CANINE IMMUNE COMPLEX DISEASES

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Several genetic and acquired hypersensitivity state diseases are characterized by markedly low serum cortisol levels, with lymphocytic infiltration and acute destruction of the adrenal cortex.

In the several immune complex diseases (ICD) the host has self-immune defenses (autoimmunity) programmed against its own tissues. The malfunction through which ICD develops is basically unknown, but the sequestered antigen and the forbidden clone theories have been suggested as pathogenetic mechanisms.[1]

According to the sequestered antigen theory, lymphocytes do not have the ability to react with antigens in embryonic development. They do, however, possess the capacity for future recognition of these antigens, which are recognized as "self." Due to this morphologic programming the lymphocytes will not form antibodies against these self antigens. Areas devoid of circulation, *eg*, lens tissue, or thyroglobulin will not be recognized as self. In the event of later contact between lymphocytes and sequestered tissue, an antigen/antibody reaction will occur. In specific tissue substance such as thyroglobulin, the end product becomes an antithyroid autoantibody.

The forbidden clone theory states that mutation is a constant phenomenon among lymphocytes. Most mutant lymphocytes carry new or depressed antigens and their progeny carry the same antigens. If such lymphocytes are antigenically positive they will elicit an antibody response from nonmutant lymphocytes. These positive mutant clones are therefore forbidden due to normal immunologic surveillance. Complications arise when a mutant is antigenically negative and does not react with nonmutant lymphocytes. These mutants proliferate freely and form clones with a potential for interacting with normal tissue antigens; thus they are pathogenic autoantibodies.

In our clinical studies we have found hyperimmune states to be far more common than hypoimmune states. Many of our observations indicate definite genetic and acquired hypersensitivity disease states which tend to facilitate immune host injury. At this point we feel that these patients are born with a genetic predisposition for allergic status, priming of which by specific or nonspecific antigens allows hypersensitivity diseases to develop. There is evidence to suggest that offspring born to hypersensitized parents may avoid hypersensitivity diseases through elimination of certain priming antigens by avoiding

traditionally allergenic foods such as milk, eggs, wheat, white potatoes, and beef during the first year of life.[2]

Genetic predisposition to ICD has been thoroughly documented in animals. Certain pedigrees manifest a serologic autoimmune abnormality so remarkable that it cannot be attributed to chance or nonspecific environmental factors. For example, New Zealand Black (NZB) mice invariably develop autoimmune hemolytic anemia antibodies, while New Zealand White (NZW) mice do not.[3] All NZB/NZW offspring eventually have positive tests for lupus erythematosus (LE) cells or antinuclear antibody (ANA). In Hartley guinea pigs, immunization with low doses of guinea pig thyroid extract results in a high incidence of thyroiditis, but similar doses induce thyroiditis in only a small percentage of strain-13 guinea pigs.

An important consideration in genetic ICD is that several different types of autoantibodies and/or disease states occur in the offspring of those affected, whether human or animal. This suggests that if genetic mechanisms are operating, they may predispose families to immunologic diseases in general rather than to just one particular condition.

It is vitally important to realize that hereditary factors alone are insufficient to trigger ICD. Animals with immune alteration due to neonatal thymectomy, cortisol administration, radiation therapy, etc, still require priming factors such as cell wall bacteria, inhalants, endotoxins, food, or drugs, or a more generally allergic status to develop ICD. Animals raised in aseptic surroundings, but with the same predisposition for ICD, do not develop signs of autoimmune disease.[3]

Mediastinal tumor associated with ICD in a dog.

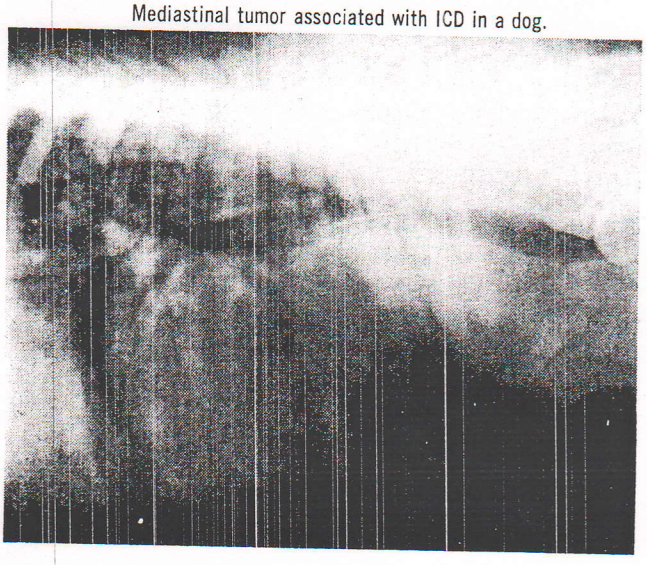

Table 1. Types of antibody reported in human ICD

Human Immune Complex Diseases	Anti-antibody
Discoid lupus	ANA, C_3
Systemic lupus	ANA, C_3, C_{1Q}
Pemphigus vulgaris	Intercellular cement, C_3
Bullous pemphigoid	Subepithelial basement membrane, C_{1Q}, C_3

In clinical practice much emphasis is placed on diagnosis of lymphogenous diseases on the basis of lymphocyte counts.[4, 5] Basically we feel that there is not so much an increase in the number of lymphocytes, but a lack of maturation of these cells, many of which, especially B-lymphocytes, may not proceed to plasma cells. When this occurs a state of hypogammaglobulinemia ensues. Thus it appears that the etiology of many ICD may be primarily related to maturation arrest of these cells, rather than a secondary hypogammaglobulinemia caused by the particular ICD.

In persons, an immunodeficient state is involved in many ICD, lymphogenous diseases, tumors, etc, [6, 7, 8] but our studies indicate a great discrepancy between canine and human patients with ICD. The classic means of diagnosis, including the Coombs test, ANA, LE preparation, and immunoglobulin and comparative cortisol levels, have given conflicting results. Although in human patients ICD is said to develop in a deficiency state, our experience indicates this to be rarely if ever the case; instead, ICD in animals develops in a normal or hyperimmune state.

Certain characteristics of several well recognized but poorly understood human ICD,[9] as described in the literature (Table 1) differ considerably from those we have found for canine ICD counterparts (Table 2). We have long suspected the existence of ICD, and many of our clinical observations have indicated other mechanisms involved in ICD of the dog. The use of immunosuppressive drugs, including corticosteroids, has given some inexplicable results, and in tissue sections we have seen many immune complex lesions.

Contrary to popular belief, our studies indicate that corticosteroids do not impose a classic immunosuppression as we know it today, and our comparative immunoglob-

Table 2. Laboratory findings in canine immune complex diseases (ICD)

	ANA	LE preparations	Coombs test	Immunoglobulins	Plasma cortisol (μg/dl)	Post-ACTH cortisol (μg/dl)
Generalized demodectic mange	—	—	—	elevated	1.2	1.2
Discoid lupus-like ICD	—	—	—	normal	3.4	5.2
Systemic lupus-like ICD	+	—	—	elevated	1.5	3.5
Pemphigus vulgaris-like ICD	—	—	—	normal	2.1	3.6
Interdigital cyst ICD	—	—	—	normal	5.2	7.4
Tumor ICD	—	—	—	normal	1.2	7.6

ulin levels support this observation. As our clinical studies have become more advanced, the actions of steroids used in ICD have become less clear.

One factor common to patients with suspected ICD (generalized demodectic mange, discoid lupus-like ICD, systemic lupus-like erythematosis, pemphigus-like ICD, interdigital cysts and tumors) has been a markedly lowered serum cortisol level which in some cases approached nonexistence (Table 2). In most of our ICD patients, pathologic examination has revealed lymphocytic infiltration and acute destruction of the adrenal cortex, suggesting that we may be dealing with a genetically induced or acquired ICD of the adrenal cortex.

If there is suppression or destruction of a target organ, our clinical studies further indicate that it is important to provide replacement therapy for that target organ's secretion. Additionally, if the autoantibody moiety is high-level and/or broad-spectrum, a general immunosuppressant, *eg*, methotrexate, cyclophosphamide, etc, is required. Much of our ICD is developmental; careful examination indicates the vast majority of our cases have had clinical evidence of hypersensitivity diseases earlier in life. It appears that when the degree of the hypersensitivity state increases, so does the risk of ICD. We have found indications that certain breeds have immunologically induced problems.

Our basic ICD diagnostic panel includes the Coombs test, ANA and LE preparations, cortisol levels, and post-ACTH cortisol levels. Formerly we also determined immunoglobulin levels by electrophoresis, which in most patients were normal to elevated. In the elevated state patients often exhibited mono- or polygammopathies, which we felt were a part, but not a specific indicator, of ICD.

In most of our generalized demodectic mange ICD cases, the mange mite tends to multiply and, in our opinion, manifests itself as merely an indicator of altered immunity. Many of these patients have hypersensitivity diseases caused by specific antigens. Upon removal of the antigen and/or hyposensitization, immune homostasis can occur. The normal immune surveillance system provides a self-limiting control of the mange mite. Animals which have exhibited a hypersensitivity state and later developed ICD often have normal to increased immunoglobulin levels, negative ANA, LE preparation and Coombs test, and decreased adrenal cortical function.[10-12]

Discoid lupus-like ICD is one of the more common and recognizable forms encountered in clinical practice.[13] Typically the patient has an apparent nasal lesion, which in most instances is developmental and an outcome of a hypersensitivity state, *eg*, erythema, exfoliation, or pruritus; often there has been a history of mild inflammation of the nares. This inflammation itself leads to hypopigmentation, erythema, and a destructive lesion. Most patients have normal to elevated immunoglobulin levels, negative Coombs test, ANA and LE preparation, low plasma cortisol levels, and diminished response to ACTH administration.

A large number of our patients with systemic "lupus-like" erythematosis have had clinical hypersensitivity diseases. Few of these patients have been ANA+, whereas the frequency among human subjects is reported to be high. Immunoglobulin levels

have been normal to elevated. The disease has occurred in young as well as older patients, possibly reflecting genetically-induced vs acquired disease. This disease is extremely severe clinically, with much endarteritis leading to generalized tissue necrosis, especially involving the integument. Many of these patients have a depressed cortisol level, unresponsive to ACTH stimulation.

Pemphigus-like ICD has been well documented in both human and veterinary medicine, with similar characteristics. Pathognomonic findings usually include acute inflammation and bullous formation involving the mucous membranes and skin; anti-intracellular substance antibody is often demonstrable. Bullous pemphigoid differs only in that the self-destruction antibody is directed toward the subepithelial basement membrane. In pemphigus vulgaris the typical microscopic lesion is suprabasal acantholysis.[14, 15] Our patients have exhibited negative Coombs tests, ANA and LE preparations, with diminished cortisol levels unresponsive to ACTH stimulation.

Most of our patients with interdigital cysts have a history of hypersensitivity disease. Immunoglobulin levels are normal to elevated, Coombs test, ANA and LE preparations have been negative so far, and some have a depressed adrenal cortex.

Patients with ICD manifested as tumors have had normal to elevated immunoglobulin levels, but many are ANA- and LE preparation-positive, and cortisol levels are reduced. Clinical histories indicate that many of these patients are in developmental through early hypersensitivity states. In human subjects, tumor formation as the end product of ICD is fairly well documented.

Summary

Though not conclusive, our primary findings indicate that a feature common to many of our tumor and ICD patients is depressed cortisol production. Additionally, the response to ACTH adrenal cortex stimulation tests, at 2-hour intervals between rest and stimulation, have ranged from negative to substantially less than would be expected in normal subjects.

Peripheral plasma cortisol values for dogs, at rest and 2 hours after ACTH stimulation, respectively, have been reported as 2-10 and 25-30 μg/dl,[16] 3-8 and 7.5-18 μg/dl,[17] and 1-12.5 and 9.5-22 μg/dl.[18] For representative patients, our resting values have been 1.2-5.2 μg/dl, vs 1.2-7.6 μg after ACTH stimulation (Table 2). Altogether we have studied 42 cases in detail, and we feel that a post-ACTH level of 8.0 μg/dl or less is a conservative indication of adrenocortical insufficiency; all levels have been between 1 and 8μg/dl. We believe these low cortisol levels indicate either a genetically-induced adrenal cortical insufficiency (evident at 2 months to 1 year of age) or an immune complex adrenal cortical suppression (occurring after 1 year of age in association with other immunodeficiency disorders).

Our studies demonstrate a need for biphasic therapy. We have found it necessary to not only initiate cortisone acetate therapy to support the deficient adrenal cortical secretion, but also use other immunosuppressive drugs to control the ICD. If the target organ has been suppressed or destroyed, the need for supplementation is obvious. However, other immune-injury moieties must be suppressed also, *eg*, ANA, anti-IgG antibodies, etc.

Fig 1. Lesions of systemic lupus erythematosis before cortisone therapy.
Fig 2. Same dog following treatment.
Fig 3. Nasal lesions of discoid lupus erythematosis.
Fig 4. Lesions of pemphigus vulgaris-like ICD.
Fig 5. Systemic lupus-like lesions on the back.
Fig 6. Interdigital cyst.
Fig 7. Generalized demodicosis before treatment.
Fig 8. Same animal after cortisone treatment.

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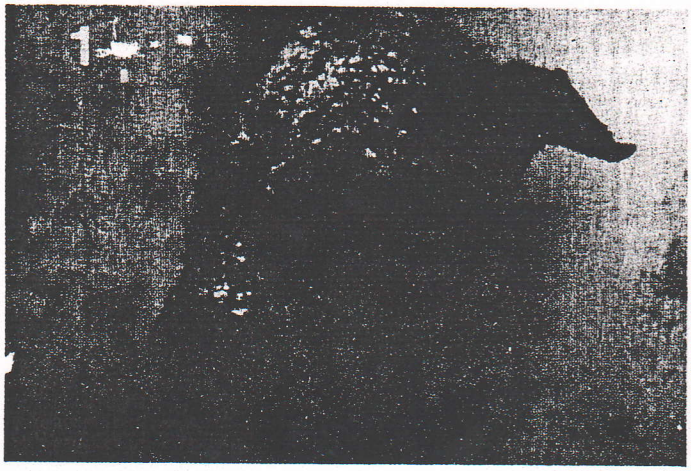
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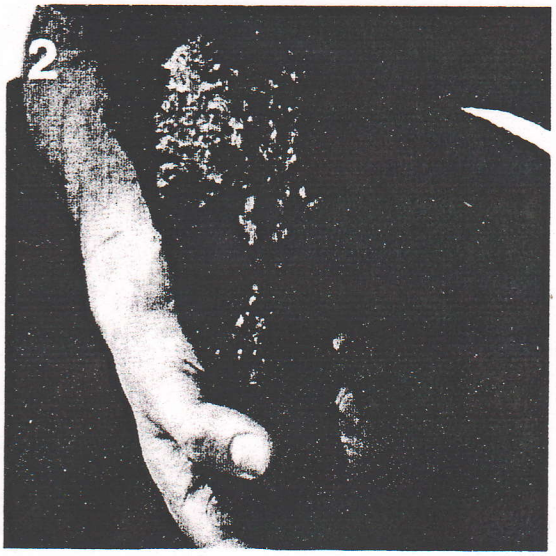
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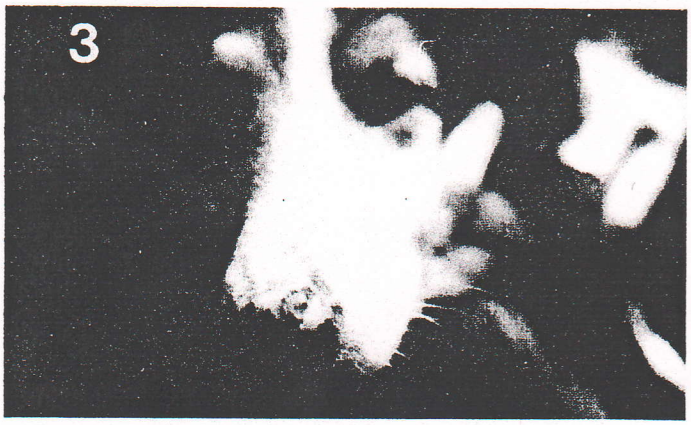
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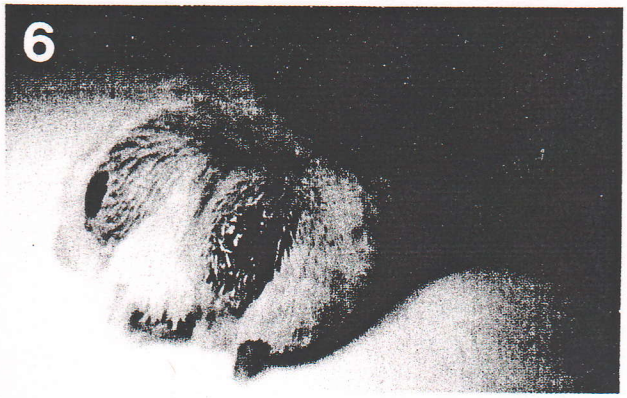
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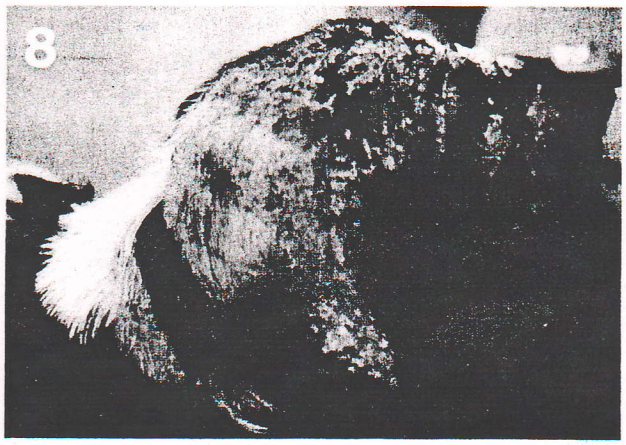
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