THE IMMUNE SYSTEM AND DISEASE RESISTANCE

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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 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).

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:

16 acutely, as a reaction to disease or inflammatory insult ("acute-phase" reaction); or

17 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 infections, 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). 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 the 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 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 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).

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. Today, given the recent major changes in vaccination guidelines for both dogs and cats, we are vaccinating less often and focusing on the core vaccines that all puppies and kittens should have (distemper virus, adenovirus, parvovirus, and rabies virus for dogs; panleukopenia virus, calicivirus, herpesvirus, and rabies virus for cats).

Vaccine Dosage

Manufacturers of combination (polyvalent) 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 along with infectious agents in triggering autoimmune disease. Therefore, vaccinating animals at the beginning, during or immediately after an estrous cycle is unwise as would be 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 herpes 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 fact that they produce more sustained protection. A long-standing question remains the comparative safety and efficacy of MLV versus killed (inactivated) virus vaccines, when a properly constituted killed vaccine is safer. 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.

Vaccine manufacturers seek to achieve minimal virulence (infectivity) while retaining maximal immunogenicity (protection). This desired balance may be 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 vaccines. 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.

Recommendations

In response to questions posed above, veterinary vaccinologists have recommended new protocols for dogs and cats. These include: 1) giving the puppy or kitten vaccine series followed by a booster at one year of age; 2) administering further boosters in a combination vaccine every three years or as split components alternating every other year until; 3) the pet reaches geriatric age, at which time booster vaccination is likely to be unnecessary and may be unadvisable for those with aging or immunologic disorders. In the intervening years between booster vaccinations, and in the case of

geriatric pets, circulating humoral immunity can be evaluated by measuring serum vaccine antibody titers as an indication of the presence of “immune memory”. Titers do not distinguish between immunity generated by vaccination and/or exposure to the disease, although the magnitude of immunity produced just by vaccination is usually lower.

Except where vaccination is required by law, all animals, but especially those dogs or close relatives that previously experienced an adverse reaction to vaccination can have serum antibody titers measured annually instead of revaccination. If adequate titers are found, the animal should not need revaccination until some future date. Rechecking antibody titers can be performed annually, thereafter, or can be offered as an alternative to pet owners who prefer not to follow the conventional practice of annual boosters. Reliable serologic vaccine titering is available from several university and commercial laboratories and the cost is reasonable.

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 be both benign (a localized mass that does not spread) or malignant (cancerous) in which the tumor grows and metastasizes to many distance sites via the blood or lymph.

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.

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).

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 B-cell leukemia exemplifies the potential role of these agents in producing leukemia and lymphomas in the dog.

The rising incidence of leukemia and lymphomas in an increasing number of dog breeds is a case in point. Similarly there has been an increase in the incidence 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, Old English Sheepdog, Irish Setter 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

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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