The Rising Storm
What Breeders Need to Know
About the Immune System

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A complex and threatening storm is gathering on horizon. Reports of immune-mediated disease are on the rise in Australian Shepherds, as well as other purebred dogs. In magazines, on Internet discussion lists and at gatherings devoted to dogs autoimmune disease and allergies are regular topics. Immune-mediated disease results from excessive or inadequate action by the immune system. But what do we know about this rising storm of health problems, and is there anything breeder's can do about it?

What is Happening Here?

Mix-breed dogs and other species, including humans, have also experienced apparent increases in immune-mediated disease. Two factors are increased knowledge about the immune system by the scientific community and improved awareness on the part of the general public in the wake of the AIDS crisis. We know a lot more today about how the immune system works and how it fails than we did only a couple decades ago.

Proper diagnosis of some of these diseases was once difficult. The presenting signs of diseases like thyroiditis are also seen in a variety of other conditions. Today improved knowledge and technology enable veterinarians to make more accurate diagnoses. Coupled with this, present day dog owners are more likely to take an ailing pet to the vet for conditions that do not present an obvious or immediate threat than was often the case in decades past. Both the increase in numbers of dogs being seen and improvements in veterinary medicine have without doubt contributed to the apparent increase in immune-mediated disease.

However, not all the increase is an artifact of better reporting. Environmental factors also play a role. We and our dogs are exposed to potentially irritating substances—ranging from food preservatives to cleaning solvents to garden chemicals—which our grandparents, not to mention our dogs' great-great-grandparents, never encountered. Some of these substances have been shown to affect various bodily functions, including that of the immune system. Our technological culture has made changes in our environment that would never occur in nature and we are only beginning to understand out what is going on.

Vaccines are a part of this technological effect. Over-aggressive administration of vaccines can compromise immune function. However, the benefits of vaccination far outweigh the risks. The "core "diseases for which we commonly vaccinate our dogs, like distemper and parvo, can be fatal. Dog owners should not avoid vaccinating, but should work with their veterinarians to implement a vaccination protocol that gives the dog sufficient protection from infectious diseases without vaccine over-use. Vaccination should be administered only if a dog is at risk for that particular disease and adequate intervals should be left between vaccinations so that the dog's immune system is not overwhelmed. Over-vaccination has been implicated as a possible cause of autoimmune hemolytic anemia.

Nutrition can also affect the efficiency of immune system function. Deficiencies in Vitamin E or selenium, a trance mineral, can result in a deficit of immune competent cells. These substances aid body mechanisms that counteract damaging free radicals that arise from normal metabolic functions such as breathing. As your dog ages, its immune system becomes less efficient in handling free radicals. Proper levels of Vitamin E and selenium in the diet can help the immune system function as well as possible for dogs that are sick or

old.

Most commercial dog feeds and the commonly used raw diets have sufficient selenium but may be lacking in Vitamin E, so supplementation may be advised. Some areas have selenium-deficient soils. (The Columbia River Gorge in Oregon and Washington is one example). If the products that form the basis of the diet you are feeding come from such an area, careful supplementing may be necessary. Eexcess selenium can be unhealthy, so follow professional advice and label directions carefully.

But despite the improvements in diagnosis and the problems stemming from environmental conditions, a dog's genetic makeup has a significant part to play in how well its immune system works.

Genetic Roots

The immune system is governed by the Major Histocompatability Complex (MHC). This group of genes is referred to as a "complex" because they are all positioned close together on one chromosome. This positioning virtually guarantees that the genes will be inherited as a unit called a haplotype. The haplotype will be passed to offspring without the usual shuffling that occurs as genes are distributed into sperm or eggs. Every individual possesses two MHC haplotypes, one inherited from each parent.

The MHC enables the immune system to respond appropriately to the intrusion of infectious agents, like viruses or bacteria. It is not unique to dogs, but exists in all species of mammals. Genes within the MHC are unusual in that they are highly polymorphic, each having many—sometimes as many as 100—different alleles, or forms. There are so many alleles it is probable that most individuals in a randomly breeding population, such as wild species, will have unique combinations of MHC genes. It is this very lack of similarity that leads to graft-vs.-host disease in transplant patients and why full siblings make the best transplant donors.

MHC genes also have the highest mutation rate of genes for any germ-line cell. Germ line cells are those that ultimately produce sperm or eggs. In other genes, mutations usually confer little benefit to the individual and may cause considerable difficulty. MHC genes mutate readily because their diversity is important to species survival. Such extreme polymorphism is unusual. Biological systems tend to be conservative, keeping energy and resource needs to a minimum. The simpler a system, the less prone it is to breakdown.

So why do we see all this complexity with the MHC? It is Nature's answer to the problem of infectious disease. The immune system must be prepared to tackle many different infectious agents. A mere handful of alleles would not allow the necessary flexibility to face down an ever-evolving array of pathogens. In most cases, each haplotype a dog has will differ from the other, thus increasing its odds of having something in its immune arsenal that will work against whatever nasty bug it may encounter. A plague may kill those individuals who don't have the correct combination of MHC alleles to fight the disease. It may even kill a major part of a population, as happened with bubonic plague among humans in centuries past. While each individual has only two haplotypes, the overall population of its species will have many. Therefore, when a new plague organism comes along, as they inevitably do, the species will survive even though some or even many individuals may be lost.

As an example, HIV-positive individuals that have considerable MHC heterozygosity—meaning they have different, rather than similar (homozygous) pairs of MHC genes—are more likely to survive to 10 years without succumbing to AIDS. On the other hand, those who are homozygous for certain MHC genes are certain to die within the same period.

Survivors of epidemics have the "right" combination of MHC alleles to combat that particular infectious disease. The same plague may occur again and again, but as time goes by it becomes less virulent because those with inadequate MHCs will have died and been removed from the breeding population. The

high MHC mutation rate guarantees that there will be plenty of ammunition for any new plagues that occur.

MHC complexity is an excellent example of the importance of biological diversity—not only among species but also within them. All naturally reproducing species will avoid or significantly limit inbreeding. (For the purposes of this article, the term inbreeding includes what dog breeders refer to as linebreeding.) Studies in mice have shown that females, given a choice, show significant preference for mates with dissimilar MHCs, thereby conferring offspring sired by those males with more flexible immune systems. Even in humans a study has indicated females have some degree of preference for males with different MHCs, though no one argues that there are a plethora of other considerations that strongly influence a woman's mate choice. No studies have been done on dogs to date, but anecdotal reports of bitches that refuse to mate with closely related dogs are not unusual. In an inbred individual, the chance that both parents have passed on identical genes within the MHC increases. This situation diminishes the body's capability to mount an effective immune response. Such dogs are more prone to infections and are more likely to suffer autoimmune disease or allergies.

Autoimmune Disease
Every living thing, whether dog, human or microbe, will sooner or later experience ill health. The cause may be a virus or bacterium, an injury or even old age, But that your dog's own body might attack itself and cause serious illness seems bizarre. But this is the case with autoimmune disease.

A bad combination of MHC genes can predispose an individual for this type of disease. Each of the more than three dozen recognized autoimmune diseases are influenced by certain MHC genes. In autoimmune disease, the immune system loses its ability to distinguish self from non-self and attacks the body's own tissues

The immune system is designed to search out and destroy microscopic invaders. Its specialized cells circulate through the bloodstream, hunting down, disabling and consuming viruses and bacteria, which they recognize by their foreign proteins. Immune cells are genetically programmed to recognize the body's own proteins as well as those of the various organisms that lead their quiet and often beneficial lives on or within our dogs. But sometimes something goes terribly wrong, resulting in immune cells that target one or more of their own body's tissues, or attack the various benign residents. The author has personally experienced this; her eyes have suffered significant damage wrought by her own immune cells.

Environmental conditions can induce autoimmune disease, but a dog's genetic make-up also plays a role. It is vital that breeders inform themselves about common canine autoimmune diseases, how they are diagnosed and whether they are inherited.

Autoimmune disease does not just happen; it requires a "trigger," an event that starts the disease process. The cause will be some sort of stress factor—another disease, an injury, exhaustion, exposure, emotional distress, toxic exposures, or even something so subtle you may never know exactly what precipitated the illness.

Sometimes the result will be temporary and the autoimmune reaction will cease as the body recovers, never to return. An example would be localized demodectic mange. The demodex mites live in the hair follicles of most if not all dogs. In normal circumstances, they are benign residents: they provide no apparent benefit but neither do they cause harm. Sometimes a puppy will have a reaction to the presence of these mites, resulting in localized demodectic mange. A small, coin-sized bald spot will develop, usually on the dog's face or forelegs. Most veterinarians will prescribe a miticide when they diagnose the disease, but treated or not it will eventually go away on its own. (There is another, more virulent, form of this disease that will be discussed below.) The disease is brought on by a temporary compromise of a young immune system still learning how to do its job. Once the crisis is past, the disease will go away.

In most cases, there will be no sequel, but the author is aware of one dog that had localized demodex mange as a pup and went on to develop lupus in later life. Early autoimmune reactions may, in some dogs, indicate an inherently faulty immune system. If a dog with localized demodex has relatives who have also had it or relatives with chronic autoimmune disease, the mange could be a precursor of things to come.

Of greater concern, especially to a dog breeder, are the chronic, genetically influenced forms of autoimmune disease—the ones that, once started, will be a health concern for the balance of the dog's life. Chronic autoimmune disease is multi-factorial, meaning several things must happen for an individual to become ill. First, the dog must be genetically pre-disposed via the makeup of its MHC. The genetically predisposed dog must then experience a trigger. A dog which never experiences a trigger will never develop disease even though it has the necessary genes.

While the affected dogs may be relatively free of symptoms when the disease is not active, there will be continuing flare-ups even with treatment. Some autoimmune diseases are readily identified, but others can be difficult to diagnose as they mimic other conditions. Diagnostic tests are available for some, but not all. These diseases cannot be cured and require life-long treatment for the affected dog. Sometimes they are fatal.

Steroids are a common treatment for many autoimmune disorders. These are medications that can have serious side effects if taken in large enough doses or administered constantly over an extended period of time. Non-steroid medication may not be available for some diseases. There may come a point where the disease ceases to respond to one or all medications though most dogs can be maintained in reasonable comfort with proper treatment.

These diseases usually do not appear until the dog is a young adult. Sometimes they will arise later in life. It is very possible affected dogs will have been bred prior to the disease becoming known.

The Major Autoimmune Players
Theoretically, any body system or tissue could fall prey to an autoimmune attack. In practice, however, there are some diseases that occur more frequently than others. The following are those most commonly encountered in Australian Shepherds:
Thyroiditis is the most frequently reported autoimmune disease in dogs, both purebred and mongrel. The slow and eventually total destruction of the thyroid gland can cause a wide variety of signs in the affected dog, with the most common being hair loss with thickened oily skin, obesity and lethargy. Less frequently, affected dogs may develop other problems, including reproductive failure, seizures and corneal dystrophy. Sometimes these dogs will not display any of the more "classic" signs of hypothyroid disease. All of these signs might also be the result of other conditions, so a thorough veterinary exam is indicated. Blood panels can be done to diagnose this disease, as well as identify probable carriers, but the tests do not always yield black and white results and may need to be repeated at intervals.
Lupus comes in two forms. The least serious is discoid lupus, a skin disease resulting in hair loss and crusty, irritated areas of skin, usually on the face and head. Discoid lupus can advance to the more serious form, lupus erythematosus, a systemic disease. Dogs with systemic lupus can suffer a variety of problems. Other autoimmune diseases, including hemolytic anemia and thrombocytopenia can be secondary to systemic lupus. In serious cases the disease can prove fatal. Lupus can be diagnosed with a biopsy but there is no screening test that will reveal carriers or affected animals that have yet to become symptomatic.
Generalized Demodectic Mange Sometimes a dog's immune system will be incapable of accepting the presence of demodex mites and will repeatedly react to them, with affected areas spreading across the body. Untreated, the entire skin surface can become involved and severe secondary bacterial infections may develop, a miserable and likely fatal state. Diagnosis is made on the appearance of the lesions and case history. There are no screening tests.

Myasthenia Gravis In this disease the immune system targets the motor end plates–the connection between the nerves and the voluntary muscles. Affected dogs tire easily and may stumble for no apparent reason. They often also have megaesophagus. Vigorous exercise may bring on collapse and severe attacks can mimic toxic exposure. The disease can be acquired, but is more likely to be inherited. There is no screening test.

Other autoimmune diseases seen less frequently in Aussies include pemphigus, Vogt-Koyanagi-Harada (uveodermatologic) Sydrome, Addison's Disease, idiopathic thrombocytopenic purpura, inflammatory bowel disease, diabetes mellitus, and glomerulonephritis.

The author's own family provides an example of the familial effect of autoimmune disease. As mentioned previously, the author suffers from an autoimmune eye disease, her sister has lupus erythematosus, her brother's daughter has rheumatoid arthritis, and her other sister's daughter has inflammatory bowel disease. All these diseases are different but all are autoimmune, indicating that the author's parents had an unfortunate combination of MHC haplotypes to pass on to their offspring. Based on her mother's extensive family genealogical studies, the author is confident that her family is not inbred. Unfortunately, Aussies and other purebred dogs generally are. The more inbred a population is, the more widespread the incidence of autoimmune disease can be.

Allergies
Dogs also get allergies, just as we do. Like us, dogs can have respiratory or digestive problems caused by allergies, but most likely they will itch. Allergic reactions are rarely fatal for dogs, though they are a persistent nuisance and, for some especially sensitive dogs, a source of ongoing misery.

A severely allergic dog may itch constantly, damaging its skin and coat with continual scratching, biting and rubbing. The skin damage may result in secondary bacterial and yeast infections. An allergic dog may also have chronic and occasionally severe respiratory or digestive problems. Or, in the worst-case scenario, succumb to anaphylactic shock. However, with proper diagnosis and treatment, most dogs can live in relative comfort.

Allergies are the physical expression of the immune system's over-reaction to substances, called "allergens." Allergens are not normally irritants and will not bother a normal individual. Allergens can range from pollens and molds to common food items. Flea bite dermatitis is the most common canine allergy; the allergen involved is the saliva of fleas.

Allergies are often discussed in the media, heightening our awareness and sometimes prompting us to call something an "allergy" when it really is not. Diagnosis of canine allergies should be made by a veterinarian; not through the owner's assumptions.

Even though allergies generally don't develop until a dog is at least six months old, allergen exposure usually takes place before four months of age. An allergy does not develop unless there has been prior exposure, which allowed the immune system to recognize the allergen and "decide" that it needed to be attacked if encountered again. This attack upon subsequent exposure is what causes the allergic reaction. Exposure can occur through breathing or eating the allergen or getting it on the skin.

Environmental factors that contribute to allergies include not only exposure to allergens, but parasite load and the administration of vaccines. If a dog has parasites, the immune system will react to their presence. The greater the parasitic load, the greater the stress on the dog's immune system. This can lead to severe allergic reactions if the dog is also exposed to allergens. Fleas are the most problematic parasites where allergies are concerned, but heartworm and intestinal parasites can also set the dog up for allergy attacks.

Both killed and modified live vaccines are potentially allergenic, though for very different reasons. Killed vaccines contain chemicals called adjuvants that enhance the efficacy of the vaccine without exposing the dog to the pathogen. The adjuvants can cause an allergic reaction. In the modified live vaccines, the toxins produced by the pathogen are what cause the reaction. One should keep in mind that in both cases, the vaccines are not the cause of the allergy, but the trigger. A dog must be genetically predisposed to allergies for the reaction to take place.

Atopic dermatitis, a hypersensitivity reaction of the skin, is the second most common form of allergic reaction in dogs. When a dog is exposed to an allergen, usually by inhaling it, the immune system begins producing Immunoglobulin E (IgE), a special type of cell designed to target the allergen. The IgE activates mast cells that release several different substances including histamine, a chemical that causes itching, inflammation and swelling. Most mast cells are found around the feet, ears and anus so allergic reactions of the skin appear more commonly in these areas. If the skin within the ear is affected, the dog may also develop secondary ear infections. Dogs may also experience allergic respiratory problems, digestive problems and eye irritation, but these are much less frequent than the skin reactions.

Respiratory reactions include an asthma-like chronic bronchitis. Affected dogs have a dry, hacking cough that can be brought on by exertion or by pressure on the trachea. Other dogs may have pulmonary infiltration with eosinophilia (PIE,) an allergic reaction in the lungs. Eosinophils are a type of white blood cell, the foot soldiers in the immune system's army. When faced with an infection or allergen, the body produces white cells to fight it. In PIE, the body produces too many of these cells in the lungs, causing respiratory distress.

Food allergies can manifest as digestive problems or skin reactions. In humans, food allergy is over-diagnosed. This is probably also the case in dogs. A number of foods contain substances that can cause mast cells to release histamine, leading to an allergy-like reaction even in a normal individual. Any food can cause reactions in an allergy-prone dog, but some are more likely culprits than others.

The portion of an allergen to which the immune system reacts is called an epitope. The proteins found in wheat have over 50 epitopes, so it is not surprising that allergic dogs often react to wheat-based feeds. Affected dogs tend to vomit within a couple hours of eating and may sometimes have loose stools. Skin reactions are not unusual. These dogs may have difficulty maintaining weight, despite a good appetite. Severely allergic individuals have chronic diarrhea, significant weight loss and poor coat quality. Food allergies often arise after a case of infectious enteritis.

The most severe—and potentially fatal—form of allergic reaction is anaphylactic shock. It can occur after eating something containing an allergen, an injection of drugs or vaccine, or the bite of an insect. Affected dogs will have difficulty breathing. Their gums will be pale due to a drop in blood pressure. Immediate veterinary treatment is necessary.

Some allergic females have fertility problems. It is uncertain whether these are secondary to the allergies or their level of inbreeding (i.e. inbreeding depression.) Allergies may commence as early as six months and have been reported to begin as late as seven years, though most affected dogs will have shown signs by the time they are two or three years old. Depending on the allergens that the dog reacts to, its problems may initially be seasonal, but most cases will advance into a year-round condition.

The Genetic Problem

The over-all canine gene pool probably contains as much MHC diversity as it ever did. However, the division of that gene pool into mutually exclusive sub-sets, or breeds, has guaranteed that any one breed cannot have the full range of MHC alleles present in the species. This limiting factor is further exacerbated

by standard breeding practices such as inbreeding and the use of popular sires.

Without diversity within the MHC, the dog will catch a disease. If the disease is bad enough, the dog may die. If there were only a few possible MHC haplotypes in a breed or species, the risk of an entire population being wiped out by a virulent plague would be very high. The cheetah provides an example from nature. This wild cat species went through an extreme genetic bottleneck sometime in the last ice age. All modern cheetahs are descended from a very few individuals, possibly from a single pregnant female. Thanks to Nature's harsh culling practices—far more stringent than those applied by any dog breeder—the cheetah has survived, but even so it is extremely susceptible to some kinds of disease.

But purebred dog breeds have been artificially selected to meet human needs. In recent decades that selection, especially in show breeds or lines, has included significant inbreeding. The regular use of popular sires over several generations can play havoc with MHC diversity. Since any individual can only have two MHC haplotypes, if a significant portion of a breed descends from a relative few individual dogs the population may not be able to respond effectively to the next canine plague that comes along. Nor may they be able to effectively utilize vaccines. Rottweilers, for example, responded poorly to early parvo vaccines. This often left them vulnerable to the disease if they encountered it. Before the immune system can mount a response to an antigen, the antigen must be first broken into pieces inside the cell and transported to special cell surface receptors. These antigen-binding molecules are called histocompatibility molecules. In Rotts, the parvo vaccines did not work because the body couldn't react to it and thereby protect itself from the disease. Fortunately, the newest generation of vaccines seems to be much more effective in this breed.

For more than a century, inbreeding has been the norm in domestic dogs. The technique is used quite effectively to "fix" traits deemed desirable. This works very well with traits that can readily be observed and measured, such as shape, size and color. It also works, though less well, with complex traits which do not lend themselves to quantification (behavior, temperament, performance drives, etc.)

The practice of inbreeding to improve breed traits has inadvertently led to a reduction of MHC diversity within the various breeds. When added to genetic bottlenecks due to wars, loss of popularity and other drastic population-reducing events, combined with the extensive use of popular sires, MHC diversity may be lowered to critical levels.

Popular sire use is especially pernicious because each such sire can have only two MHC haplotypes--nowhere near the hundreds that exist in the canine genome. Therefore, when a significant portion of a breed descends from one individual, those dogs' resistance to infectious disease or susceptibility to autoimmune disease can be seriously affected.

A correlation has been drawn between the coefficient of inbreeding (COI) and MHC heterozygosity. The COI is a measure of how inbred an individual is. Individuals with low COIs (less inbred) are more likely to have two different MHC haplotypes.

Indications of MHC homozygosity are not always as obvious as an Aussie's susceptibility to autoimmune diseases like thyroiditis or a Rott's inability to react to parvo vaccine. Sometimes the effects are quite subtle. The dog may be a "poor keeper." Or it may be sickly, catching one minor infection after another, but never coming down with anything really serious. Or it may be unable to shake an infection in spite of diligent treatment.

What to do?
While homozygosity of some genes is desirable, particularly those for breed traits like physical type or character, it clearly is not where the MHC is concerned. Most important breed traits are already "fixed"—one doesn't see a purebred Aussie that looks like a Chinese Crested or trails with the obsession of a

Bloodhound. Aussies look and act like Aussies, however much we quibble over the fine points. Given that, breeders must give the prevention of immune-mediated disease a much higher priority, maintaining MHC heterozygosity through reduced inbreeding and not using individuals with chronically impaired immune systems

Unfortunately, there is no way for a dog breeder to determine what MHC haplotypes his breeding stock have. However, there are several steps a he can take to limit the risk of producing dogs with immune-mediated disease.

First, no dog affected with chronic autoimmune disease or serious allergies should be bred. If an animal is being maintained successfully on medication, the breeder should not delude himself that it is "cured" and the disease is not a problem. The sickly and poor keepers should also be removed from breeding programs. At all costs, avoid the over-use of any individual dog, no matter how fine a specimen it might be.

When making breeding decisions, the breeder should avoid crosses that increase the COI above that of the parents and, wherever possible, seek to reduce it. Breeders should be aware of their dogs' COIs. To detect inbreeding that is not apparent in the common three to five generation written pedigrees, the COI should be calculated over several more generations. How many generations depends on the genetic history of the breed, but for most, including Aussies, ten will be adequate. If the COI is high (12.5% or more), mates should be selected which will give a COI in the puppies that is lower than that of the parent with the family history of immune-mediated disease. No matter what the COI, any dog from a family with these diseases should be bred to mates whose families do not.

Neither parents, siblings nor offspring of affected individuals should be bred back on the affected pedigree. Members of affected families used for breeding should be paired with mates from families free of disease. Breeding pairs should be selected that produce puppies with a lower COI than that of the parent from the autoimmune affected family. This will increase the probability of diversity in the MHC. The closer the relationship between an individual and its affected family member, the more care should be taken in mate selection as regards this kind of disease.

If an individual dog has produced multiple cases of autoimmune disease or allergies, especially in different and relatively unrelated mates, serious consideration should be given to withholding it from further breeding. Crosses that produce autoimmune disease or allergies should never be repeated.

If there is significant risk that a particular dog may develop autoimmune disease

or allergy, as is the case with the siblings or offspring of one already affected, it would be wise to hold off breeding that dog until it is 3 or 4 years old to be reasonably assured it will not develop disease.

As with any inherited problem, breeders would do well to record as much information as possible on the allergy and autoimmune disease status of numerous relatives of the dogs they intend to use for breeding. This includes "his sisters and his cousins and his aunts"—those dogs not directly on the pedigree. The more affected family members a dog has, the more likely it is to develop allergies or produce young who will. If screening tests are available for a disease that is frequently encountered, such as thyroiditis they should be used, as should screening tests for diseases that have occurred in a dog's family.

It is up to us

The storm is upon us and will not soon dissipate. Due to the complex nature of immune-mediated disease, its total eradication is unlikely the foreseeable future. Potential impact on breed health is great. Even though we lack the ability to eliminate this kind of disease, damage control must be instituted. We can shelter our dogs from this rising storm if we commit to working within our own breeding programs and in cooperation

with fellow breeders to make that reduction a priority. While no breeder can guarantee he will not produce a dog affected with immune-mediated disease, with good record keeping, diligence and foresight the risk of producing these costly, potentially devastating, and sometimes-fatal diseases can be significantly reduced.