unfortunately, many malignant tumors are identified after they have grown for a while, and they may be large, highly infiltrative, or have already sent clusters of tumors cells to distant sites, like the lung, liver, brain, or bones (tumor metastases). When these malignant tumors are spread, they are more difficult, if not impossible, to get under control and to cure.

Figure 2 - A great time to start examining your dog is when it is three-weeks old. (Photo courtesy of Bebe Pinter and Kay McGuire, DVM, MS).

Detecting and Diagnosing Tumors

Most tumors are detected by dog owners, not veterinarians! You are your Westie's best friend and spend the most time with your dog. It is very common for owners to be the first to detect "lumps and bumps" that appear on the skin, simply by seeing them, or feeling them as they pet or groom their dog. So, Strategy #1 in fighting tumors – regularly (every day) examine all the parts of your dog you can see and feel. Early detection of tumors is one of the best ways to effectively prevent serious problems – since small tumors are relatively easy to treat and have rarely spread extensively in tissue around them or to distant sites.

Regular examination should start when dogs are very young and continue throughout their life. A great time to start examining your dog is when it is three-weeks old. (see ***Figure 2*** at left, courtesy of Bebe Pinter and Kay McGuire, DVM, MS). This activity helps you bond with your dog and helps the dog get used to being examined; your veterinarian will thank you for doing this. Most importantly, this will help you identify abnormalities like swellings/lumps and potentially painful spots that are often hard to see because they are covered by hair or they are on parts of the dog (the belly, for example) that may not be easy to see. A good routine is to start by patting and stroking the head and face and then moving your hands down the entire body. Palpation (i.e., careful, systematic touching) should extend to the neck, under the legs, the belly and the groin. Your examination should include looking at the eyes, eyelids, ears and into the mouth. Being thorough and starting early in life are keys to success, as dogs get used to the examination as part of their daily routine.

Male dogs need to get used to examination of their penis and testicles; testicular tumors can cause asymmetrical (uneven) swelling of the testicles, generally in older dogs. The absence of a testicle in the scrotal sac ("cryptorchidism"), after dogs have reached 6-12 weeks old, should trigger a visit to the veterinarian. Testicles that are retained in the inguinal canal or abdomen may develop tumors later in the dog's life. Breeders need to be especially diligent about regular evaluation of the testes of their male breeding dogs, since testicular tumors are most common in older male dogs. Neutering at a young age effectively eliminates the chance that a male dog will develop testicular tumors.

The careful examination and palpation of the mammary glands is very important, as tumors of the mammary glands are common in all breeds of dogs. Most of these tumors start as small lumps, perhaps the size of a pea, but can grow steadily larger. It is not uncommon for some dogs to have several small lumps develop in the mammary glands over time. Many mammary gland tumors in dogs are benign and can be easily controlled with surgery.

If you find a lump….see your veterinarian! There are many, many things that can cause lumps, bumps, and other abnormalities on the skin, eyes, ears, and "outside parts". Lumps that are scabbed over or which bleed easily, as an example, could be anything ranging from a localized skin infection to a tumor. You and your veterinarian then will determine the next steps to take. If the clinical diagnosis is that the mass may be a tumor, a small sample, called a tissue biopsy, may be obtained. Usually this procedure is performed with the dog under general anesthesia and by surgical incision so the sample can be evaluated by a pathologist. The piece of tissue is first preserved in a solution of formaldehyde and then processed to produce a thin piece of stained tissue on a glass microscope slide. It generally takes 1-2 weeks to process and examine a surgical biopsy. This slide is evaluated by a pathologist trained to recognize the abnormalities in cell size and architecture that differentiates normal cells from tumor cells.

When pathologists examine a biopsy, in most cases they are able to determine if a tumor is benign or malignant. If the veterinarian did a surgical procedure aimed at removing the entire tumor, the pathologist will evaluate the edges of the tissue – the boundary between normal and abnormal tissue (called "the margins") – to see if the tumor has been completely removed. In most cases, surgery to treat tumors (see *Treating Tumors*) is designed to remove all tumor cells, as remaining tumor cells may regrow.

At times, your veterinarian may decide to use other methods to make a diagnosis. One technique, called needle biopsy, involves anesthetizing the mass and surrounding skin with a local anesthetic, and puncturing it with a needle. Fluid and cells drawn out of the lump are examined by the veterinarian or a pathologist to see if changes in cell size and shape indicate a tumor may be present.

While tumors on the outside of the body (skin, mammary glands, testes, eyes, eyelids, ears) can be easily detected by regular and repetitive examination, some tumors grow in tissues inside the body. These tumors are not easily detectable but may produce some signs that your dog needs further evaluation. Some clinical signs that may trigger further evaluation include:

- Unexplained loss of weight and changes in eating habits, including loss of appetite
- Unusual discharges from body orifices including ears, mouth, reproductive tract, or digestive tract
- Unusual behavior, including lethargy or sleepiness that is not normal for your dog
- Unusual weakness or lameness
- Pale gums
- Other changes in the normal routine of your dog that make you think "Something is not right". In fact, this is how I detected tumors in several of my dogs and cats. My dog Heidi, age 11, suddenly collapsed because a tumor in her abdomen was making hormones that interfered with blood calcium concentrations.

When you suspect that "something is not right", your veterinarian will conduct a thorough physical evaluation of your dog, very likely will take blood samples to evaluate general health (hematology and clinical chemistry evaluation) and potentially detect abnormalities, and may recommend radiographs (x-rays) to examine your dog's internal organs. In many cases, this more thorough evaluation will help determine if a tumor is present, where it is located, and which tissues are involved. This process will help you and your veterinarian determine the best course of treatment. If an internal mass is detected, it is common for veterinarians to recommend that a biopsy sample be collected. This sample will be examined to determine the type of tumor present and, based on its characteristics and what is known about tumors of this type, to predict how the tumor will behave (grow and potentially spread) and which therapies might be effective.

Common Tumor Problems in Westies

A couple of generalizations about tumors in dogs will help put things in perspective:

- Tumors are more common in middle age (over 5 years old) and older aged dogs, than in young dogs.
- Most tumors develop slowly and the cause of the tumors is never known; owners need to know they very likely could not have prevented the development of a tumor, except…
- Early neutering of male dogs will eliminate development of testicular tumors and may affect development of prostate problems.
- Spaying of female dogs less than one year of age will decrease the incidence of mammary gland tumors as the dog ages. Early spaying eliminates the possibility of developing both ovarian and uterine tumors, although neither of these types of tumors are common in dogs.
- Regular examinations by owners and veterinarians help detect tumors at earlier stages, when they are more likely to be controlled with surgery, radiation, and chemotherapy – the standard types of treatment.
- Skin tumors are common in all dogs and are usually and effectively treated with surgical removal.

Most Common Types of Tumors
Blood/Lymph Tissue 22.6%
Urinary 17.7%
Skin 14.5%

- Malignant tumors are more difficult to treat and control, are more likely to have poor outcomes, and can be costly to manage if chemotherapy and/or radiation therapy is used.

Tumors in Westies by site of occurrence (62 animals total; number in parentheses is the number of neoplasms)

- Digestive System (7)
- Endocrine System (1)
- Epithelial and Melanocytic Tumors of the Skin (9)
- Hematopoietic/lymphoreticular System, including Malignant Lymphoma (14)
- Mesenchymal Tumors of Skin & Connective Tissue (3)
- Mammary Glands (5)
- Male Genital System (2)
- Nervous System or Eyes (4)
- Respiratory System (6)
- Urinary System (11)

The most common types of neoplasms, based on percentages were: hematopoietic/lymphoreticular system neoplasms including malignant lymphoma (14/62 = 22.6%) and urinary system neoplasms (11/62 = 17.7%).

While the information in this Veterinary Cancer Registry database search is very useful for identifying overall trends in the incidence of neoplasms in dogs, it has limitations. First, only a small number of total cases are submitted for entry into the database, and it is very likely that there are many more dogs with tumors whose records are not submitted for inclusion. Second, only cases in which there has been a biopsy confirmation of the tumor type are included. Many dogs with masses may not be biopsied and their information may not end up in the database. Third, it is very hard to tell if the numbers presented in the Veterinary Cancer Registry database represent all of the dogs at risk. There is no way to know how many Westies (or Scotties, or Cairns, or dogs of mixed heritage) are in the United States. As a result, we can only make rough estimates of 'dogs at risk' for developing neoplasms.

The work of breed clubs like the WFA in conducting surveys of health problems in specific breeds is one of the best ways to know how many Westies (or Scotties, or Cairns, or dogs of mixed heritage) live in the United States. Data from these organizations can help provide rough estimates of 'dogs at risk' for developing neoplasms and is a great help in making more accurate data available.

Bladder Cancer in Westies and Scotties

One type of cancer that is of very serious concern to owners of Westies and Scotties is bladder cancer. The medical designation of this type of malignant neoplasm is "transitional cell carcinoma" of the urinary bladder. Bladder cancer can occur in any dog breed, but is more common in Shetland Sheepdogs, Scottish Terriers and Westies. The median age of occurrence for dogs is around 8 years old.

There are several excellent websites which discuss bladder cancer in dogs, how this tumor is diagnosed and how it is treated. While owners may wish to "Google" this subject, a more comprehensive, scientific literature review and list of references are found at the end of this section.

A brief summary of important aspects of this disease will help to alert Westie owners that their dog may have a problem.

Bladder cancer develops from cells that line the urinary bladder and the kidney. There appear to be several factors that influence whether or not this neoplasm will develop. In dogs, the genome appears to play a major role, as some breeds (the short legged Scots breeds like Westies and Scotties) appear to have a higher incidence per capita than other breeds of dogs (see below). This increased breed incidence suggests that during the development of the breed, certain mutations in the genome were acquired and linked to desirable breed characteristics. It is very likely that several mutations may be present and research scientists are actively looking for them, in order to see what is causing cancer to develop. Remember, not every dog will inherit mutations that can lead to the development of cancer, and it

may take the complex interactions of several mutations to lead to the initiation and development of neoplasms.

One other important factor in the development of bladder neoplasms in Scotties, though not proven to be a factor in Westies, is exposure to certain environmental chemicals. Glickman and his colleagues at the Purdue University School of Veterinary Medicine have shown that repeated exposure to one type of common lawn chemical – phenoxy herbicides – may lead to an increased risk for developing bladder cancer. There are several other important factors (see below).

Diagnosing Urinary Bladder Cancer in Dogs

The first clinical signs that there may a problem with the health and function of the urinary bladder may be one or more of the following:

- Difficulty urinating
- Frequent attempts to urinate (a change in the pattern of urination)
- Dribbling urine
- Loss of housebreaking in adult dogs
- Blood in the urine ("hematuria), evidenced by pink or red spots on floors and carpets
- Abdominal tenderness

These signs only indicate a potential problem with the health and function of the bladder and are not specific for any disease. For example, these signs might indicate bladder infection, the presence of bladder stones, a neurologic problem leading to altered bladder function, or the presence of a neoplasm, among other diseases. However, if Westie owners detect any of these signs, it is important for them to take their dog to their veterinarian for further evaluation.

The veterinarian will perform a physical examination and suggest some additional tests to narrow down what is causing the dog to have signs of bladder disease. During the physical examination, it is very likely the veterinarian will gently palpate the dog's abdomen, paying attention for signs of tenderness, especially around the area of the urinary bladder.

The veterinarian may suggest collecting a urine sample, either by catching urine in a pan or a cup during spontaneous urination (a "freecatch' specimen), by passing a catheter into the bladder, or by taking a small sample with a syringe and needle, through the abdominal wall ("cystocentesis'). Urine samples collected with a catheter or by cystocentesis can be used for bacterial culture – to see if there is an infection present. Urine samples can also be analyzed for the presence of blood and to see what types of cells and other suspended materials are present. In some cases, veterinarians and clinical pathologists will identify clumps of cells that may indicate the presence of tumors.

It is very likely that your veterinarian will also suggest additional tests (see below). Recently, a test called the bladder tumor antigen test ("VBTA') was developed to help detect the presence of some unique proteins associated with transitional cell carcinoma in dogs. Other "tumor marker" tests that detect proteins in urine associated with the development of bladder cancer are also being developed. Eventually, these tests may be especially helpful in screening for the presence of a neoplasm.

It is quite common now for veterinarians to use radiography (the old term was "xrays"), ultrasonograpy, or computed tomography (CT) to look for masses in the bladder. Shown on the following page is a CT image of the urinary bladder of a Sheltie dog which was seen by a veterinarian for blood in the urine (See ***Figure 4,*** below). In this image, the arrow points to a dark mass (a "filling defect") which is a transitional cell carcinoma projecting into the center of the bladder. These imaging techniques are very helpful in differentiating between bladder stones and tumors.

Definitive Diagnosis and Options for Therapy

If there is a high likelihood that a tumor is present, your veterinarian may want to perform a surgical biopsy. This will involve general anesthesia, an exploratory surgical procedure of the abdomen, and opening of the urinary bladder. Some veterinarians will remove as much tumor as possible during this procedure. Others may choose to take a small biopsy to be sent to a pathologist (see above), and then to treat the bladder with one or more chemotherapeutic agents.

Chemotherapeutic drugs used to treat cancer of the urinary bladder in dogs are identical to those used to treat this neoplasm in people. All cancer chemotherapy drugs are given to kill tumor cells. They do this in a variety of ways, including interrupting tumor cell division, blocking tumor cell metabolism, breaking down tumor cell DNA and genes, or poisoning other tumor cell activities.

Cancer chemotherapy drugs are usually given by mouth or injection, or a combination of these methods. Treatment may continue for months, depending on the extent of the tumor, response of the tumor to therapy, and tolerance for the side effects of the drugs. Typical unpleasant side effects seen in some dogs may include vomiting and diarrhea, loss of energy, changes in patterns of urination, and potentially increased susceptibility to infections.

It is very important to know that veterinarians are experienced in treating cancer, that they understand the effects and side effects of drug therapy, and that they are trying to help you and your pet overcome a serious disease problem. Most side effects of drug therapy are transient and temporary, and can be managed with supportive care.

You need to discuss this with your veterinarian when deciding how and if to treat your dog. Most veterinarians will also discuss the use of medications to control any discomfort and will be candid about the probability of the treatments being effective.

The outlook ("prognosis") for dogs with bladder cancer is guarded and depends a great deal on:

- Initial size and location of the tumor
- Amount of invasion of the bladder wall and surrounding tissues in the abdomen
- Metastasis of tumor cells to lymph nodes and other locations
- Age and overall health of the dog

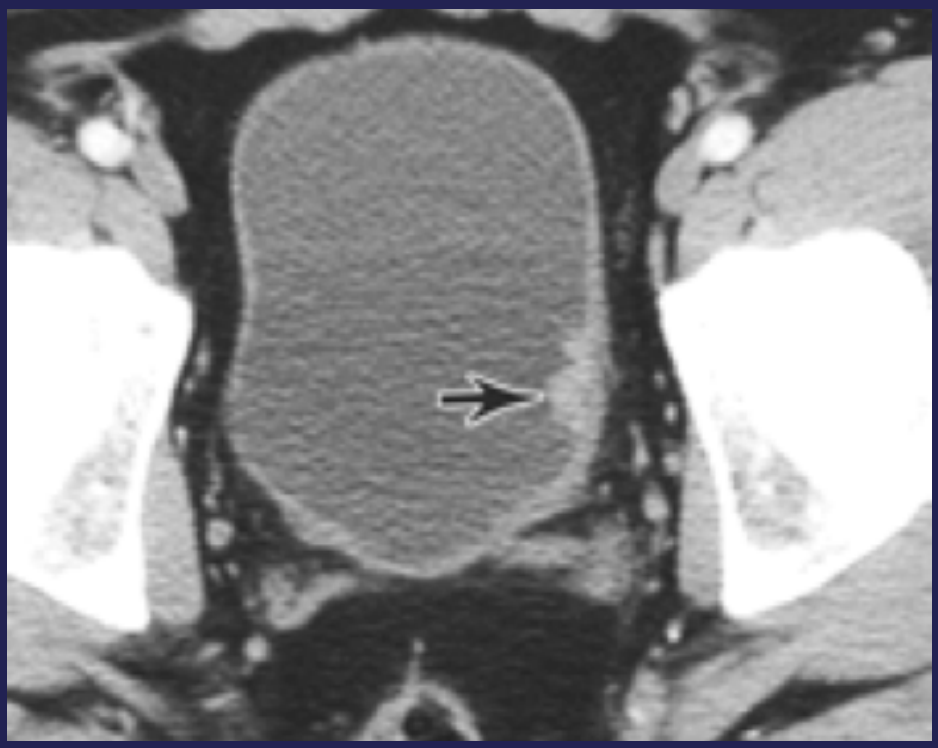

Figure 3 - A CT image of the urinary bladder of a Sheltie dog which was seen by a veterinarian for blood in the urine. The arrow points to a dark mass (a "filling defect") is a transitional cell carcinoma projecting into the center of the bladder.

- Type of tumor, including degree of differentiation and cellular patterning
- Response of tumor cells to chemotherapy
- Toxic side effects of chemotherapy

According to Dr. Deborah Knapp, et al, the median survival of all breeds of dogs with the early stages of transitional cell carcinoma is 218 days. For dogs with more advanced disease, the survival is about half of that interval. Of course, the outcome for any individual dog is hard to predict, but transitional cell carcinoma of the urinary bladder is one of the most serious health problems affecting Westies and other short legged Scots breed terriers (see below).

The early detection of bladder cancer in "high risk" dogs (including Scottish and West Highland White Terriers, Shetland Sheepdogs, among others) would allow more timely intervention (chemotherapy, surgery) and is likely to be associated with better prognosis. Development of simple, economical tests using urine specimens will allow life-long sampling of high-risk dog breeds and may decrease the devastating effects of bladder cancer in these breeds.

Transitional Cell Carcinoma

According to several excellent, comprehensive papers and review articles (Norris et al, 1992; Knapp et al, 2014), bladder cancer is common in all dogs; about 2% of all dogs in a post-mortem research study had bladder cancer. It is estimated, based on the size of the dog population, that there may be at least 15,000-20,000 new cases each year. Bladder cancer is especially common in several breeds of dogs. In one recent study, the odds that a particular breed would develop bladder cancer was compared against the odds that the disease would occur in mixed breed dogs. These comparisons involved calculating 'odds ratios' [OR], with an OR value of 1.0 meaning that a specific breed and mixed breed dogs were equally likely to develop bladder cancer. Furthermore, if the OR was greater than 1, then the breed was more likely to develop the disease. In that study, Scottish Terriers (OR=21.12), Eskimo Dogs (OR = 6.58), Shetland Sheepdogs (OR=6.05), West Highland White Terriers (OR=5.84), and Beagles (OR=3.09) were found more likely to develop bladder cancer (Knapp et al, 2014). In addition to breed-associated (genomic) predispositions, risk factors for the development of bladder cancer in dogs include advancing age (more common in middle-aged and older dogs), sex and neutering status (more common in female dogs than male dogs, and more common in neutered dogs), obesity (Glickman et al, 1989) and exposure to some chemicals, including commonly-used herbicide lawn treatments (Glickman et al, 1989, 2004; Knapp et al, 2013), water disinfection products (Backer et al, 2008) and older generation flea control products (Glickman et al, 1989).

As indicated above, bladder cancer is suspected in dogs with clinical signs of difficulty urinating, hematuria, changes in patterns of housebreaking, frequent attempts at urination, and evidence of pain when urinating. Many of these clinical signs resemble those seen dogs with bladder infection ("cystitis"). As a result, it is important for dogs with these clinical signs to be examined thoroughly by a veterinarian. In many of those cases, diagnostic testing will include urinalysis with cytology evaluation, hematology and chemistry profile (to include or exclude systemic and/or urinary tract disease), urine culture (to include or exclude inflammatory/infectious cystitis), and diagnostic imaging, such as ultrasonography (Hanazono et al, 2014), standard radiography with and without contrast agents, and computed tomography. While a definitive diagnosis may be made based on abnormal urine cytology findings, the gold-standard is by evaluating a biopsy specimen procured with cystoscopy under sedation/anesthesia. The cost of such a comprehensive work-up often will exceed several hundreds of dollars.

When the diagnosis of bladder cancer is made, most dogs have relatively advanced disease –tumor cell growth has penetrated the musculature of the bladder wall, or spread to tissues adjacent to the bladder in the abdomen (Higuchi et al, 2013), or elsewhere in the body (e.g., lung, lymph node, bone, and other sites) (Knapp et al, 2000). Dogs with bladder cancer are most commonly treated with single- or multi-agent chemotherapy, with remissions up to 50% being reported and median survival times ranging from 130-250 days (Robat et al, 2010; McMillan et al, 2011; Knapp et al, 2013, Fulkerson et al, 2015). Bladder resection, radiotherapy, or combinations of therapies are not commonly used in dogs. Dogs rarely are cured or live more than one year, even with therapy.

Routine screening for hematuria, which may be associated with bladder cancer in asymptomatic dogs, is not practical. This would require regular collection of urine samples, probably at least on a yearly basis. Likewise, routine screening of all dogs is not economically viable. Many owners would be reluctant to pay $25 -$75 for a yearly urinalysis, which might not be either sensitive enough or specific enough to detect a disease affecting less than 5% of 'normal risk' dogs.

For decades, veterinary clinicians have relied on examination of urine cytology as a reliable first diagnostic test when bladder cancer is suspected (primarily due to detection of hematuria and/or pain), followed by cystoscopic bladder inspection and biopsy of suspect lesions. Such methods are valuable in detection of high-grade bladder cancer, but lack sensitivity for detecting low-grade tumors (Lokeshwar et al, 2001).

Over this same period, veterinary clinicians and researchers have searched intensively for biological markers of tumor

growth that may be present in urine specimens (including cytologic markers) and biopsy specimens. The obvious value of these biomarkers would be rapid, sensitive/specific identification of bladder cancer, the ability to differentiate bladder cancer from inflammatory or degenerative diseases affecting the kidneys, bladder or urethra, and the ability to screen "high-risk" individuals for early bladder cancer. Biomarkers that might be present in urine would facilitate non-invasive, repetitive analysis without the need for sedation or anesthesia. A number of non-invasive biomarker probes have been developed. These include NMP-22 (a protein associated with apoptosis) (Grossman et al, 2005), BTA (bladder tumor basement membrane protein) (Irani et al, 1999), FISH (fluorescent, in-situ hybridization) probes for cell chromosomal abnormalities (UroVysion) (Hajdinjak et al, 2008), tumor sensitive monoclonal antibodies (ImmunoCyt) (Vriesema et al, 2001), and gene product-based assays (Allen et al, 1996; Borjesson et al, 1999; Mochizuki et al, 2015a,b; Decker et al, 2015).

None of these markers have gained wide acceptance, become a standard-of-care for patient screening, or are used for routine screening of either "normal-risk" or "high-risk" individuals – be they canine or human patients. They are somewhat costly, require some degree of expertise to achieve valid results, and are highly dependent on sample quality and stage of tumor growth. The fact these biomarker assays have not seen wide use in human medicine in nearly two decades makes it seem unlikely they will see wide use in veterinary practice, although multiplex marker approaches may have limited use (Bracha et al, 2014).

Most recently, a single mutation in the canine BRAF gene was identified in tissue samples obtained from some dogs with transitional cell carcinoma and urothelial/bladder cancer. This discovery was made by comparing the DNA and RNA sequences of genes from dogs with bladder cancer against those from dogs lacking cancer. This mutation changed a single amino acid in the BRAF protein, which was associated with development of cell proliferation and the development of cancer. (Mochizuki H et al, 2015). In subsequent work, a laboratory assay was developed to see if the mutation could be detected in cells shed in urine samples collected from dogs at high risk of developing either of these diseases (Decker et al, 2015). This assay has now been used suc cessfully to identify small masses in the bladder of dogs 3 to 4 months before they developed any clinical signs associated with the disease condition. This is an exciting step forward in helping detect these problems in dogs at the earliest possible time point, thereby improving their likelihood for a positive response to treatment. Additional information about this assay is available at www.SentinelBiomedical.com

In summary.

We collectively (owners, breeders, veterinarians, and research scientists) need to put forth our best efforts to identify the causes and to find effective treatments for tumors in our dogs.

We owe them that.

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