PRELIMINARY OBSERVATIONS ON ENDOCRINE-ASSOCIATED IMMUNODEFICIENCIES IN DOGS

A clinician explores the relationship of immunodeficiencies to endocrinopathy.

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Are immunodeficiencies associated with endocrine disorders? Are they heritable and therefore predictable? These questions came to mind when I originally began investigating endocrine-immune disease in dogs. Although the following are preliminary observations, circumstantial evidence indicates a possible endocrine association with immunodeficiency and clinical disease in dogs.

The Immunoglobulins

Immunoglobulins are proteins with antibody activity and are the mediators of humoral immunity. They are present in the blood, tissues and endocrine secretions, and are produced by plasma cells, lymphocytes and some reticular cells.[1,2] The 5 major classes of immunoglobulins are IgG, IgM, IgA, IgD and IgE.

The IgG molecule consists of 2 light and 2 heavy polypeptide chains. The normal IgG level in adult dogs is 1000-2000 mg/dl. The IgM molecule consists of 5 subunits, each of which contains 2 light and 2 heavy polypeptide chains. In humans the IgM molecule contains Forssman and Wasserman antibodies, cold agglutinins and specific antibodies for lipopolysaccharide antigens of Gram-negative bacteria. The normal IgM level in adult dogs is 100-200 mg/dl.[3]

Large quantities of IgA are found in parotid saliva, colostrum, tears and respiratory and intestinal secretions. The IgA molecules of serum and secretions are apparently different. One type of IgA called secretory IgA is produced in some glandular secretions and is resistant to proteolytic enzymes. Normal adult dogs

cells are lacking in lymph nodes, bone marrow and the intestines. Treatment includes administration of gamma globulin and antibiotics.[24,25]

X-Linked Immunodeficiency With Hyper-IgM

This syndrome is characterized by antibody deficiency, recurrent bacterial infections, hematologic disorders, absence of lymphoid follicles and germinal centers in lymph nodes, normal or elevated IgM levels, and decreased levels of IgG and IgA. An acquired form occurs in both sexes and differs from the inherited form by the presence of normal lymph nodes.[26] Gamma globulin replacement is the treatment but mild bacterial infections may still occur.

Adult Antibody Deficiency

This deficiency occurs in children and adults of either sex and is characterized by recurrent bacterial infections, decreased immunoglobulin levels and impaired antibody response. Associated sprue-like and autoimmune diseases are common. Cellular immunity is usually normal. It is uncertain whether this deficiency constitutes a single entity or a group of disorders.[27]

Affected patients usually have a history of chronic diarrhea and moderately severe respiratory infections. Complications such as autoimmune hemolytic anemia, iron deficiency anemia, hypersplenism, amyloidosis, arthritis, granulomas and ulcerative colitis have been reported.[28]

Clinical Research

Preliminary investigation was undertaken to assess the relationship of endocrine-related immunodeficiencies with various clinical disorders in dogs. In addition to a standard battery of hematologic determinations, the following tests were performed on each animal:

- T_3, T_4—These were performed using the radioimmunoassay method.
- IgG, IgM, IgA—Blood samples were drawn and serum assayed using double diffusion on agar plates against canine anti-IgG, anti-IgM, anti-IgA and control serum (Miles Laboratories).
- resting and ACTH-stimulated cortisol—Blood samples were drawn at 9 AM and IM ACTH gel (Adrenomone: Burns-Biotec) given at 1 mg/lb. A second blood sample was collected 2 hours later and both tested by the radioimmunoassay method.

Using Miles Laboratories reagents and an outside veterinary clinical pathology laboratory* for testing, the following were derived as normal values:

T_3	37-54%
T_4	1.8-5.6 μg/dl
cortisol-resting	1.0-2.5 μg/dl
cortisol-stimulated	12.0-24.0 μg/dl
IgG	1000-2000 mg/dl
IgM	100-200 mg/dl
IgA	50-150 mg/dl

Although many clinicians classify a T_4 of 1.0 μg/dl or less as deficient, I consider up to 1.8 μg/dl as deficient when associated with altered adrenal zona fasciculata function. Decreased serum cortisol from the zona fasciculata alters the negative feedback to the pituitary so that ACTH production continues unabated. The zona reticularis, the innermost ACTH-responsive layer of the adrenal cortex, responds to continued ACTH stimulation with increased production of estrogens, prostaglandins and androgens.[29] Estrogens bind certain thyroid compounds, and estrogens in association with prostaglandins bind active cortisol into transcortin to further reduce available cortisol. Massive amounts of glucocorticoids cause conversion of T_3 to T_4;[29] therefore, one must consider the possibility that low cortisol levels may maintain normal T_3 levels, but may cause decreased T_4 levels from less T_3 conversion.

An elevated resting cortisol value may indicate a deficit in negative feedback to the pituitary. Although sufficient cortisol is produced by the adrenal zona fasciculata, the cortisol may be in an inactive bound form so that ACTH production does not cease.

An ACTH-stimulated cortisol level of less than 12 μg/dl is considered deficient because normal cortisol levels may be present even with severe adrenal disease if enough functional zona fasciculata cells remain. Histologic examination of the adrenal glands from animals

* A & E Clinical Veterinary Laboratories, West Los Angeles, CA.

values (Case 40) reflect IgG and IgA deficiencies similar to her affected puppy's. Another of her puppies (Case 39) had deficient cortisol, IgG, IgM and IgA levels, but had normal T_3 and T_4 values. The puppy is clinically normal, but will be monitored for disease similar to that of the originally affected puppy.

Treatment of the affected puppy consisted of oral lincomycin for the staphylococcal infection, oral sodium levothyroxine (Synthroid: Flint) given BID at 0.1 mg/10 lb bodyweight, and 15 mg prednisolone SID. The puppy's muzzle and ears were nearly normal after 3 days of treatment (Figs 3,4).

A 6-year-old altered male Basset underwent intradermal testing and desensitization over a 3-year period for nonresponsive generalized pruritus and circular seborrheic lesions (Fig 5). The dog was obese and had been treated with prednisolone every other day. Blood values (Case 3) revealed an elevated IgG level and

Table I

Case No.	T_3 %	T_4 µg/dl	Resting Cortisol µg/dl	Stimulated Cortisol µg/dl	IgG mg/dl	IgM mg/dl	IgA mg/dl	Classification
23. 3 yr Fa Collie generalized dermatitis	3.6	4.7	6.5	14.8	2300	170	60	hypothyroid, hyper-IgG
24. 9 yr M G. Shepherd generalized dermatitis	49.2	1.2	7.5	13.5	2600	160	32	hypothyroid, hyper-IgG, hypo-IgA
25. 4 yr M Dalmatian generalized demodecosis	49	2.7	0.8	15	3200	270	47	hyper-IgG, -IgM
26. 3 yr M Beagle generalized dermatitis	41.8	2.2	2.7	8.8	1300	350	65	hypoadrenal, hyper-IgM
27. 12 yr Fa Mix food allergy	30	0.1	0.9	10	1300	240	400	hypothyroid, hypoadrenal, hyper-IgM, -IgA
28. 2 yr M Mix generalized demodecosis	4.8	2.5	3.0	14.0	1380	500	110	hypothyroid, hyper-IgM
29. 5 yr M Malamute polymyositis	47	2.7	4.2	10.7	2200	270	50	hypoadrenal, hyper-IgG, -IgM
30. 10 yr Fa Yorkie generalized dermatitis	38	1.1	0.1	0.1	720	70	43	hypothyroid, hypoadrenal, hypo-IgG, -IgM
31. 3 yr M Doberman generalized dermatitis, lick granuloma	40	0.7	7.6	13.8	1550	145	86	hypothyroid
32. 4 yr M Irish Setter generalized dermatitis	34	1.0	2.6	8.4	2100	170	270	hypothyroid, hypoadrenal, hyper-IgG, -IgM
33. 13 mo M Bichon idiopathic epilepsy	45.3	3.6	3.6	11.5	600	110	60	hypoadrenal, hypo-IgG
34. 10 mo M Bulldog viral myelitis	42	3.1	0.1	1.1	2600	180	100	hypothyroid, hyper-IgG
35. 4 yr M Keeshond generalized dermatitis	42.6	1.5	5.1	12.8	1052	250	130	hypothyroid, hyper-IgM
36. 6 yr M G. Shepherd discoid lupus erythematosus	47.8	2.3	1.1	17.1	3100	90	80	hyper-IgG, hypo-IgM
37. 5 yr M Mix endocrine dermatitis	43	2.3	24.0	28.0	1750	70	54	hyperadrenal, hypo-IgM
38. 10 wk M Golden Retriever generalized pyoderma	38	1.3	0.9	2.5	280	110	23	hypothyroid, hypoadrenal, hypo-IgG, -IgA
39. 10 wk M Golden Retriever normal littermate	42	2.1	1.4	3.6	100	75	23	hypoadrenal, hypo-IgG, -IgM, -IgA
40. 6 yr F Golden Retriever seasonal dermatitis	44	2.7	6.5	16.0	600	100	28	hypo-IgG, -IgA
41. 4 yr F Poodle idiopathic epilepsy	48.1	2.3	2.3	12.5	980	110	20	hypo-IgG, -IgA
42. 4 mo F B. Terrier generalized demodecosis	39	2.6	0.1	1.5	210	84	38	hypoadrenal, hypo-IgG, -IgM, -IgA
43. 8 yr M Viszla generalized dermatitis	46	3.5	3.6	11.1	1200	78	46	hypo-IgM
44. 4 yr Ma Basset generalized dermatitis	57	2.2	2.2	11.2	3200	280	185	hypoadrenal, hyper-IgG, -IgM, -IgA

chelated form, only those minerals needed by the dog will be absorbed. Even dogs with cardiac problems need a certain amount of sodium chloride, but in a chelated form, only the necessary amount will be absorbed.

Remember, as with your own diet, no matter how healthy the food ingredients are (organically grown), they only can be as good as their parent soil. Therefore, if the soil is imbalanced, so will be the food product. These micronutrients lead not only to deficiency and toxicity diseases but also create a loss of proper funding of certain specific enzymatic reactions occurring in the gut. These definitely can lead to a loss of uptake and utilization of necessary nutrients.

IDENTIFICATION

How can you identify a food allergy? A careful history plus an open mind are essential. A food allergy may occur within a few weeks of age or as late as 10 to 12 years of age. There certainly are dogs that develop food allergies so early in life that inherited food allergy sensitivity must be suspected with an associated IgA antibody imbalance. Other dogs acquire a food allergy after a number of years of exposure to the same food. Breeds that appear to be predisposed to inheriting food allergies should not be exposed as puppies to classic food allergens. It is a general misconception that the new dog food is usually the cause of the food allergy. Actually the food sensitivity occurs only after a given time of exposure to the *old* food.

New foods with improper formulations and/or improper processing can mimic a food allergy. Generally, a food allergy is chronic. Therefore, by reviewing the history, you may find that the disorder has occurred more than once. To try to identify a food-related disorder in a dog may be difficult, but I believe that many more food-related diseases and trace mineral imbalances exist than ever imagined.

What methods are available to identify these food allergies? The most common method is food elimination, meaning that all foods are considered guilty until proven innocent. Stop all foods and either feed a complete non-meat formulation with trace elements, or feed a lamb-based trace mineral food. Note: Lamb is the least allergenic of all meats, not only because it has a less stimulatory molecular structure, but also because fewer dogs in this country have been exposed to lamb. If, after feeding a less allergenic diet and no other segments of the allergy environment have been changed (except food), and the clinical signs of the dog's disease disappear or lessen, it is reasonable to assume that the dog has a food related disorder.

In certain instances, all food may be withheld for three to four days to see if the disease improves. This certainly is a little extreme in my opinion since current thinking suggests that food allergens may remain in a dog's system and cause disease up to 21 days.

Skin testing (injecting certain food substances directly into the skin) falls quite short diagnostically, because once the allergenic food is ingested, broken down and cleaved by the gut enzymes, the specific allergenic compound at best is difficult to identify.

NEW TESTS

The above methods relate to the dog's classic immune cells, the lymphocytes. A new method has been developed to identify food sensitivities and appears to be quite promising. These tests involve a different cell than the lymphocyte, a neutrophil. This method called cytotoxic testing, first was developed in humans. It was found that by injesting certain foods a predictable toxic reaction could be observed in the patient's neutrophil. This test has been adapted for use in dogs and cats. The test is done simply by taking a blood sample, spinning down the white blood cells and then exposing these cells to various prepared food allergens that have been placed on a glass slide. Through the use of a microscope, the toxic reactions that occur in the white blood cells are graded from one to four, with four being the most severe. The test appears to be 85% accurate, but if the dog has not been eating certain specific food allergens within the past nine-month period, there is a good chance that its neutrophil will not react. Even though negative on the cytotoxic test, if the dog's lymphocyctes are sensitive, a severe allergic reaction may occur.

Often accompanying a dog's food allergy is an increase in a peripheral blood cell, eosinophil. It is thought that this cell is associated with the release of histamine. That may occur secondary to ingestion of certain food allergens. If this is the case, a veterinarian can identify this cellular phenomenon and then start the dog on a non-meat trace mineral diet or lamb-based trace mineral diet. After seven days, the dog's blood should be checked again for eosinophils. If the eosinophil count has dropped, food allergy must be considered.

It is obvious that no method of detecting food allergies is 100% accurate. When many of these methods are used in conjunction with common sense, however, the food-related disease can be identified. It also is just as important to realize that diagnosis and treatment of food-related diseases is in its infancy, even though some of the methods discussed above have been used for years. This is a creative area of medicine that is vital to a dog's health. It is important to rule out food-related and trace mineral disorders before moving on to more exotic areas of medicine. Otherwise, if a food or trace mineral-related disease is missed, the patient will be treated for naught, forever. □

Alfred J. Plechner, DVM, is a graduate of the University of California at Davis in 1966. His veterinary clinical studies over the past 15 years have been related to the tolerance in dogs and cats and the ability or inability to use modern diets.

Dr. Plechner's efforts have been directed toward identifying various genetic endocrinology-immunology imbalances that have led to an inability of dogs and cats to tolerate their environment with particular intolerance of today's diets.

Since these specific imbalances now are identifiable, they are preventable through testing of prospective parents.

Dr. Plechner's special interests include clinical allergy, endocrinology and immunology.

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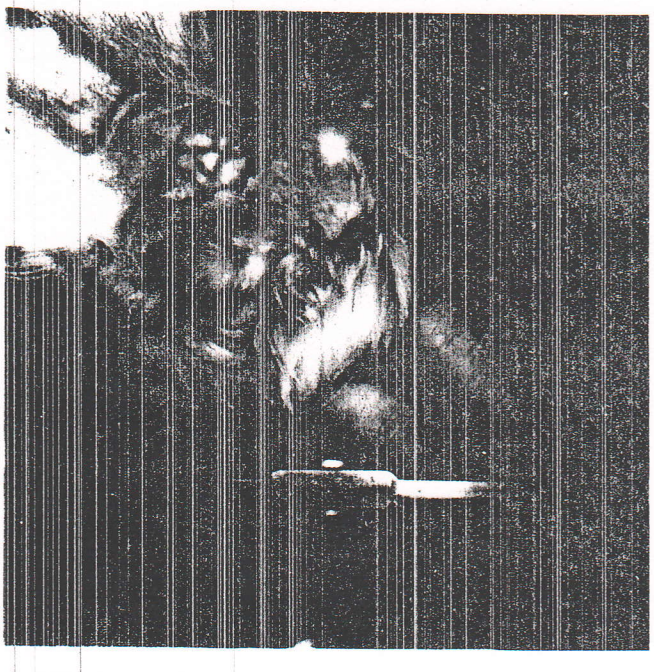


Fig 3. Remarkable improvement is evident after only 3 days of treatment.

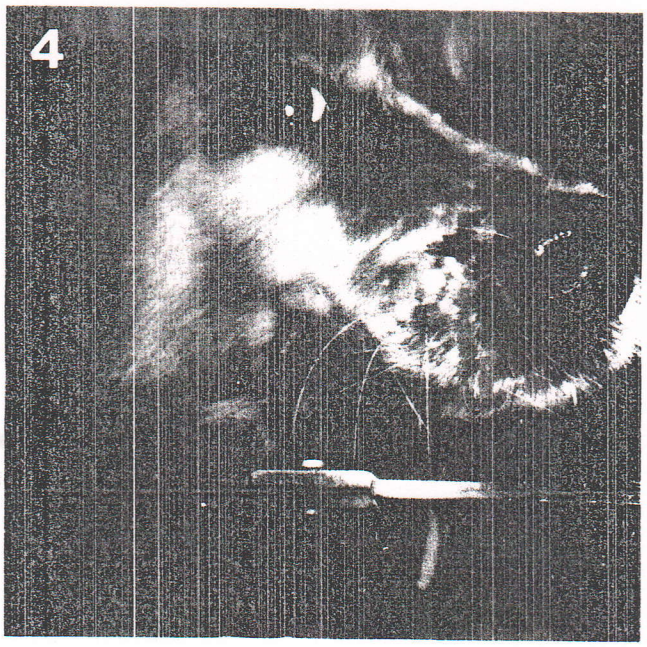
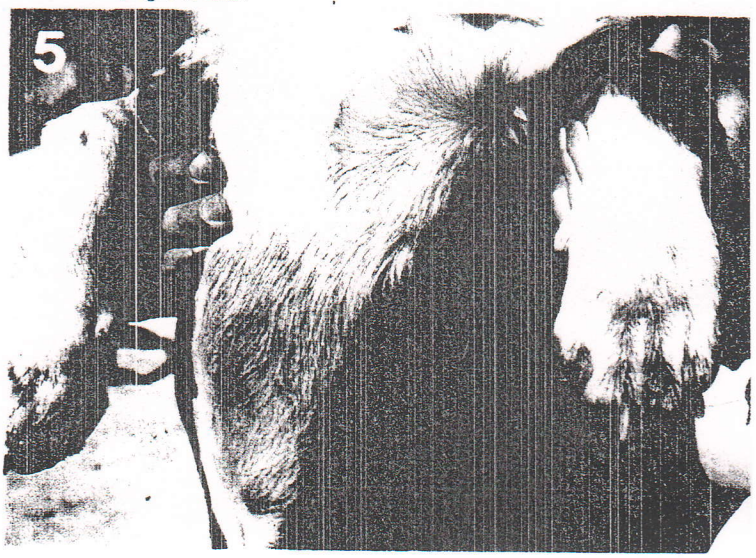


Fig 4. The muzzle is nearly normal after 3 days of treatment.

The findings from the Golden Retriever bitch and her puppies indicate that some of these conditions may be predictable and, therefore, avoidable through selective breeding. More detailed investigations are needed to assess, predict and treat endocrine-immune disorders. ■

Fig 5. Pruritic areas on a 6-year-old Basset with low T_4, cortisol and IgA levels.



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