Autoimmune Disease

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What is an autoimmune disease?
When a body encounters something foreign in its environment it needs to be able to mount an immune response against that substance to protect itself from potential harm. In order to do this effectively it must be able to recognize what is self in order to respond to non-self or foreign. In autoimmune diseases there is a failure to recognize some part of self. Such autoimmunity may be restricted to a single organ, a localized region, or the whole animal. The consequences may vary from minimal to catastrophic, depending on the extent to which the body is affected. In autoimmune disease pathologic signs are seen as a result of the autoimmune response. Frequently more than one autoimmune disease will be seen in the same animal, as well as an increased susceptibility to bacterial infection. There are four basic mechanisms underlying autoimmune disease:

1. Antibody mediated diseases: a specific antibody exists targeted against a particular antigen (protein) which leads to its destruction and signs of the disease. Examples are: auto-immune mediated hemolytic anemia, where the target is on the surface of the red blood cell; myasthenia gravis where the target is the acetylcholine receptor in the neuromuscular junction; hypoadrenocorticism (Addison's) where the targets are the cells of the adrenal gland.

2. Immune-complex-mediated diseases: antibodies are produced against proteins in the body, these combine into large molecules which circulate around the body. In systemic lupus erythematosus (SLE) antibodies are formed against several components in the cell's nucleus (hence the anti-nuclear antibody test (ANA) for SLE). Most notably antibodies are made against the body's double stranded DNA, and form circulating soluble complexes of DNA and antibody, which break down in skin causing an increased sensitivity to ultraviolet light and a variety of signs. As the blood is filtered through the kidneys the complexes are trapped in the glomeruli and blood vessels, causing the kidney to leak protein - glomerulonephritis. They also cause leakage in other blood vessels, and there may be hemorrhaging, as well as accumulating in synovial fluid and causing signs of arthritis and joint pain. Rheumatoid

arthritis results from immune complexes (IgM class antibody called rheumatoid factor) against part of the animal's own immune system (part of its IgG molecules). These form complexes which are deposited in the synovia of the joint spaces causing an inflammatory response, joint swelling and pain. The collagen and cartilage of the joint breaks down and is eventually replaced by fibrin which fuses the joints - ankylosis.

3. Antibody and T Cell-mediated diseases: T cells are one of two types (the other being B-cells) which mediate immune reactions. Upon exposure to a particular antigen they become programmed to search for and destroy that particular protein in future. Once an animal has been exposed to an antigen it will be able to mount a much faster response to it the next time it encounters it. This is the basis of vaccination. Thyroiditis (autoimmune hypothyroidism) seems to be of mixed etiology. Several target antigens have been identified, including thyroglobulin, the major hormone made by the thyroid. Autoantibodies to antigens in the epithelial cells of the thyroid have also been found. The thyroid becomes invaded by large numbers of T and B cells as well as macrophages which are cells that engulf and destroy other cell types. T cells specifically programmed for thyroglobulin have been identified.

4. Diseases arising from a deficiency in complement: When an antigen and antibody react they may activate a series of serum enzymes (the complement system) with the end result being either lysis (breakup) of the antigen molecule or a process which makes it easier for phagocytic cells like the macrophages to destroy it. Animals with deficiencies in enzymes activated early in the complement system develop autoimmune diseases like SLE.

Which diseases are autoimmune?
Those diseases of greatest concern in the Bearded Collie are:

1. **Auto-immune mediated anemia (AIMA) also called autoimmune hemolytic anemia (AIHA) and immune mediated hemolytic anemia (IMHA). Antibodies formed against antigens in the red blood cell membrane cause these cells to burst open. The resulting anemia compromises the dog's ability to provide sufficient oxygen for cell function throughout the body.**
2. **Immune-mediated thrombocytopenia (ITP). This results in a dangerously low level of platelets - either due to an increase in antibody and complement-mediated phagocytosis of platelets in the spleen, bone marrow and liver, or decreased production due to antibody and/or complement mediated phagocytosis of platelet stem cells**

(megakaryocytes) in the bone marrow. The low platelet levels lead to spontaneous bleeding, often nose bleeds or petechiae (bleeding just under the skin and mucous membranes) are seen. Blood in the stool, urine or vomit is less common. (Often seen with AIHA, SLE and RA.)

3. Autoimmune thyroiditis (hypothyroidism) is generally found with the other autoimmune diseases or may occur by itself. Loss of thyroid hormones is manifested early by behavioral changes - aggression, hyperactivity, anxiety/fear, compulsive behaviors, phobic behaviors; allergies and reduced resistance to bacterial, viral, fungal and protozoal infection - often manifest as skin and respiratory disorders. Seizure disorders are also often related to low thyroid levels. As the disease progresses lethargy, obesity, alopecia (loss of hair/poor haircoat especially on the sides) and infertility are more common.
4. Hypoadrenocorticism (Addison's disease): The adrenal gland produces hormones which regulate the level of sodium and potassium (mineralocorticoids) and mediate the body's response to physiologic and psychological stress (corticosteroids). The former are needed to maintain proper cell function, their loss is seen as muscle weakness and eventually heart failure as the heart's muscle cells can no longer produce the nervous impulses needed for the heart to contract. Gastrointestinal function is also usually impaired, and weight loss is frequently seen. Animals are less able to cope with mild, everyday occurrences and hide, refuse to eat, and show other symptoms of stress.
5. SLE: Known as the great imitator can be hard to diagnose as it can manifest as a disease of the skin/mucous membranes/nails, kidney and/or joints as has already been described. SLE can also affect the brain producing signs of cognitive dysfunction. It is also hard to diagnose definitively as not all dogs with SLE have postive ANA titers.
6. Pemphigus folliaceus is a skin disease in which pustules are formed. In Beardies they seem to be more common on the feet, but can be restricted to the face or appear patchily all over the dog. After the pustules burst the skin appears crusty or scaly and loses its hair. The dog may chew on or scratch the lesions increasing the damage and ulcers and serious skin erosion may result. Although the antigen has not been specifically identified, pemphigus is a result of autoantibodies directed against the cell membrane of epithelial cells, causing them to become round and separate instead of forming a solid sheet.
7. Rheumatoid Arthritis (RA) was described above.
8. Myasthenia gravis results in a loss of muscle function because nerve signals are no longer received by the muscles. The dog loses muscle mass, due to disuse, and becomes weak and reluctant to move. Enlargement of

the esophagus (megaesophagus) may result. This is often seen as regurgitation of food as soon as it is swallowed, and frequently results in aspiration of food into the lungs. Even when treated, dogs are liable to die of aspiration pneumonia due to megaesophagus. Untreated dogs eventually lose the use of swallowing and respiratory muscles.

9. **Autoimmune myositis is usually divided between polymyositis and masticatory muscle myositis. In the former there is often generalized weakness made worse by exercise. Most frequently the muscles over the top of the head waste away. Fever and depression are common as is megaesophagus. Concomittant SLE, RA and myasthenia gravis have been reported. Masticatory muscle myositis, as the name implies, is limited to the chewing muscles, antibodies are formed to a particular type of muscle fiber.**
10. **Inflammatory Bowel Disease (IBD) is neither a specific disease nor is it clearly an autoimmune disease. In general, it is a catch-all for animals with excessive numbers of inflammatory cells in the mucosa of the stomach, small and/or large intestine for which no other cause can be found and which result in vomiting and/or diarrhea. Although autoantibodies have been found, it is likely that these have been formed secondary to the initiating factor which exposed previously hidden antigens by increasing the permeability of the g/i mucosa.**

What causes autoimmune diseases?

Genetic: It has been shown in humans that particular major histocompatibility complex (MHC) genes are associated with the incidence of specific autoimmune diseases. MHC genes are present in all vertebrates, and are unusual in that they are inherited as a unit, they encode for two major categories of molecules that form part of cell membranes and cross the entire membrane. In particular they have a role in selecting the antigens recognized by T-cells.

An analysis of the pedigrees received of Beardies affected by hypoadrenocorticism in the last survey by the BCCA suggests that this disease is caused by an autosomal recessive gene with incomplete penetrance. A study, funded in part by donations from the BCCA, is being sponsored by AKC-CHF. The researchers hope to identify a gene or genes at one or more loci which correlate with hypoadrenocorticism. To date they have received blood samples and pedigrees from well over 100 Beardies who are either affected with the disease or are closely related to affected dogs. Other breed clubs are now becoming involved in the project. Clearly a blood test for the disease would enable us to reduce the incidence dramatically.

Analysis of pedigrees from an extremely large population of Old English sheepdogs and smaller populations of other breeds, has shown that (almost) all cases of autoimmune disease occur in particular blood lines. Vaccinosis reactions occur in the same blood lines. However, it is equally clear that not all dogs within these groups will develop an autoimmune disease, the majority will live normal, healthy lives, although some may have sub-clinical autoimmune disorders.

Conclusion: It seems likely that a dog must have a genetic tendency in order to develop an autoimmune disease. However, for overt disease to manifest itself specific insults to the animal's immune system must also be presented.

Other factors: We are gradually piecing together some of the factors which can influence whether a dog will develop an autoimmune disease. The health of its immune system in general seems to be a major factor. Dogs are at far more risk when they are already stressed by disease. For this reason it is imperative that we do not further stress a sick dog by vaccinating it (more on this in the other talk). The reported incidence of autoimmune disease is on the rise, and there is some debate as to whether this is because it is really more common or because we are better at detecting it. I believe that both factors are probably involved.

A couple of recent papers suggest that both an increase in pollution and an increase in sanitation could be problematic.

Study 1: Over the last 25 years or more we have received (as have our dogs) small daily doses of insecticides, weed killers and artificial fertilizers in our drinking and bath water. Levels tend to be higher in rural areas where wells are the water source. Most commonly found are carbamate insecticides and triazine herbicides. The government in its wisdom has looked at the effect (mostly looking for cancer) of each chemical individually at low levels when given to lab rodents, and deemed the levels in groundwater "safe". For the last five years a group in Wisconsin have fed cocktails of these contaminants as they are typically found in tap water to male mice via their drinking water. They report a measurable effect on nervous, immune and endocrine systems. Specifically they found the mice less able to mount an antibody response to foreign proteins, increased or reduced levels of thyroid hormones (depending on the mixture) and an increase in aggressive behavior. (They only measured these 3 parameters so other effects on the body were not tested for.) These results were found if the mice received mixtures but not individual chemicals at these low levels. A study of 4 and 5 year old, lowland living children in Mexico

exposed to pesticides compared to a highland group living where there is no pesticide use found increased aggression, reduced stamina and impaired cognitive ability in the former group - all symptoms of hypothyroidism although thyroid levels were not measured in these groups. How about the pesticides we put on our dogs for fleas and ticks, or the lawn and other garden chemicals?

Study 2: A recent article in New Scientist reports a small study from the University of Iowa looking at IBD. It was noted by the group that the reported incidence of IBD correlated with the elimination of intestinal worms. They gave 6 people with chronic IBD a drink with eggs from intestinal worms that don't normally affect people. Five went into complete remission. A larger study is planned. Throughout history until very recently our immune system has been used to the presence of worms in the g/i tract, it seems their removal may have caused the immune system to go into overdrive. It also makes me wonder about the effect of monthly worming our dogs.

Drugs. A number of drugs have been associated with the onset of autoimmune disease. Please contact the author for more information.

Stress is important, whether it is environmental, psychological or physiological. Pregnancy is a stress, as is lactation. Reproductive abnormalities may point to an underlying autoimmune problem or prime the dog's immune system so that it is more susceptible to other stresses. The same is true of many diseases - viral diseases, lymphoma and bone marrow problems as well as failure of immunity seem to be particularly dangerous, however.

Food can also be a source of chemicals which have been implicated in the acquisition of autoimmune disease. Processing resulting in the loss of protective agents from the diet as well, may also be a contributing factor.

Summary. Clearly we cannot protect our dogs - or ourselves - from all potential risk factors, not least because there are still so many which have yet to be identified. Running a complete thyroid panel every year or two on all dogs used for breeding is at present still our best defense. However, we should be careful to not stress our dogs' immune systems. Never vaccinate sick animals - or stress them unnecessarily. Don't worm and vaccinate at the same time, avoid multivalent vaccines. At the same time don't stress yourself by worrying about things over which you have no control. It is important to remember that Beardies are still one of the healthier breeds. In any attempt to reduce the incidence of one problem whether it is poor tail set, bad bites or autoimmune

disease we must avoid throwing out the baby with the bathwater, and maintain the loveable, outgoing breed which has been entrusted to our stewardship.

Vaccination
Together with improved sanitation and epidemiological control vaccination has helped reduce to almost insignificant levels many of the major diseases affecting both humans and animals. It is only because their incidence has been so dramaticaly reduced that we are now able to address concerns relating to vaccine efficacy and safety. While some problems have been traced to poorly attenuated batches of vaccine that revert to virulence after injection or to contamination, others reflect the animals' genetic predisposition to adverse reaction.

These reactions may be immediate anaphylactic hypersensitivity; or acute (24 - 72 hours) or chronic (10 - 30 or more days) immunologic responses. The incidence is low. Estimates vary between a low of 1: 1to 3.5 million to a high of 1: 50,000 to 100,000 animals. Part of the difficulty in obtaining accurate estimates comes in the case of delayed reactions when it is sometimes not possible to establish whether the vaccination was causal or coincidental. However, it is also possible that many of these cases will be missed as the relationship to vaccination a month or more earlier will not seem relevant. Unfortunately, predicting which animals will be susceptible is anywhere from difficult to impossible, and if one owns one of those animals which does react the low odds are unimportant.

Anaphylactic collapse is dramatic and life threatening. Animals have been previously sensitized to the antigens in the vaccine. Signs include vomiting, diarrhea, coldness, pale/colorless mucous membranes, loss of voluntary muscle control, rapid breathing and heart rate. It results from the release of histamine and other amines which cause blood vessels to dilate and blood to pool in peripheral vessels. Death may occur before epinephine and antihistamines can be administered.

Less dramatic reactions may result in fever, stiffness, abdominal tenderness, increased susceptibility to infection, encephalitis, neurological signs, uveitis, autoimmune disease - most often AIHA and/or ITP - and the signs associated with them. Liver and kidney enzyme levels may be elevated, and either organ may collapse. Bone marrow suppression may occur as well. Transient seizures are seen quite often especially in animals prone to thyroiditis or AIHA or ITP. A postvaccination polyneuropathy has been associated with distemper, parvovirus and rabies vaccines among others. This may result in muscle

atrophy, reduced neuronal control of organs and tissues, muscle excitation, incoordination or weakness and seizures.

Contamination of vaccines has indicated a need for greater quality control during vaccine production. Most notably a canine distemper vaccine was contaminated with sheep blue-tongue virus and led to abortion and death in pregnant bitches. Potent adjuvants are commonly added to killed vaccines to produce a more sustained and stronger immune response. These adjuvants have also produced adverse effects, the worst probably resulting from those added to a killed leptospirosis vaccine which has since been withdrawn from the market. The presence of adjuvants calls into question the supposition that killed vaccines are safer than modified-live vaccines. The latter make up the majority of products available currently. They are easier and cheaper to produce, and elicit a longer and more complete antibody response than killed vaccines. Mixing combinations of MLV products with killed bacterins added in the diluent (common in some multivalent vaccines) appears to particularly stress susceptible individuals. MLV vaccines continue to replicate in the host after injection, and trigger a much stronger response, particularly if given in combination with other vaccines. In most cases this may produce a better immune response but in stressed, immature or sick animals who are genetically susceptible the results can be disasterous. Puppies with their immature immune systems are particularly vulnerable, and should not receive vaccines closer than 3 weeks apart (3 to 4 weeks seems optimal). There is some evidence that over vaccinating puppies (some vets advocate weekly vaccination) can make them more susceptible to chronic debilitating diseases as adults. Dogs with atopic allergies tend to have a worsening of signs after vaccination, and it is better to vaccinate them when their seasonal allergies are not active.

Overvaccination is a concern. This may manifest not only as vaccinating more frequently than is necessary, but in giving vaccines which are ineffective or prevent infection by agents which produce a mild disease which may not be noticed. Leptospirosis vaccines have provided short lived (3-6 month) protection against serovars which dogs are not presenting with clinically. A new vaccine was promised to combat varieties which dogs are now getting, but I have not heard any more about it recently, and doubt its long term efficacy. Not only has the leptospirosis vaccine been implicated in numerous vaccinosis reactions, but both owners and veterinarians may overlook a diagnosis of the disease in the mistaken belief the dog is immune to it as a result of vaccination. Vaccination against Lyme disease frequently results in positive Lyme titers if the dog is suspected of having the disease. Most Lyme vaccines have limited

efficacy. Corona virus does not cause illness in adult dogs and generally only mild disease in puppies. A new vaccine against rotavirus has been introduced although there has been no evidence that it causes disease except perhaps in newborns. Canine hepatitis seems to have been eradicated, yet dogs still routinely receive the vaccine. The adminstration of each vaccine introduces more foreign substances into the dog's body with the potential for causing adverse reactions. Meanwhile the owners are having to pay for this. Studies have also shown that immunity induced by giving a puppy series of shots is generally protective for far more than a year, sometimes being effective for life.

A sick dog should never be vaccinated until it is well and recouperated. Vaccination can wait, with the possible exception of the rabies vaccine which some states require be given to the day to consider a dog legally vaccinated (for this reason it may be wise to plan to give a three year shot a month or so early in case the dog is ill when the shot is due). MLV vaccines are shed in the feces for several days after vaccination, and recently vaccinated dogs should be exercised in separate areas from immunocompromised or sick dogs, puppies and pregnant/lactating bitches. Hormonal changes can trigger autoimmune disease, and for this reason it is wise to avoid giving vaccinations before (30 days before expected onset) during or immediately after a bitch's estrus (heat) period. (It has been shown that giving MLV vaccines to heiffers in estrus induces necrotic changes in their ovaries.) Pregnant and lactating bitches should also not be vaccinated. It can affect their puppies as well as the bitch herself. When should a puppy receive its first vaccination? In North Ameica we usually initiate puppy shots at 6 weeks, in Britain the first shot is not given until the puppy is 10 weeks old and in its new home. Certainly I do not believe puppies should be vaccinated at less than 6 weeks of age, although puppies which did not receive colostrum might represent a special case. Maternal immunity transferred to the puppy in the colostrum has a varaible duration, but in general the puppy will respond optimally to the vaccine only when it is 12 weeks old or more. Breed and individual variation within breed can have a significant effect, however. Most dogs have mature immune systems by 22 weeks of age.

In general, all dogs no matter their age or size receive the same dose of vaccine. This makes sense for MLV viruses, but not for killed vaccines. Dose size is based on the minimal immunizing dose for the giant breed and optimal dose has rarely been examined. In humans, attempts to overcome maternal antibodies to measles by giving greater vaccine titers tragically led to high levels of infant mortality, not from measles but from other infectious diseases.

Library Article

Some breeds of dogs or lines within a breed, or those with double dilute factors may be at such high risk of adverse vaccine reactions that their owners will choose not to vaccinate them. Studies have shown that exposure to shedding dogs, particularly if the unvaccinated individual is a show dog, tends to produce some level of immunity against the illnesses for which the majority of dogs receive vaccination. For dogs which have had previous reactions to vaccines, those whose owners do not wish to risk over vaccination for diseases against which their dog already has adequate protection one alternative is to take titers (commonly available only for distemper and parvovirus) every 2 or 3 years and only vaccinate if titers drop below protective levels. They and owners of geriatric dogs ot those with chronic illness may also consider the use of homeopathic nosodes. These are made from an isolate of the particular disease agent. This is prepared as a tincture which then undergoes serial dilutions (potentiation) and succussions (shaking to add kinetic energy). The nosode retains only the energy of the starting isolate and cannot produce infection. While illegal for protection against rabies, nosodes are available for most of the diseases against which there are vaccinations including Lyme disease and kennel cough, as well as heartworm disease. Properly designed controlled studies have not been performed to compare the efficacy of nosodes against allopathic vaccines. A preliminary clinical trial of a nosode for parvovirus failed to protect against challenge from naturally occurring disease. At this point they can only be considered an experimental therapy.

Vaccine manufacturers are being spurred to activity which is perhaps the best result of the vaccine controversy which is being waged in both the veterinary and pet owning communities. In future we can expect to have killed vaccines in doses appropraite for different sizes, breeds and ages of dogs. Recombinant vaccines may also be developed although early experiments have produced unexpected and unacceptable side-effects. Safer, new adjuvants which boost and prolong the effect of killed vaccines can also be expected. So can more research into the length of efficacy of vaccines.

In the meantime, I would recommend asking whether the vaccine you plan to give is needed - is this a disease the dog has any chance of being exposed to, does it cause significant illness in dogs of this age? Is this vaccine effective? If the answer to each is yes, then you may wish to determine whether the dog is still effectively protected against this disease by previous vaccinations (i.e. have blood titers done). If the dog is healthy, not stressed (I would plan to give shots at least 2 to 3 weeks before a trip for example, or avoid them if the whole of your local club will be coming over on the weekend), and has a determined need for the vaccine, go ahead. Watch the dog for at least an hour

after the shot. Try to separate shots, especially MLV from killed, by at least 3 weeks. Make sure your dog has regular check-ups, including base-line blood work annually until he's 10 and then increase the frequency to every 6 months. Even if he seems healthy there may be something you are missing. Do not start puppy shots before 6 weeks of age, and space them every 3 to 4 weeks. Do not worm and vaccinate together, preferably 2 to 3 weeks apart.