THE IMMUNE SYSTEM *‡

W. Jean Dodds, DVM
938 Stanford Street
Santa Monica, CA 90403
310-828-4804; FAX 310-828-8251
www.hemopet.com

Overview of the Immune System

Immune competence is provided and maintained by two cellular systems which involve lymphocytes, 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 constitute 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). [1-3]

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.[1-3] 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.[1]

Hypoactive or decreased levels of immunoglobulins can result from the rare genetically based immunodeficiency states such as agammaglobulinemia or hypogammaglobulinemia, and from the immune suppression associated with chronic viral, bacterial, or parasitic infections, cancers, aging, malnutrition, drugs, toxins, pregnancy, lactation, and stress.[2]

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. [1-3]

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). [2]

New Directions in Immunology

The effects of immune responses are diverse and include the pathologic changes seen in tissues following immunologic challenge such as occurs with viral infections. For example, the immunopathologic changes induced by feline upper-respiratory virus infection (herpes and rhinotracheitis viruses) are a consequence of the immune response to these agents rather than the viruses themselves. The specific type of immune response further complicates predicting results in the end organs.

Recent studies in human and animal immunology have focused on responses mediated by T-helper 1 (TH1) and T-helper 2 (TH2) cell types. [3] TH1 cells release interleukin (IL)-1, interferon, and tumor necrosis factor (TNF) after antigen stimulation. This cascade of effects leads to cell-mediated immune responses, which are responsible for macrophage activation, delayed-type hypersensitivity reactions, and defense against intracellular organisms. TH2 responses lead to release of IL-4, IL-5, IL-10, and IL-13, which stimulate B-cell proliferation and antibody secretion. Pathology associated with autoimmune, infectious and allergic diseases may be due to primary TH1- or TH2-like responses, and much recent research has focused on characterizing and modulating their responses. [4, 5]

Genetically Based Immune Disorders (Table 1)

Autoimmune Diseases

Distinguishing between self and nonself antigens is a vital function of the immune system and serves as a specific defense against invading microorganisms. Failure of this self tolerance leads to "autoimmunity", which literally means immunity against self and is caused by an immune-mediated reaction to self-antigens. [6] Susceptibility of the host to pathological autoimmune states has a genetic basis in humans and animals, although numerous viruses, bacteria, chemicals, toxins and drugs have been implicated as the triggering environmental agents.[1,3] This mechanism operates by a process of molecular mimicry and/or non-specific inflammation, and is most often mediated by T-cells or their dysfunction. The resultant autoimmune diseases reflect the sum of the

genetic and environmental factors involved. As stated in a landmark review "perhaps the biggest challenge in the future will be the search for the environmental events that trigger self-reactivity". [6]

The four main causative factors of autoimmune disease have been stated to be: [1]

- Genetic predisposition;
- Hormonal influences, especially of sex hormones;
- Infections, especially of viruses; and
- Stress.

The more commonly recognized autoimmune disorders in animals include those affecting: endocrine glands, namely the thyroid (thyroiditis), adrenals (Addison's disease), pancreas (diabetes), and parathyroid ; bone marrow and hematologic cells, marrow stem cells, erythrocytes, platelets, and leukocytes; muscle, myasthenia gravis, masticatory muscle myositis, polymyositis, and dermatomyositis; the eyes, keratoconjunctivitis sicca (dry eye), uveitis, pannus, and uveodermatologic syndrome (VKH); skin, pemphigus disorders, systemic lupus erythematosus, and vitiligo; neurologic tissue, immune-complex meningoencephalitis; the kidneys, immune-complex glomerulonephritis, and systemic lupus erythematosus; the joints, rheumatoid arthritis. [1, 3, 7]

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 and adrenal glands, and pancreas. [8-13]

Viral disease and recent vaccination with single or combination modified live-virus (MLV) vaccines, especially those containing distemper virus, adenovirus 1 or 2, and parvovirus are increasingly recognized contributors to immune-mediated blood disease, bone marrow failure, and organ dysfunction. [8, 10, 14-20] Potent adjuvanted killed vaccines like those for rabies virus also can trigger immediate and delayed (vaccinosis) adverse vaccine reactions.[17, 18, 20] Genetic predisposition to these disorders in humans has been linked to the leucocyte antigen D-related gene locus of the major histocompatibility complex, and is likely to have parallel associations in domestic animals. [8, 10]

Drugs associated with aggravating immune and blood disorders include the potentiated sulfonamides (trimethoprim-sulfa and ormetoprim-sulfa antibiotics), the newer combination or monthly heartworm and flea preventives, and anticonvulsants, although any drug has the potential to cause side-effects in susceptible individuals. [1, 21]

Immune Deficiency Diseases

Immune deficiency diseases are 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 nonspecific 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; immune deficiency states). [2,3]

The more commonly recognized immune deficiency states include defects in : mechanical barriers, namely primary ciliary dyskinesia; nonspecific host defenses, cyclic hematopoiesis, Chediak-Higashi syndrome, Pelger-Huet anomaly, and C3 complement deficiency; and specific host defenses, combined immunodeficiency syndrome, selective IgA deficiency, growth hormone deficiency, and lethal acrodermatitis. [2]

Thyroid Disease and the Immune System

Thyroid dysfunction is the most commonly recognized endocrine disorder of the dog and cat. [1, 7, 11-13] The most common form of canine thyroid disease is autoimmune thyroiditis (equivalent to Hashimoto's disease of humans), a familial autoimmune disease of inherited predisposition. [8] 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. 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 comprehensive thyroid profiles run at a veterinary diagnostic laboratory in combination with an experienced professional interpretation of the test results. [1, 12] More specific details about the accurate diagnosis of thyroid disease can be found in the literature cited at the end of this article. [12]

In the cat, hyperthyroidism is seen and typically affects geriatric animals as well as some of middle age.[1] Hypothyroidism is rare in cats, although a family of Siamese cats recently produced kittens with classical clinical and laboratory signs of congenital hypothyroidism (goiter).

Immunological Effects of Vaccines

Combining viral antigens, especially those of MLV type which multiply in the host, elicits a stronger antigenic challenge to the animal and presumably mounts a more effective and sustained immune response. [3, 14, 15, 17, 18, 20] This more potent immunologic challenge, however, could adversely affect the immunocompromised animal or even the healthy animal genetically predisposed to react adversely to viral exposure upon repeated bombardment with other

environmental stimuli. [18] While young puppies exposed frequently to polyvalent vaccine antigens may not demonstrate overt adverse effects, their relatively immature immune systems may be temporarily or more permanently harmed from such antigenic exposures. Consequences in later life may be the increased susceptibility to chronic debilitating diseases. [15, 18] Some veterinarians trace the increasing current problems with allergic and immunological diseases to the introduction of MLV vaccines some 20 years ago. [14, 15] 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. [14, 18, 20]

Accordingly, clinicians need to be aware of this potential and offer alternative approaches for preventing infectious diseases in susceptible animals. [15, 20, 22-24] Appropriate alternatives to current vaccine practices include: measuring serum antibody titers; avoidance of unnecessary vaccines or over vaccinating; caution in vaccinating ill, geriatric, debilitated, or febrile individuals, and tailoring a specific minimal protocol for dogs or families of breeds known to be at increased risk for immunological reactions.[15, 20, 22, 23, 25, 26] The accumulated evidence indicates that vaccination protocols should no longer be considered as a one size fits all program. [22]

Cancer and the Immune System

Tumor cells also express a variety of neoantigens on their surface, and many of these are different to the antigens found on normal cells. Such new or altered proteins are recognized as foreign by the immune system and can trigger an immunological attack. These include tumor-specific or tissue-specific antigens, as well as others that recognize the blood group systems, histocompatibility complex, and viruses. [3]

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. [33] 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. [3]

Cytokines, including interleukins, interferons, TNF, and lymphocyte-derived growth factors, provide a protective effect against tumors and other immunologic or inflammatory stresses. Recent studies have shown that normal levels of zinc are important in protecting the body against the damaging effects of TNF, which disrupt the normal endothelial barrier of blood vessels. Inadequate levels of zinc have been shown to promote this effect of TNF, which could significantly promote the metastasis of tumor cells to different sites, thereby hastening the spread and growth of a particular cancer. [3]

Currently about 15% of human tumors are known to have viral causes or enhancement. Viruses also cause a number of tumors in animals, and the number of viruses involved will undoubtedly 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 rising incidence of leukemia and lymphomas in an increasing number of dog breeds is a case in point. [3, 13] Similarly, there has been an increase in the incidence of hemangiosarcomas 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, old English sheepdog, Irish setter and vizsla have shown a significantly increased incidence especially in certain families. This suggests that both 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 immune surveillance mechanisms protect the body against the infectious and environmental agents which induce carcinogenesis and neoplastic change. [21, 26]

Nutrition and the Immune System

Wholesome nutrition is the key to maintaining a healthy immune system and resistance to disease. Commercial foods ingested by animals on a regular basis may not be balanced in terms of major nutrients, minerals and vitamins, and some continue to add chemicals to the final product to enhance its stability and shelf-life. Nutritional deficiencies or imbalances as well as exposures to various chemicals, drugs and toxins present a continual immunological challenge which can suppress immune function, especially in those animals genetically susceptible to immune dysfunction (immune deficiency, autoimmunity, allergies).

Genetic differences between individuals lead to quantitative variations in dietary requirements for energy, nutrients and to maintain health. [26] Also, genetic defects may result in inborn errors of metabolism that affect one or more pathways involving nutrients or their metabolites. Many inborn errors of

metabolism are fatal, whereas others may show significant clinical improvement with nutritional management. While minimal and maximal nutrient requirements have been established for most vitamins and trace mineral elements, optimum amounts for every individual cannot be assumed. Examples of important vitamin and mineral requirements in this regard include vitamin C, vitamin E and selenium, vitamin A, copper and vitamin B_{12} . Similarly, a wide variation occurs in the energy needs of dogs depending on their breed, age, sex, and size. Breeders quickly learn to adjust the caloric intake of their animals depending on the optimal requirements of each individual. [26, 27]

According to a recent review, [26, 27] genetic diversity in nutritional requirements will be an area of intense research in human nutrition, particularly since the human genome has been sequenced. In the future, we will determine what levels of diversity exist in addition to the practical implications of nutritional individuality. Presently, 30-40 nutrients are recognized as essential. If the metabolic pathway influencing nutritional requirements for each of these nutrients was affected independently by only two alternative alleles at a single genetic locus (which is probably an oversimplification), the number of alternative genotypes for that specific nutrient would be over 200 trillion. Knowledge of individual nucleotide sequences will, in the future, be used to optimize elements of an individual's lifestyle, forcing veterinarians to face dietary concerns in every animal as an individual and adopt nutritional counseling as a routine medical practice.

Nutritional factors that play an important role in immune function include zinc, selenium and vitamin E, vitamin B_6 (pyridoxine), and linoleic acid. Deficiency of these compounds impairs both 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 not be viewed as a substitute for feeding premium quality fresh and/or commercial pet foods. [26]

Synthetic antioxidants like butylated hydroxyanisole (BHA) and butylated hydroxy-toluene (BHT) have been used as preservatives in human and animal foods for more than 30 years. [26, 27] Many pet food manufacturers prefer to use ethoxyquin today, however, because of its excellent antioxidant qualities, high stability and reputed safety. But significant ongoing controversy surrounds issues related to its safety when chronically fed at permitted amounts in dog and cat foods. The same antioxidants have been linked to inducing or promoting a wide variety of cancers, although the published literature is both disturbing and contradictory in this regard. These safety questions pertain mostly to genetically

susceptible breeds of inbred or closely linebred dogs. Toy breeds may be particularly at risk because they ingest proportionately more food and preservative for their size in order to sustain their metabolic needs. [27]

Naturally occurring antioxidants (vitamins E and C) are also used in pet foods, and have become more popular in response to consumer and professional queries about the chronic effects of feeding synthetic chemical antioxidants to pets. These concerns have resulted in a major change in the pet food industry, as manufacturers of premium pet foods and most newly introduced foods now offer foods preserved with natural antioxidants. [26, 27]

Nutrition and Thyroid Metabolism

Nutritional influences can have a profound effect on thyroid metabolism.[28, 29] The classical example is the iodine deficiency that occurs in individuals eating cereal grain crops grown on iodine-deficient soil. This will impair thyroid metabolism because iodine is essential for formation of thyroid hormones. Iron and zinc also are important minerals in regulating thyroid metabolism.

Another link has recently been shown between selenium deficiency and hypothyroidism. 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 animals having varying genetic backgrounds and metabolic needs.

The selenium-thyroid connection has significant clinical relevance, because blood, but not tissue, levels of thyroid hormones rise in selenium deficiency. [28] Thus, selenium-deficient individuals showing clinical signs of hypothyroidism could be overlooked on the basis that blood levels of thyroid hormones appear normal. The selenium issue is further complicated because the synthetic antioxidants still used in some foods to protect fats from rancidity can impair the bioavailability of vitamin A, vitamin E and selenium, and alter cellular membrane function, metabolism and detoxification.

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, chemicals and toxins, and to optimize their nutritional status with healthy balanced diets.

Families of dogs susceptible to thyroid and other autoimmune diseases show generalized improvement in health when fed premium cereal-based diets preserved naturally with vitamins E and C rather than with the synthetic chemical antioxidants mentioned above. Fresh vegetables cooked with Italian herbs and garlic, dairy products such as yogurt or low fat cottage cheese, or a variety of

meats and whitefish can be added. [27]

Nutritional Management (Commercial, Home-Made and Raw Food Diets)

Many veterinarians treating animals suffering from immunologic diseases appreciate that alternative nutritional management is an important step in minimizing their patient's environmental challenges. The results of this approach have been remarkable. The replacement food must be of good quality and preferably of relatively low protein content (20-22%).

Increasing carbohydrate and reducing protein content, while maintaining high quality protein, has been shown to be beneficial for many affected animals and is also believed to have a positive effect on behavior. Diet and behavior appear to be linked because certain highly nutritious foods may contribute to deterioration in the condition of dogs with behavioral problems (dominant aggression, hyperactivity, and fear).

For allergic animals, elimination diets with restricted or novel antigen source commercial source are given for 6-12 weeks to evaluate their benefit to the patient. Homemade diets can also be used provided that the formula is properly balanced. [26] All other food supplements, including treats, are withdrawn. Example ingredients that have been used successfully, include whitefish, rabbit, venison, duck, ostrich, emu, buffalo, and turkey mixed with potato, sweet potato and other vegetables (except onions and cruciferous vegetables). Grains are often avoided, at least initially, although novel grains like quinoa, sorghum, barley or flax usually have been well tolerated. [26, 27]

Raw food diets have been gaining in popularity as well. A key feature of these diets is the variety they provide. One of the prototype diets [BARF (bones and raw food)] of Dr. Ian Billinghurst recommends feeding a dog 60% raw meaty bones (chicken backs,wings and necks), with the rest of the diet composed of ground vegetables mixed with ground meat, and supplements such as kelp, vitamin E and vitamin C. Nutritional analyses on some commercially available raw diets suggest that the raw meaty bones commonly used provide 40-70% protein, and the meat/vegetable mixtures range from 20-50% protein. The question has arisen about the potential for such high protein diets to affect renal function when fed continuously, as high protein diets are reported to induce renal hypertrophy, and increase renal blood flow and glomerular filtration rate. While this concern may not pertain to healthy dogs, it could play a role in dogs with previously compromised renal function. At present, there are no data to support or refute this issue. [30]

Maintaining the appropriate ratio of trace minerals, vitamins, fatty acids and other nutritive elements is especially important for patients with acute and chronic diseases, as their metabolic demands have increased to sustain cell

turnover and tissue repair. [31] Typical supplements include: vitamin-mineral mix, antioxidants (vitamins A,C, D, and E and selenium), digestive enzymes, brewer's yeast, kelp, honey, coat additives, apple cider vinegar, hydrochloric acid (used sparingly), yoghurt, Willard Water, liver, eggs, garlic, and plenty of fresh potable water. [26]

Vitamin A and E have been shown to enhance immune function in small animals, as the former can benefically influence TH_1/TH_2 responses, and the latter is known to improve both cellular and humoral immunity.[29, 31] Dietary carotenoids, especially lutein and beta-carotene, have been reported to modulate both cell-mediated and humoral immunity in dogs but not in cats.[26, 31]

Holistic Alternatives to Allopathic Treatment

Standard allopathic treatments for immunologic disorders can be replaced with holistic alternatives and homeopathic remedies. [27] Rather than suppress the immune system with corticosteroids, alternative means of down-regulating the cytokines that trigger cell-mediated immunity can be used.

Some clinicians utilize polyvalent hyperimmune egg protein [http://www.HyperimmuneEgg.org] to modulate autoimmune and inflammatory responses. This protein is produced by repeatedly stimulating the immune systems of hens with inactivated common human pathogens[33] [typically enteric in nature]. The process results in eggs with concentrated immune factors[34]; many exhibiting cytokine-like properties[35]. Inhibition of diarrhea[36,37], and support of digestive[33, 36,37], joint[33,38,39] and cardiovascular health[40] has also been reported. Other treatments that offer immune support include plant sterols and sterolins, herbs such as echinacea, and medicinal mushrooms. [41-44]

Perhaps as important as the nutritional and other supplemental support for patients is the need to avoid or minimize toxic exposures (e.g. pesticides on pets or their surroundings, chemical fertilizers, radiation, high tension powerlines), booster vaccinations, preventative chemicals for heartworm, fleas and ticks, and drugs known to exacerbate immunologic disorders (*e.g*. potentiated sulfonamides, sex hormones). Alternative strategies to protect against common infectious diseases, such as annual vaccine titers, homeopathic nosodes, natural methods of heartworm, flea and tick control, should be implemented. [1, 2, 15, 17, 18, 20, 21, 26, 27]

References

1. Dodds WJ. Genetically based immune disorders: Autoimmune diseases, Parts 1-3. Vet Pract STAFF, 4 (1, 2, and 3): 8-10, 1, 26-31, 35-37, 1992.
2. Dodds WJ. Immune deficiency diseases: Genetically based immune disorders, Part 4. Vet Pract STAFF, 4 (5): 19-21, 1992.
3. Tizard IR, Schubot RM. Veterinary Immunology: An Introduction, 6th ed. WB

Saunders, Philadelphia, 2000, 480 pp.
4. Infante-Duarte C, Kamradt T. Th1/Th2 balance in infection. Springer Semin Immunopathol 21: 317-338, 1999.
5. Singh VK, Mehrotra S, Agarwal SS. The paradigm of Th1 and Th2 cytokines: its relevance to autoimmunity and allergy. Immunol Res 20: 147-161, 1999.
6. Sinha AA, Lopez MT, McDevitt HO. Autoimmune diseases: the failure of self tolerance. Science 248:1380-1388, 1990.
7. Happ GM. Thyroiditis - A model canine autoimmune disease. Adv Vet Sci Comp Med 39: 97-139, 1995.
8. Tomer Y, Davies TF. Infection, thyroid disease, and autoimmunity. End Rev 14: 107-120, 1993.
9. Schmidt MA, Bland JS. Thyroid gland as sentinel: Interface between internal and external environment. Altern Ther 3: 78-81, 1997.
10. Cohen AD, Shoenfeld Y. Vaccine-induced autoimmunity. J Autoimmunity 9:699-703, 1996..
11. Dodds WJ. Autoimmune thyroiditis and polyglandular autoimmunity of purebred dogs. Can Pract 22 (1): 18-19, 1997.
12. Dodds WJ. What's new in thyroid disease ? Proc Am Hol Vet Med Assoc 1997; pp 82-95.
13. Dodds WJ. Estimating disease prevalence with health surveys and genetic screening. Adv Vet Sci Comp Med 39: 29-96, 1995.
14. Tizard I. Risks associated with use of live vaccines. J Am Vet Med Assoc 196:1851-1858, 1990.
15. Schultz RD. Current and future canine and feline vaccination programs. Vet Med 93:233-254,1998.
16. Duval D, Giger U. Vaccine-associated immune-mediated hemolytic anemia in the dog. J Vet Int Med 10:290-295, 1996.
17. Dodds WJ. Vaccine-related issues, Chapter 40. In: Complementary and Alternative Veterinary Medicine. Mosby, St. Louis, 1997; pp 701-712.
18. Dodds WJ. More bumps on the vaccine road. Adv Vet Med 41:715-732, 1999.
19. Hogenesch H, Azcona-Olivera J, Scott-Moncreiff C, et al. Vaccine-induced autoimmunity in the dog. Adv Vet Med 41: 733-744, 1999.
20. Dodds WJ. Vaccination protocols for dogs predisposed to vaccine reactions. J Am An Hosp Assoc 38:1-4, 2001.
21. Dodds WJ. Holistic approaches for immune-mediated disease. Proc Am Hol Vet Med Assoc 1997; pp 96-100.
22. Smith CA. Are we vaccinating too much? J Am Vet Med Assoc 207:421-425, 1995.
23. Hustead DR, Carpenter T, Sawyer DC, et al. Vaccination issues of concern to practitioners. J Am Vet Med Assoc 214: 1000-1002, 1999.
24. Paul MA. Credibility in the face of controversy. Am Anim Hosp Assoc Trends Magazine XIV(2):19-21, 1998.
25. Tizard I, Ni Y. Use of serologic testing to assess immune status of companion animals. J Am Vet Med Assoc 213: 54-60, 1998.
26. Twark L, Dodds WJ. Clinical application of serum parvovirus and distemper virus antibody titers for determining revaccination strategies in healthy dogs. J Am Vet Med Assoc 217:1-4, 2000.
27. Dodds WJ, Donoghue S. Interactions of clinical nutrition with genetics, Chapter 8. In: The Waltham Book of Clinical Nutrition of the Dog and Cat. Pergamon Press Ltd., Oxford, 1994, p.105-117.
28. Dodds WJ. Pet food preservatives and other additives, Chapter 5. In: Complementary and Alternative Veterinary Medicine. Mosby, St. Louis, 1997; pp 73-79.

29. Berry MJ, Larsen PR. The role of selenium in thyroid hormone action. End Rev, 13(2): 207-219, 1992.
30. Burkholder WJ, Swecker WS Jr. Nutritional influences on immunity. Sem Vet Med Surg (Sm An), 5(3): 154-156, 1990.
31. Wynn SG, Bartges J, Dodds WJ. Raw meaty bones-based diets may cause prerenal azotemia in normal dogs. AAVN Nutrition Research Symposium, June 2003 (abstr.).
32. Roudebush P. Ingredients associated with adverse food reactions in dogs and cats. Adv Sm An Med Surg, 15(9): 1-3, 2002.
33. See, DM. Complementary therapies in arthritis. J Amer Nutr Assoc 1:7-14, 1998.
34. Dean, KL. Hyperimmune eggs capture natural immune support. Alter Compl Ther 6:118-124, 2000
35. Iyer S, Nguyen TN, Wu D-R, Xing R. Highly purified cytokine activating factor and methods of use. United States Patent #6,420,337 2002
36. Jacoby HK, Moore G, Wnorowski G. Inhibition of diarrhea by immune egg: a castor-oil mouse model. J Nutr Func Med Foods 3: 47-53, 2001.
37. Greenblatt HC, Adalsteinsson O, Brodie DA, Jacoby H. Anti-diarrheal and method for using the same United States Patent #6,803,035 2004
38. Greenblatt HC, Adalsteinsson O, Kagen L. Administration to arthritis patients of a dietary supplement containing immune egg: an open-label pilot study J Med Food 1:171-179, 1998.
39. Trentham D. Hyperimmune egg in the collagen-induced arthritis model and anti-inflammatory assays Inter Soc Rheum Ther 6th Biennial Congress Speaker 1998
40. Adalsteinsson O, Hunchar J, Iyer S. Glucosamine and egg for reducing inflammation. United States Patent #6,706,267 2004
41. Karge, WH, DeLuca, JP, Marchitelli, LJ., Champagne, C., Tulley, R., Rood, J., Paulos, M., Lieberman HR. Pilot study on the effect of hyperimmune egg protein on elevated cholesterol levels and cardiovascular risk factors. J Med Food 2:51-63, 1999.
42. Bonic PJD, Lamprecht JH. Plant sterols and sterolins: A review of their immune-modulating properties. Alt Med Rev 4: 170-177, 1999.
43. Percival SS. Use of echinacea in medicine. Biochem Pharmacol 60:155-158, 2000.
44. Bone K. Echinacea: What makes it work? Alt Med Rev 2:87-93, 1997.
45. Der Marderosian QA. The Review of Natural Products. Facts and Comparisons, St. Louis, MO, Lippincott, Williams & Wilkins, 2001, pp 389-390, 508-509.

Table 1. Genetically Based Immune Disorders

Autoimmune Diseases

- Autoimmune Endocrine Diseases
  - Thyroid
  - Adrenal
  - Pancreatic
- Autoimmune Hematologic Diseases
  - Erythrocyte
  - Platelet
  - Leukocyte
- Autoimmune Muscle Diseases
  - Myasthenia gravis
  - Masticatory muscle myositis

Polymyositis
Dermatomyositis
Autoimmune Eye Diseases
Keratoconjunctivitis sicca
Uveitis
Pannus
Uveodermatologic syndrome (VKH)
Autoimmune Skin Diseases
Pemphigus disorders
Systemic lupus erythematosus
Vitiligo
Autoimmune Neurologic Diseases
Immune-complex meningoencephalitis
Autoimmune Renal Diseases
Immune-complex glomerulonephritis
Systemic lupus erythematosus
Autoimmune Joint Diseases
Rheumatoid arthritis

Immune Deficiency Diseases

Defects in Mechanical Barriers
Primary ciliary dyskinesia
Defects in Nonspecific Host Defenses
Cyclic hematopoiesis
Chediak-Higashi syndrome
Canine granulocytopathy
Pelger-Huet anomaly
C3 complement deficiency
Defects in Specific Host Defenses
Combined immunodeficiency
Selective IgA deficiency
Growth hormone immunodeficiency
Lethal acrodermatitis

*Updated from: Clinical Techniques in Small Animal Practice, 17(1); 58-63, 2002.
‡ Printed with the permission of the author