W. Jean Dodds, DVM
HEMOPET
938 Stanford Street
Santa Monica, CA 90403

Immune System & Disease Resistance

This article discusses the essential role of the immune system in maintaining the body's overall general health and resistance to disease. The focus will be on environmental factors or events which may cause or trigger immune dysfunction leading to either immune deficiency or immune stimulation (reactive or autoimmunity). Related to these events is the development of cancer which is a disruption of cell growth control.

Overview of the Immune System

Immune competence is provided and maintained by two cellular systems which involve lymphocytes. Lymphocytes are cells produced by the body's primary (bone marrow and thymus) and secondary (lymph nodes and spleen) lymphatic organs. They are descendants of the bone marrow's pool of stem cells, and produce a circulating or humoral immune system derived from B-cells (bursa-dependent or bone marrow derived), and a cellular or cell-mediated immune system that derives from T-cells (thymus dependent).

B-Cell Immunity

B-cell immunity includes the circulating antibodies or immunoglobulins such as IgG, IgM, IgA, IgD, and IgE. These antibodies provide an important defense mechanism against disease in healthy individuals but can become hyperactive or hypoactive in a variety of disease states. Hyperactive or increased levels of immunoglobulins can occur in two ways: acutely, as a reaction to disease or inflammatory insult ("acute phase" reaction); or chronically, as in autoimmune or immune-mediated diseases, chronic infections, and certain types of bone marrow

and organ cancers. Hypoactive or decreased levels of immunoglobulins can result from rare genetically based immunodeficiency states such as agammaglobulinemia or hypogammaglobulinemia, and from the immune suppression associated with chronic viral, bacterial, or parasitic infection, cancers, aging, malnutrition, drugs, toxins, pregnancy, lactation, and stress.

T-cell Immunity

T-cell, or cell-mediated immunity is the cellular mechanism whereby T-cells act as coordinators and effectors of the immune system. Cell-mediated immunity involves the lymph nodes, thymus, spleen, intestine (gut-associated lymphoid tissue), tonsils, and a mucosal secretory immunity conveyed by IgA. The major classes of T-cells are designated as helper, cytotoxic, and suppressor cells. The helper cells "help" coordinate the immune response whereas the cytotoxic cells comprise the effector network that participates in removing virus-infected cells from the body. The third class of suppressor T-cells is important in dampening the immune response when it becomes overactive or out of regulatory control. Finally, cooperation between the various T-cell classes and between T- and B-cells is an important component of the normal humoral and cellular immune response. Hyperactive cellular immune responses produce autoimmune and other immune-mediated diseases while hypoactive cell-mediated immunity causes immune suppression and incompetence. Classical examples of this latter situation occur with retroviral infection such as human AIDS or the animal equivalents (e.g. feline immunodeficiency virus, feline leukemia virus, bovine leukemia virus, equine infectious anemia).

Introduction to Autoimmune Diseases

The term "autoimmunity" literally means immunity against self and is caused by an immune-mediated reaction to self-antigens (i.e. failure of self-tolerance). Susceptibility to autoimmune disease has a genetic basis in humans and animals. Numerous viruses, bacteria, chemicals, toxins, and drugs have been implicated as the triggering environmental agents in susceptible individuals. This mechanism operates by a process of molecular mimicry and/or non-specific inflammation. The resultant autoimmune diseases reflect the sum of the genetic and environmental factors involved. Autoimmunity is most often mediated by T-cells or their dysfunction. As stated in a recent review, "perhaps the biggest challenge in the future will be the search for the environmental events that trigger self-reactivity" (Sinha, Lopez and McDevitt; Science, 248: 1380, 1990). Table 1 lists factors commonly associated with autoimmune diseases.

The four main causative factors of autoimmune disease have been stated to be: Genetic predisposition; Hormonal influences, especially of sex hormones; Infections, especially of viruses; and Stress.

Immune-Suppressant Viruses

Immune-suppressant viruses of the retrovirus and parvovirus classes have recently been implicated as causes of bone marrow failure, immune-mediated blood diseases, hematologic malignancies (lymphoma and leukemia), dysregulation of humoral and cell-mediated immunity, organ failure (liver, kidney), and autoimmune endocrine disorders especially of the thyroid gland (thyroiditis), adrenal gland (Addison's disease), and pancreas (diabetes). Viral disease and recent vaccination with single or combination modified live-virus vaccines, especially those containing distemper, adenovirus 1 or 2, and parvo virus are increasingly recognized contributors to immune-mediated blood disease, bone marrow failure, and organ dysfunction. Genetic predisposition to these disorders in humans has been linked to the leucocyte antigen D-related gene locus of tile major histocompatibility complex, and is likely to have parallel associations in domestic animals. Drugs associated with aggravating immune and blood disorders include the potentiated sulfonamides (trimethoprim-sulfa and ormetoprim-sulfa antibiotics), the newer combination or monthly heartworm preventives, and anticonvulsants, although any drug has the potential to cause side-effects in susceptible individuals.

Immune Deficiency Diseases

Immune deficiency diseases sire a group of disorders in which normal host defenses against disease are impaired. These include disruption of the body's mechanical barriers to invasion (e.g. normal bacterial flora; the eye and skin; respiratory tract cilia); defects in non-specific host defenses (e.g. complement deficiency; functional white blood cell disorders), and defects in specific host defenses (e.g. immunosuppression caused by pathogenic bacteria, viruses and parasites; combined immune deficiency; IgA deficiency; growth hormone deficiency).

Thyroid Disease and the Immune System

Thyroid dysfunction is the most frequently recognized endocrine disorder of the dog. The most common form of canine thyroid disease is autoimmune thyroiditis (equivalent to Hashimoto's disease of humans), which is a familial autoimmune disease of inherited predisposition. As the thyroid gland regulates metabolism of

all body cellular functions, reduction of thyroid function leading to hypothyroidism can produce a wide range of clinical manifestations (Table 2). Because so many of the clinical signs of thyroid dysfunction mimic symptoms resulting from other causes, it is difficult to make an accurate diagnosis of thyroid-related illness without appropriate veterinary laboratory tests combined with an experienced professional interpretation of the test results. More specific details about the accurate diagnosis of thyroid disease can be found in the literature cited at the end of this article.

Genetic Screening for Thyroid Disease

Complete baseline thyroid panels and thyroid antibody tests can be used for genetic screening of apparently healthy animals to evaluate their fitness for breeding. Any dog having circulating antithyroid autoantibodies can eventually develop clinical symptoms of thyroid disease or be susceptible to other autoimmune diseases because their immune system is impaired. Therefore, thyroid prescreening can he very important for selecting potential breeding stock.

Thyroid testing for genetic screening purposes is unlikely to be meaningful before puberty. Screening is initiated, therefore, once healthy dogs and bitches have reached sexual maturity (between 10-14 months in males and during the first anestrous period for females following their maiden heat). Anestrus is a time when the female sexual cycle is quiescent thereby removing any influence of sex hormones on baseline thyroid function. This period generally begins 12 weeks from the onset of the previous heat and lasts 1 month or longer. The interpretation of results from baseline thyroid profiles in intact females is more reliable when they are tested in anestrus. Thus, testing for health screening is best performed at 12-16 weeks following the onset of the previous heat. Screening of intact females for other parameters like vWD, hip dysplasia, inherited eye disease, and wellness or reproductive checkups should also he scheduled in anestrus.

Once the initial thyroid profiles are obtained, dogs and bitches should be rechecked on an annual basis to assess their thyroid and overall health. Annual results provide comparisons for early recognition of developing thyroid dysfunction. This permits treatment intervention, where indicated, to avoid the appearance or advancement of clinical signs associated with hypothyroidism. For optimal health, young dogs under 15-18 months of age should have thyroid baseline levels in the upper half of the adult normal ranges. This is because puppies and adolescent dogs require higher levels of thyroid hormones as they

are still growing and maturing. Similarly, older animals beyond 8 or 9 years of age have slower metabolisms and so baseline thyroid levels of normal (euthyroid) dogs may be slightly below midrange. For optimum thyroid function of breeding stock, levels should be close to the midpoint of the laboratory normal ranges, because lower levels may be indicative of the tarry stages of thyroiditis among relatives of dog families previously documented to have thyroid disease.

The difficulty in accurately diagnosing early thyroid disease is compounded by the fact that some patients with typical clinical signs of hypothyroidism have circulating thyroid levels within the normal range. A significant number of these patients will improve clinically when given thyroid medication. In such cases, blood levels of the hormones can be normal but tissue levels are inadequate to maintain health, and so, the patient shows clinical signs of hypothyroidism. This situation pertains in selenium deficiency (discussed below). While animals in this category should respond well to thyroid medication, only experienced clinicians are likely to recognize the need to place these dogs on a 6-8 week clinical trial of thyroid supplementation. This approach is safe and clinically appropriate, but it requires rechecking blood levels of thyroid hormones towards the end of the 6-8 week period to assure that the patient is receiving the correct dose of medication.

Other Factors Influencing Thyroid Metabolism

Because animals with autoimmune thyroid disease have generalized metabolic imbalance and often have associated immunological dysfunction, it is advisable to minimize their exposures to unnecessary drugs, toxins, and chemicals, and to optimize their nutritional status with healthy balanced diets. Wholesome nutrition is a key component of maintaining a healthy immune system. In our experience, families of dogs susceptible to thyroid and other autoimmune diseases show generalized improvement in health and vigor when fed premium cereal-based diets preserved naturally with vitamins E and C (without the addition of chemical antioxidant preservatives such as BHA, BHT, or ethoxyquin). Fresh home-cooked vegetables with herbs, low fat dairy products, and meats such as lamb, chicken, and turkey can he added as supplements. Challenging the immune system of animals susceptible to these disorders with polyvalent modified-live vaccines has been associated with adverse effects in some cases (see below). Table 1 lists other agents that should be avoided in susceptible or affected animals.

Nutritional influences can have a profound effect on thyroid metabolism. For example, iodine deficiency in areas where cereal grain crops are grown on iodine-deficient soil will impair thyroid metabolism because this mineral is

essential for formation of thyroid hormones. Recently an important link has been shown between selenium deficiency and hypothyroidism. Again, cereal grain crops grown on selenium-deficient soil will contain relatively low levels of selenium. While commercial pet food manufacturers compensate for variations in basal ingredients by adding vitamin and mineral supplements, it is difficult to determine optimum levels for so many different breeds of dogs having varying genetic backgrounds and metabolic needs. The selenium-thyroid connection has significant clinical relevance, because blood levels of total and free T4 rise with selenium deficiency. However, this effect does not get transmitted to the tissues as evidenced by the fact that blood levels of the regulatory thyroid stimulating hormone (TSH) are also elevated or unchanged. Thus, selenium-deficient individuals showing clinical signs of hypothyroidism could be overlooked on the basis that blood levels of T4 hormones appeared normal. The selenium issue is further complicated because chemical antioxidants can impair the bioavailability of vitamin A, vitamin E and selenium and alter cellular metabolism by inducing or lowering cytochrome p-450, glutathione peroxidase (a selenium-dependent enzyme), and prostaglandin levels. As manufacturers of many premium pet foods began adding the synthetic antioxidant, ethoxyquin, in the late 1980's, its effects along with those of other chemical preservatives (BHA. BHT), are surely detrimental over the long term. The way to avoid this problem is to use foods preserved with natural antioxidants such as vitamin E and vitamin C.

Immunological Effects of Vaccines

Combining viral antigens, especially those of modified live virus (MLV) type which multiply in the host, elicits a stronger antigenic challenge to the animal. This is often viewed as desirable because a more potent immunogen presumably mounts a more effective and sustained immune response. However, it can also overwhelm the immunocompromised or even a healthy host that is continually bombarded with other environmental stimuli and has a genetic predisposition that promotes adverse response to viral challenge. This scenario may have a significant effect on the recently weaned young puppy that is placed in a new environment. Furthermore, while the frequency of vaccinations is usually spaced 2-3 weeks span, some veterinarians have advocated vaccination once a week in stressful situations. To me, this practice makes no sense from a scientific or medical perspective. While young puppies exposed this frequently to vaccine antigens may not demonstrate overt adverse effects, their relatively immature immune systems may he temporarily or more permanently harmed from such antigenic challenges. Consequences in later life may be the increased susceptibility to chronic debiliatating diseases. Some veterinarians trace the

increasing current problems with allergic and immunological diseases to the introduction of MLV vaccines some 20 years ago. While other environmental factors no doubt have a contributing role, the introduction of these vaccine antigens and their environmental shedding may provide the final insult that exceeds the immunological tolerance threshold of some individuals in the pet population (Figure 1).

Vaccine Dosage

Manufacturers of MLV combination vaccines recommend using the same dose for animals of all ages and different sizes. It has never made any sense to vaccinate toy and giant breed puppies (to choose two extremes) with the same vaccine dosage. While these products provide sufficient excess of antigen for the average sized animal, it is likely to be either too much for the toy breeds or too little for the giant breeds. In addition, combining certain specific viral antigens such as distemper with adenovirus 2 (hepatitis) has been shown to influence the immune system by reducing lymphocyte numbers and responsiveness.

Hormonal State During Vaccination

Relatively little attention has been paid to the hormonal status of the patient at the time of vaccination. While veterinarians and vaccine manufacturers are aware of the general rule not to vaccinate animals during any period of illness, the same principle should apply to times of physiological hormonal change. This is particularly important because of the known role of hormonal change alone with infectious agents in triggering autoimmune disease. Therefore, vaccinating animals at the beginning of, during, or immediately after an estrous cycle is unwise, as would he vaccinating animals during pregnancy or lactation. In this latter situation, adverse effects can accrue not only to the dam but also because a newborn litter is exposed to shed vaccine virus. One can even question the wisdom of using MLV vaccines on adult animals in the same household because of exposure of the mother and her litter to shed virus. Recent studies with MLV heroes virus vaccines in cattle have shown them to induce necrotic changes in the ovaries of heifers that were vaccinated during estrus. The vaccine strain of this virus was also isolated from control heifers that apparently became infected by sharing the same pasture with the vaccinates. Furthermore, vaccine strains of these viral agents are known to be causes of abortion and infertility following herd vaccination programs. If one extrapolates these findings from cattle to the dog, the implications are obvious.

Killed Versus Modified Live Vaccines

Most single and combination canine vaccines available today are of MLV origin. This is based primarily on economic reasons and the belief that they produce more sustained protection. A long-standing question remains, however, concerning the comparative safety and efficacy of MLV versus killed (inactivated) virus vaccines. A recent examination of the risks posed by MLV vaccines concluded that they are intrinsically more hazardous than inactivated products. The residual virulence and environmental contamination resulting from the shedding of vaccine virus is a serious concern. More importantly, the ability of new infective agents to develop and spread poses a threat to both wild and domestic animal populations. The controversy in weighing the risks and benefits of MLV versus killed vaccines is building. Vaccine manufacturers seek to achieve minimal virulence (infectivity) while retaining maximal immunogenicity (protection). This desired balance may he relatively easy to achieve in clinically normal, healthy animals but may be problematic for those with even minor immunologic deficit. The stress associated with weaning, transportation, surgery, subclinical illness, and a new home can also compromise immune function. Furthermore, the common viral infections of dogs cause significant immunosuppression. Dogs harboring latent viral infections may not be able to withstand the additional immunological challenge induced by MLV vaccines. The increase in vaccine-associated distemper and parvovirus diseases are but two examples of this potential. So — why are we causing disease by weakening the immune system with frequent use of combination vaccine products? After all vaccines are intended to protect against disease. It is well-recognized by experts in the field that a properly constituted killed vaccine is always preferable to one of MLV origin. Killed vaccines do not replicate in the vaccinated animal, do not carry the risk of residual virulence and do not shed attenuated viruses into the environment. On the other hand, MLV vaccines are capable of stimulating a more sustained protective response. So what does the future hold here? Veterinarians, scientists, breeders and owners need to voice their concern and discontent with the present industrial vaccine practices. We need to urge manufacturers to seek alternatives. Even if killed vaccines are proven to be somewhat less efficacious (produce lower levels or less sustained protection) than MLV products, they are more safe. All killed vaccines on the market today have passed current efficacy and safety standards in order to be licensed for use by the USDA. The issue is to what extent being more effective elicits a benefit rather than a risk. The future will evolve new approaches to vaccination including sub-unit vaccines, recombinant vaccines using DNA technology, and killed products with new adjuvants to boost and prolong protection. These are not simple solutions to a problem, however, because early data from recombinant vaccines against some human and mouse viruses have shown potentially dangerous side-effects by

damaging T-lymphocytes. Contributing factors were shown to be the genetic background of the host, the time or dose of infection, and the makeup of the vaccine. We are obviously still a long way from producing a new generation of improved and safe vaccines. In the meantime, we need to return to using killed products whenever they are available and should consider giving them more often (twice yearly rather than annually) for high-risk exposure situations. Vaccines, while necessary and generally safe and efficacious, can be harmful or ineffective in selected situations.

Cancer and Immunity

Proper regulation of cellular activity and metabolism is essential to normal body function. Cell division is a process under tight regulatory control. The essential difference between normal and tumor or cancerous cells is a loss of growth control over the process of cell division. This can result from various stimuli such as exposure to certain chemicals, viral infection, and mutations, which cause cells to escape from the constraints that normally regulate cell division. Proliferation of a cell or group of cells in an uncontrolled fashion eventually gives rise to a growing tumor or neoplasm. Of course, tumors can he both benign (a localized mass that does not spread) or malignant (cancerous), in which the tumor grows and metastasizes to many different sites via the blood or lymph.

Tumor cells also express a variety of proteins called "neoantigens" on their surface, and many of these are different from antigens found on normal cells. These new or altered proteins are recognized as foreign by the immune system, and so trigger an immunological attack. There are a large number of them known as tumor-specific or tissue-specific antigens, whereas others recognize the blood group systems, histocompatibility complex, and viruses. The situation in cancer is complex because not only can immunologically compromised individuals become more susceptible to the effects of cancer-producing viral agents and other chemical carcinogens, the cancer itself can be profoundly immunosuppressive. The form of immunosuppression usually varies with the tumor type. For example, lymphoid tumors (lymphomas and leukemia) tend to suppress antibody formation, whereas tumors of T-cell origin generally suppress cell-mediated immunity. In chemically induced tumors, immunosuppression is usually due to factors released from the tumor cells or associated tissues. The presence of actively growing tumor cells presents a severe protein drain on an individual which may also impair the immune response. Blocking factors present in the serum of affected animals exist which can cause enhancement of tumor growth. Additionally, immunosuppression in tumor-bearing animals can be due to the development of suppressor cells.

The body also contains a group of complimentary factors that provide a protective effect against tumors and other immunologic or inflammatory stresses. These are mixtures of proteins produced by T-cells and are referred to as "cytokines." Cytokines include the interleukins, interferons, tumor-necrosis factors, and lymphocyte-derived growth factors. Recent studies have shown that normal levels of zinc are important to protect the body against the damaging effects of the specific cytokine, tumor-necrosis factor (TNF). Inadequate levels of zinc have been shown to promote the effect of TNF in disrupting the normal endothelial barrier of blood vessels. This could have a significant effect in promoting the metastasis of tumor cells to different sites, thereby hastening the spread and growth of a particular cancer.

Currently about 15% of human tumors are known to have viral causes or enhancement. Viruses also cause a number of tumors in animals and no doubt the number of viruses involved will increase as techniques to isolate them improve. The T-cell leukemias of humans and animals are examples of those associated with retroviral infections. This same class of viruses has been associated with the production of autoimmunity and immunodeficiency diseases. The recent isolation of a retrovirus from a German Shepherd with T-cell leukemia exemplifies the potential role of these agents in producing leukemia and lymphomas in the dog.

The increased prevalence of leukemia and lymphomas in the Golden Retriever and several other breeds is a case in point. Similarly, there has been an increase in the prevalence of hemangiosarcomas (malignant tumors of the vascular endothelium) primarily in the spleen, but also in the heart, liver and skin. They occur most often in middle age or older dogs of medium to large breeds. The German Shepherd dog is the breed at highest risk, but other breeds including the Golden Retriever and Vizsla have shown a significantly increased incidence especially in certain families. This suggests that genetic and environmental factors play a role. It is tempting to speculate that environmental factors that promote immune suppression or dysregulation contribute to failure of immune surveillance mechanisms. These protect the body against the infectious and environmental agents which induce carcinogenesis and neoplastic change.

Nutritional Factors and the Immune System

As alluded to above, an adequate nutritional state is important in managing a variety of inherited and other metabolic diseases as well as for a healthy immune system.

Examples where nutritional management is important in inherited disorders includes: adding ingredients to the diet to make it more alkaline for Miniature Schnauzers with calcium oxalate bladder or kidney stones; use of the vitamin A derivative, etretinate in Cocker Spaniels and other breeds with idiopathic seborrhea of the skin; management with drugs and diet of diseases such as diabetes mellitus and the copper-storage disease prevalent in breeds like the Bedlington Terrier, West Highland White Terrier, and Doberman Pinscher; and treatment of vitamin B-12 deficiency in Giant Schnauzers. Other nutritional influences include the vitamin K-dependent coagulation defect elicited in Devon Rex cats following vaccination; hip dysplasia in puppies fed excessive calories; osteochondritis dissecans in dogs fed high levels of calcium; and hypercholesterolemia in inbred sled dogs fed high fat diets.

Nutritional factors that play an important role in immune function include zinc, selenium and vitamin E, vitamin B-6 (pyridoxine),and linoleic acid. Deficiencies of these compounds impairs both circulating (humoral) as well as cell-mediated immunity. The requirement for essential nutrients increases during periods of rapid growth or reproduction and also may increase in geriatric individuals, because immune function and the bioavailability of these nutrients generally wanes with aging. As with any nutrient, however, excessive supplementation can lead to significant clinical problems, many of which are similar to the respective deficiency states of these ingredients. Supplementation with vitamins and minerals should only be given with the advice of a professional nutritionist and should not be viewed as a substitute for feeding premium quality fresh and/or commercial dog foods.

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TABLE
I.
FACTORSASSOCIATED WITH AUTOIMMUNE DISEASE Sex (2:1F

Genetic or familial history • Increasing frequency **Pregnancy** • Stunted fetal growth • Congenital malformations **Stress** • environmental • emotional • physiological **Hormonal Irregularities** • polyglandular • autoimmunity (endocrinopathy) • pituitary-thyroid axis dysfunction • reproductive failure • abnormal heat cycles • pyometra • false pregnancy • hypogonadism • oliogospermia • aspermia • anestrus **Nutritional Influences**	**Viral Infection** • parvovirus • retroviruses • cytomegalovirus • measles and distemper viruses • hepatitis viruses **Frequent or Recent Use of MLV V** • parvovirus • distemper • hepatitis - Lyme (vaccines alone or • bordetella • rabies **Underlying or Concomitant Disea** • lymphoma or leukemia (retrovirus • bone marrow failure (low red and • immune dysregulation • humoral - cellular (immunodeficien • chronic infections (bacterial, viral, **Other Autoimmune Disorders** • Hashimoto’s thyroiditis • Addison’s disease • rheumatoid arthritis

• deficiency or imbalances • trace minerals • nutrients • vitamins • chemical preservatives • toxins in feeds • chemical or drug residues • spoiled feeds **Adverse Drug Reactions** • trimethoprim-sulfas • ormetoprim sulfa • nitrofurans • butazolidin • Phenobarbital • primidone • diethylcarbamazine-oxybendazole • ivermectin • milbemycin oxime	• lupus crythematosus • idiopathic thrombocytopenic purpu • hemolytic anemia • chronic active hepatitis • diabetes mellitus • hypogonadism • myasthenia gravis • pemphigus, vitiligo • glomerulonephritis • alopecia • Graves’ disease • hypoparathyroidism • seizures and other neurologic man • uveitis and other immunologic eye

TABLE 2. CLINICAL SIGNS OF CANINE HYPOTHYROIDISM

Alterations in Cellular Metabolism • lethargy • mental dullness • exercise intolerance • neurologic signs • polyneuropathy • seizures • weight gain • cold intolerance • mood swings • hyperexcitability • stunted growth chronic infections **Cardiac Abnormalities** • slow heart rate (bradycardia) • cardiac arrhythmias • cardiomyopathy	**Neuromuscular Problems** • weakness • stiffness • laryngeal paralysis • facial paralysis • "tragic" expression • knuckling or dragging feet • muscle wasting • megaesophagus • head tilt • drooping eyelids **Ocular Diseases** • corneal lipid deposits • corneal ulceration • uveitis • keratoconjunctivitis sicca or "dry e

Dermatologic Diseases • dry, scaly skin and dandruff • coarse, dull coat • bilaterally symmetrical hair loss • "rat tail"; "puppy coat" • hyperpigmentation • seborrhea or greasy skin • pyoderma or skin infections • myxedema • chronic offensive skin odor **Gastrointestinal Disorders** • constipation • diarrhea • vomiting **Hematologic Disorders** • bleeding • bone marrow failure • low - red blood cells (anemia), white blood cells, platelets	• infections of eyelid glands (Meibom • Vogt-Koyanagi-Harada syndrome **Other Associated Disorders** • IgA deficiency • loss of smell (dysosmia) • loss of taste • glycosuria • chronic active hepatitis • other endocrinopathies (adrenal, p **Reproductive Disorders** • infertility • lack of libido • testicular atrophy • hypospermia • aspermia • prolonged interestrus interval • absence of heat cycles • silent heats • pseudopregnancy • weak, dying or stillborn pups