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Possible Association of Thymus Dysfunction with Fading Syndromes in Puppies and Kittens

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"Wasting" or "fading" syndromes are common causes of death in both puppies and kittens. These poorly defined syndromes are generally characterized by anorexia, lethargy, and emaciation during the first few weeks of life and often lead to death with no apparent cause. The terms "wasting" and "fading" describe this general syndrome and will be used interchangeably throughout this article. The fading syndrome can cause major problems in breeding colonies, especially if inbreeding has occurred.¹¹ Many possible causes have been suggested, including viral infections, bacterial septicemias, nutritional inadequacies, toxins, and environmental factors.^{6,7,11,27,28,31,33,40-42,44} Several of these factors are probably capable of causing neonatal wasting and death and should be considered in a differential diagnosis. Infectious canine hepatitis virus and beta-hemolytic streptococcus infection in puppies^{7,28,44} and feline infectious peritonitis infection in kittens^{6,27,31,33,40,41} have been strongly implicated as causes of fading and death in some cases. However, several authors have reported that infectious agents could not be isolated from a large proportion of puppies and kittens that fade and die, and that lesions severe enough to cause death could not be found.^{6,7,11,20,33,42} Therefore, the cause of the fading syndrome remains a mystery in most cases. The status of the thymus gland has not received adequate attention in diagnosis and therapy of wasting syndromes of puppies and kittens. In some species, neonatal thymectomy results in a fatal wasting syndrome^{17,29} that can be prevented by soluble factors from the thymus.^{25,32} This article will focus on the role of the thymus gland in maintaining the health of young animals and on how thymus dysfunction may contribute to some cases of wasting and death. Current knowledge about thymus hormones will be reviewed briefly, and

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one form of a wasting syndrome in pups that is responsive to thymus hormone therapy will be described.

WASTING AND FADING SYNDROMES OF PUPPIES AND KITTENS

In a survey of catteries representing 790 litters with a total of 3468 kittens, kitten mortality was found to be a serious problem: 10.2 per cent of the kittens were stillborn, 15.2 per cent of the kittens born alive had died by 1 week of age, and 27.1 per cent of the kittens born alive did not reach 1 year of age.^{40,41} Because this survey was based on cattery records, reliable information on causes of death was apparently not available in most cases. The authors of the report indicated that most breeders commonly complained of fading kittens. In some cases, the kittens born emaciated and weak died within 1 or 2 days. In other cases, the kittens appeared healthy for a few days or weeks, then became depressed and anorectic and gradually faded. Specific clinical signs or lesions were usually absent, except for evidence of emaciation and malnutrition. Several of the catteries reported kitten losses that were diagnosed clinically or histologically as feline infectious peritonitis (FIP).

The FIP virus has been implicated as a cause of the fading kitten syndrome based on serologic evidence⁴¹ and the isolation of an FIP-like virus from a 4-day-old fading kitten.²⁸ However, FIP virus lesions are not observed in many fading kittens.³³ The consensus seems to be that the FIP virus, or other feline coronaviruses, can contribute to kitten mortality, but there is insufficient evidence to conclude that these viruses are the major cause of the fading kitten syndrome.^{6,33,41} More research is needed to understand the causes of the fading kitten syndrome and to find ways of reducing the incidence of kitten mortality.

A fading syndrome that results in death is also prevalent in puppies.^{7,11,20,28,42,44} Epidemiologic data concerning the incidence of a fading syndrome in pups are apparently unavailable. Several infectious agents can cause death in neonatal puppies, including bacterial infection of the umbilicus, bacterial septicemia, and a number of viruses (canine herpesvirus, canine adenovirus, canine distemper virus, coronavirus, and parvovirus).⁴² With a careful postmortem examination and suitable laboratory tests, these causes of puppy mortality can be diagnosed.

Fading syndromes of puppies and kittens are a major problem. In many cases, the infectious agent responsible for illness cannot be identified.^{33,42} There are undoubtedly many causes of fading and death in young animals. In order to achieve a better understanding of the causes of wasting, owners, clinicians, and researchers need to pay careful attention to this problem. Such an understanding may lead to measures for prevention or to effective therapeutic approaches.

THE ROLE OF THE THYMUS IN WASTING SYNDROMES

The status of the thymus gland should receive special attention in fading puppies and kittens. Clinicians have known for many years that the removal

of the thymus from young animals of some species will result in a fatal wasting syndrome.^{17,29} Yet, in most reports of fading syndromes in puppies and kittens, there is no mention of the gross or histologic appearance of the thymus.

The thymus gland and the immune system of the puppy and kitten are well developed at birth.^{23,24} The seeding of the peripheral lymphoid tissues with T lymphocytes apparently occurs early in these species. Reports of the effects of thymectomy in the kitten were not found; however, a number of investigators have reported the effects of thymectomy in the puppy. Dennis and coworkers reported that dogs thymectomized as 48-day-old fetuses had defective humoral and cell-mediated immune responses but normal lymphoid tissue development and did not show signs of a wasting disease.⁸ Other authors reported that neonatally thymectomized dogs had a normal humoral response, no impairment of allograft rejection, and no signs of wasting disease.^{10,49} In contrast, Than and colleagues⁴⁶ observed prolonged survival of skin grafts in dogs thymectomized at 1 month of age (an indication of defective immune function). Tilney and colleagues demonstrated that all 18 puppies thymectomized at 3 to 6 weeks of age died of a typical wasting syndrome, whereas only 1 of 9 puppies thymectomized between 10 to 12 weeks of age died of a wasting syndrome.⁴⁷ Sham-thymectomized littermates of these puppies did not develop a wasting syndrome. It is difficult to draw firm conclusions from these reports regarding the importance of the thymus in the prevention of wasting syndromes because in puppies there were differences in surgical procedures, age of animal at thymectomy, breed of dog, indigenous infectious agents, and other factors. If one assumes that the thymectomies were complete in all cases, the most obvious difference would be in the age of the dog at thymectomy. Puppies thymectomized in utero, as neonates, or at 10 to 12 weeks of age did not develop the wasting syndrome, whereas puppies thymectomized at 3 to 6 weeks of age uniformly died of a wasting disease. It seems illogical that removal of the thymus at 3 to 6 weeks of age would result in wasting when removal at birth or at 10 to 12 weeks of age did not. Nevertheless, this possibility should not be dismissed.

A number of factors, including stress, glucocorticoids, toxins, malnutrition, and systemic infectious diseases, can cause thymus atrophy.⁵ Certain viruses, including feline panleukopenia virus,⁴ FIP virus,^{33,51} and canine parvovirus, cause rapid atrophy of the thymus gland.³⁵ Zinc deficiency in pups has also been shown to result in severe atrophy of the thymus gland.³⁹ The role of these factors in fading syndromes in puppies and kittens is unresolved.

THYMUS HORMONES

The thymus exerts at least some of its influence on the development and maintenance of the immune system through soluble factors, thus acting as an endocrine gland. Mice that are thymectomized at birth are immunodeficient and die of a wasting syndrome.^{17,39} Shortly after this discovery, it was observed that implantation of thymus tissue inside of a cell-impermeable chamber into a thymectomized mouse would improve immune function and

prevent death due to wasting.^{25,32} It was concluded that the thymus was functioning as an endocrine gland, releasing a hormone (or hormones) that diffused out of the chamber, enhancing immune function, and preventing wasting. These results stimulated the search for thymus hormones. A number of thymus hormones have now been isolated and identified, and more will probably be found. The nature, function, and potential clinical applications of these hormones have recently been reviewed.^{12,16,21,26}

Thymosins

One of the first thymus hormones to be described was isolated from a calf thymus and was termed "thymosin."^{14,26} A semipurified form of this hormone has been termed thymosin fraction 5 and has been shown to contain more than 30 peptides. Several of these peptides have biologic activity. Thymosin alpha 1 was the first peptide isolated from thymosin fraction 5. It consists of 28 amino acid residues and has a molecular weight of 3108 daltons. Thymosin alpha 1 is 10 to 1000 times more active than thymosin fraction 5 in several *in vivo* and *in vitro* bioassays. It is also a potent inducer of helper T lymphocytes. Thymosin alpha 7 is a partially purified extract of thymosin fraction 5 that induces the development of suppressor T lymphocytes. Over 100 children have received thymosin fraction 5 for a variety of primary immunodeficiency diseases. These patients were treated with injections of up to 400 mg per m² of thymosin fraction 5, usually daily for 2 to 4 weeks, then once per week for an indefinite period (some patients were maintained for over 6 years). No evidence of serious toxicity due to thymosin was reported for these patients. Some forms of primary immunodeficiency had a positive clinical response to the thymosin fraction 5 therapy. At least six human patients with autoimmune conditions (five with systemic lupus and one with rheumatoid arthritis) have been treated with thymosin fraction 5 in phase-I protocols. Based on the lack of toxicity and positive immunologic responses, phase-II randomized trials in systemic lupus erythematosus and rheumatoid arthritis have been initiated.²⁶ More than 200 patients with cancer have been treated according to phase-I and phase-II protocols. No major side effects of thymosin therapy were observed in the majority of these patients. A significantly prolonged survival was noted for patients with non-resectable small cell carcinoma of the lungs when given thymosin fraction 5 in conjunction with intensive chemotherapy.²⁶

Thymopoietin

Although thymopoietin is a protein hormone that was also isolated from the bovine thymus, it is different than thymosin fraction 5.¹⁵ It contains 49 amino acids and exists in 2 forms that differ by 2 amino acids. A sequence of five amino acids within the thymopoietin molecule has the same biologic activity as the whole molecule and is termed "thymopoietin pentapeptide" or "thymopentin." Thymopentin has been used in over 386 people for several conditions, including herpesvirus infection, acute burns, leprosy, rheumatoid arthritis, pyoderma, selective IgA deficiency, and trichophyton infections.⁴⁵ Positive clinical responses were observed in some of these conditions. Acute, subacute, and chronic toxicity studies with thymopentin have been performed in various species (including dogs). The drug was found to be

safe and devoid of major side effects.¹² The dosage and route of administration are quite important for obtaining a positive response with thymopentin.

Thymic Humoral Factor

Thymic humoral factor (THF) is another peptide that has been isolated from the bovine thymus.⁴⁶ It consists of 30 amino acids and plays a role in the differentiation and maturation of T lymphocytes. The administration of THF to humans suffering from either primary or secondary immunodeficiencies resulted in the restoration of cellular immunocompetence; progressive clinical improvement was observed in some cases.^{1,21}

Thymulin

Facteur thymique serique (FTS), a nine amino acid peptide isolated initially from the serum of swine, was later found in the serum of man and cattle.^{2,3,21} It was discovered that the FTS peptide chelates zinc, which it requires to be active. The active form of the hormone containing zinc is called thymulin. A deficiency of zinc in the diet results in a deficiency of thymulin activity in the serum.²² Thymulin has been used to treat a limited number of patients in the course of a phase-I clinical trial. No signs of toxicity were observed, confirming earlier results of animal trials. Normalization of deficient T-cell numbers or functions was observed in a number of cases (immunodeficiency syndromes, viral infections). Thymulin treatment induced the appearance of IgA in the serum of children presenting with IgA deficiency with T-cell deficiencies.²

NEUROENDOCRINE INTERACTIONS WITH THE THYMUS

Because the hypothalamoadenohypophyseal system is an important regulator of other endocrine glands, it is logical to assume that it may influence the function of the thymus gland as well. In early experiments examining this possibility, Pierpaoli and Sorkin²⁴ were able to show that a single inoculation (intraperitoneally) of rabbit antimouse hypophysis serum into a normal mouse produced inhibition of growth, involution of the thymus gland, and a wasting syndrome similar to that observed after neonatal thymectomy. The effect of the antihypophysis serum was age-dependent. The serum most effectively induced a wasting syndrome at the age when the same strain of mice, if they had been thymectomized as neonates, would have developed the disease. Pierpaoli and Sorkin obtained similar results by injecting several doses of a rabbit antibovine growth hormone. Body growth was inhibited and a wasting syndrome was observed. The depletion of thymocytes in the cortex reduced the size of the thymus. The thymus-dependent areas of the spleen also were reduced or absent.

Sorkin and associates⁴³ used Snell-Bagg hypophyseal dwarf mice to study further the relationship between the thymus gland and the adenohypophysis. These mice produce only about one one-thousandth of the normal amount of growth hormone. Hypoplasia of the thymus gland and peripheral lymphoid tissues, lymphopenia, and impairment of transplantation immunity are typical of these mice with a deficiency of growth hormone.⁹ Treatment of adult

dwarf mice with bovine growth hormone normalized the histologic features of the thymus and restored the impaired immune capacity.⁴³ However, this restoration was not observed in dwarf mice thymectomized as adults and then treated with growth hormone. There is now considerable evidence to indicate that the adenohypophysis and the neuroendocrine system have important effects on the thymus gland and, conversely, that thymus gland activity influences the neuroendocrine system.³⁰

WASTING SYNDROME ASSOCIATED WITH IMMUNODEFICIENT DWARFISM IN DOGS

A neuroendocrine abnormality associated with thymus dysfunction and a wasting syndrome has been described in Weimaraner dogs.³⁶⁻³⁸ This condition is referred to as immunodeficient dwarfism and is characterized by deficiency of growth hormone, absence or deficiency of thymic cortical tissue, and deficient lymphocyte blastogenic responsiveness to mitogens. Affected pups appear relatively normal at birth; however, at a few weeks of age, they develop a wasting syndrome characterized by reduced appetite, lethargy, emaciation, and failure to thrive. Most of the affected pups die with this syndrome in spite of conventional supportive therapy. Either thymosin fraction 5 or bovine growth hormone therapy reverses the symptoms of the wasting syndrome.^{37,38} Information on the characteristics of the wasting syndrome in immunodeficient dwarf pups as well as the experiences with thymus hormone and growth hormone therapy may be useful to clinicians attempting to treat wasting puppies or kittens.

Clinical Syndrome

An inbred colony of dogs, all three quarters to purebred Weimaraners, was maintained at Iowa State University for studies on spinal dysraphism. About 5 to 10 per cent of the pups from this colony of dogs developed a wasting syndrome near or after the time of weaning, characterized by reduced appetite, lethargy, emaciation, and failure to thrive (Fig. 1). Most of the affected pups died in spite of conventional supportive therapy. Necropsy revealed a small thymus gland in 10 of 13 pups that had died at 4 to 13 weeks of age. Histologic examination performed on available tissues from the 10 pups revealed a marked deficiency of thymic cortex. All of the dogs in this inbred colony were observed to be 30 to 40 per cent smaller than expected for normal Weimaraners, but had normally proportioned features.³⁸

Immunologic Characteristics

Puppies with the wasting syndrome had relatively normal white blood cell counts and were not lymphopenic. Humoral immunity was not severely compromised in the pups with the wasting syndrome in that they had normal serum gamma globulin concentrations (as determined by serum protein electrophoresis). The pups with the wasting syndrome produced an approximately equivalent antibody response to killed *Brucella abortus* as did their unaffected littermates.³⁸

It is not known whether the thymus glands in the wasting pups under-



Figure 1. Two male Weimaraner siblings (15 weeks old) from a colony of dogs affected with immunodeficient dwarfism. The smaller dog has the wasting syndrome; his littermate is unaffected.

went atrophy or if they never developed fully and, therefore, were hypoplastic. A few neonatal pups from the Weimaraner colony that died from maternally inflicted trauma or were euthanized had a small rudimentary thymus without a discernible cortex. This suggests that the thymus glands failed to develop normally in utero in the affected pups.

The T cell-dependent areas of the spleen and lymph nodes of both wasting and nonwasting dogs from the Weimaraner colony appeared relatively normal.³⁸ The mechanism by which the T-cell areas in the secondary lymphoid tissues of the immunodeficient dwarf dogs became populated with lymphocytes is not known, but there are several possible explanations. It may be that the thymus is still sufficiently functional to allow some T-cell maturation, or perhaps the thymus was relatively well developed for a brief period in utero, allowing for the seeding of the secondary lymphoid tissues with T lymphocytes. Another possible explanation is that maternal hormonal factors obtained in utero, through the colostrum or milk, could have allowed some T-cell maturation and prevented the development of the wasting syndrome until after weaning.

One litter of pups from this colony was chosen for a more thorough study of immunologic function. This litter was exceptional in that 50 per cent of the pups (four of eight) were thymus-deficient. The *in vitro* blastogenic responsiveness of lymphocytes to phytohemagglutinin (PHA) was evaluated in these pups periodically from the age of 2 weeks to 11 months.³⁸ Compared with normal adult dogs, all of the pups in the litter had deficient lymphocytic blastogenic responses to PHA for the first 14 weeks of life. Normal pups reportedly have depressed lymphocytic blastogenic respon-

siveness to PHA for the first 4 to 5 weeks of life, but it usually reaches adult levels by 7 weeks of age.¹³ From the entire litter, the one pup that developed the wasting syndrome and survived (due to thymosin fraction 5 therapy) had depressed lymphocytic responsiveness to PHA until it was 7 months of age.

When lymphocyte blastogenesis data obtained from normal dogs, from inbred Weimaraners that were not affected with the wasting syndrome, and from two dogs that survived the wasting syndrome were compared, it became evident that the inbred Weimaraners unaffected by the wasting syndrome had a marginally, but significantly ($p < 0.05$), lower response to the mitogens PHA and concanavalin A (ConA) than did the normal controls, but their responsiveness to pokeweed mitogen (PWM) was similar to that of the normal controls.³⁷ The two pups that survived the wasting syndrome (after growth hormone therapy) had, on the average, a markedly lower lymphocytic blastogenic response to all three mitogens when compared with that of the normal controls or the unaffected Weimaraner pups. The blastogenic activity of lymphocytes from the affected pups was highly variable and, on occasion, did approach normal values. Therefore, several lymphocyte blastogenic assays were required over a period of time in order to establish whether or not a pup was affected by this characteristic of immunodeficient dwarfism.

Neuroendocrine Abnormalities

All of the dogs in the inbred Weimaraner colony were smaller than expected for their breed. Because the resting concentration of growth hormone in the plasma of dogs is too low to be reliably detected by radioimmunoassay and because growth hormone is released episodically, provocative tests are required to evaluate pituitary secretion of growth hormone. Clonidine hydrochloride has been shown to be a dependable stimulator of growth hormone release in the dog.¹⁸ Ten pups from the colony were given clonidine intravenously (16.5 μg per kg), and the growth hormone concentration in their plasma was determined at 0, 15, 30, and 60 minutes after administration. These pups had an increase in the concentration of plasma growth hormone after administration of clonidine, but it was significantly lower than the concentration found in age-matched controls at 15, 30, and 60 minutes after administration.³⁸ Of the 10 pups tested, 1 had recovered from the wasting syndrome after being treated with thymosin fraction 5. It also had a detectable growth hormone response to clonidine administration that was similar to the response of his littermates that did not develop the wasting syndrome.³⁸ It may be that factors other than deficiency of growth hormone or in addition to deficiency of growth hormone are responsible for the lack of thymus development and the onset of the wasting syndrome, or it may be that a certain concentration of growth hormone is required at critical stages in the development of the immune system (for example, in utero).

Three puppies from two different litters in the Weimaraner colony were selected for a thyroid stimulating hormone (TSH) response test and an adrenocorticotrophic hormone (ACTH) response test.³⁰ None of these puppies had the wasting syndrome; however, they all had a significantly lower concentration of growth hormone at 15, 30, and 60 minutes after clonidine administration than did age-matched controls. These puppies all had normal concentrations of serum thyroxin before and after the administration of TSH.

The concentrations of plasma cortisol before and after the administration of ACTH were also normal in the six puppies studied. Two male siblings from the Weimaraner colony (one of which had recovered from the wasting syndrome after treatment with growth hormone) developed symptoms compatible with hypothyroidism at 16 months of age and had deficient TSH response tests. These dogs may have a defect in either the thyroid or the pituitary gland. It was concluded that puppies from the inbred Weimaraner colony typically have abnormal growth metabolism, but normal TSH and ACTH response tests.

Therapy

The wasting condition is not responsive to conventional supportive therapy, but is responsive to treatment with thymosin fraction 5 or growth hormone. Thymosin fraction 5 (1.0 mg per kg) was administered (subcutaneously) daily for 7 days, then once per week for one or two more doses. The treated pups had good clinical responses, gained weight, and increased vigor.³⁸ Thymosin fraction 5 therapy did not enhance lymphocyte blastogenesis. In a similar manner, thymosin fraction 5 therapy for an immunodeficient child resulted in clinical improvement without improvement in lymphocyte blastogenesis.⁵⁰

To date, three immunodeficient dogs have been treated with growth hormone by our research group. Pretreatment thymic biopsies were performed after the pups developed clinical signs of the wasting syndrome. Growth hormone therapy was initiated after surgery and consisted of injecting 0.1 mg of pituitary-derived bovine growth hormone per kg of body weight subcutaneously daily for five doses, then on alternate days for five doses, and finally, every third day for an additional four doses. No other therapeutic agents were administered. The posttreatment thymic biopsy was performed 6 weeks after the first thoracotomy and 2 weeks after the last dose of growth hormone. Response to growth hormone therapy was monitored by (1) performing thoracotomies to obtain thymus biopsies; (2) lymphocyte blastogenesis in response to mitogens; (3) radioimmunoassay for thymosin alpha 1; and (4) observing the clinical response to therapy. The pups responded to growth hormone therapy with improved appetite, weight gain, and increased vigor. After growth hormone therapy, a large, well developed thymus was present in the anterior mediastinum of the dogs. Histopathologic examination revealed the presence of well defined medullary and cortical areas where, before treatment, only a minimal amount of cortex was present (Figs. 2 and 3).³⁷

In immunodeficient dwarf pups, growth hormone therapy did not improve the ability of peripheral blood lymphocytes to undergo blastogenesis in response to phyto mitogens.³⁷ Therefore, the growth hormone did not completely normalize the immunologic responsiveness in these pups, even though it did result in clinical improvement. Growth hormone therapy did result in increased size and cellularity of the thymus, with a distinct differentiation into the cortex and medullary regions. Thymosin fraction 5 therapy did not induce a regeneration of thymus morphology in a similarly affected dog.³⁸ The thymic hypertrophy and hyperplasia following growth hormone treatment may be due to a direct effect of the growth hormone (or growth



Figure 2. Biopsy of the thymus gland from the 15-week-old Weimaraner with the wasting syndrome shown in Figure 1. There is an overall decrease from normal in the size of the gland and the cortex-to-medulla ratio. In some areas, the cortex is distinguishable only as a rim of tissue in the periphery of the lobule. There is increased width and adipose tissue content of the interlobular septae. 30 X-magnification.

hormone-induced somatomedin activity) or it may be due to a thymic hormone (or hormones) that is (are) induced by growth hormone. The growth hormone therapy did not cause a consistent increase in the serum concentration of thymosin alpha 1. The pups were apparently not deficient in thymosin alpha 1 before therapy with growth hormone.

Thymus Histopathology

The thymus gland of a normal prepubescent dog is characterized by connective tissue interlobular septae that are thin and contain no adipose tissue, a cortex to medullary ratio of about 1:1, and a relatively large number of thymic corpuscles. The average number and size of thymic corpuscles change with age, ranging from about 5 per lobule in the neonate to a maximum of about 15 per lobule in the 20-week-old dog.⁵²

Thymic tissue was analyzed from three dogs that had recovered from a wasting syndrome after treatment with bovine growth hormone. Before growth hormone treatment, the glands of the 13- to 14-week-old dogs were characterized by severe cortical depletion of lymphocytes; the cortex was recognizable in some areas only as a thin rim of lymphocytes at the periphery of the lobule (see Fig. 2). Interlobular septae were increased in width and were infiltrated with a moderate amount of adipose tissue. The number of thymic corpuscles was about three to five per lobule, which was considered low for dogs of this age. After growth hormone treatment, the most obvious

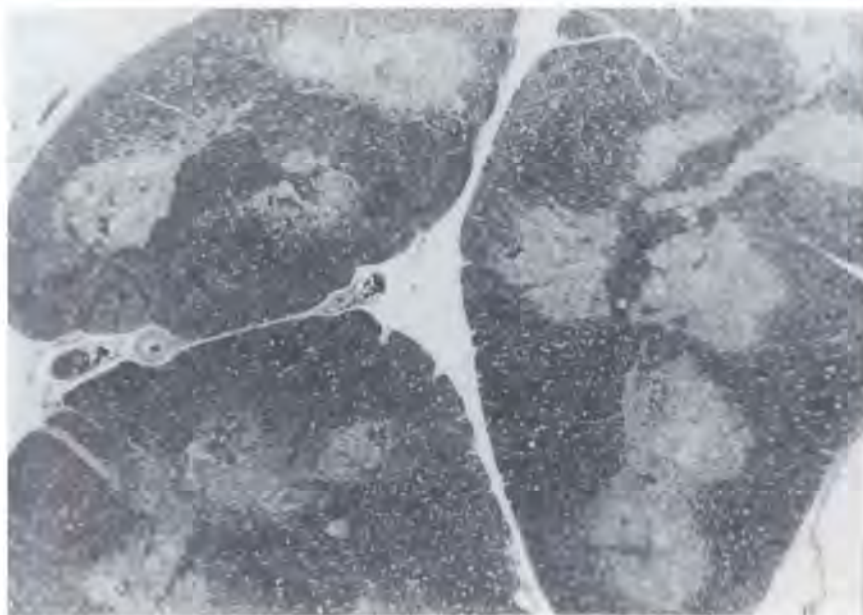


Figure 3. Biopsy of the thymus gland from the same dog as in Figure 2, at 22 weeks of age, after treatment with bovine growth hormone. The morphology of the gland now resembles that of a normal young dog with narrow interlobular septae and a cortex-to-medulla ratio of about 1:1. 30 X-magnification.

change was the normalized cortex to medullary ratio of approximately 1:1 (Fig. 3). The interlobular septae were now mostly of the normal, narrow configuration, although a minimal amount of adipose tissue remained in the septae. The number of thymic corpuscles remained below the norm for dogs of 11 to 20 weeks, averaging only four to six per lobule.

Other conditions in which the thymus undergoes involution include accidental involution (also called stress or steroid involution), zinc deficiency,³⁹ and parvovirus infection.³⁵ Lesions characteristic of accidental involution include, acutely, a clumping and degeneration of cortical lymphocytes and, later, an increase in interlobular septal thickness usually without much fatty infiltration at first.¹⁹ Because the dogs were lethargic and emaciated for some time during which there may have been a nonspecific stress effect, this type of involution must be considered as playing a part in the histologic appearance of the thymus in immunodeficient dwarf dogs with the wasting syndrome. However, the dogs' thymus glands showed a more severe form of depletion than may be associated with stress involution as well as an abnormal increase of fatty infiltration.

Zinc deficiency in dogs causes a thymic lymphocyte depletion.³⁹ Serum samples from all Weimaraners in our colony and from 27 control dogs were analyzed for zinc content by flame atomic-absorption spectrophotometry. All of the Weimaraners had serum zinc values similar to the values for the control dogs.^{13a} Zinc deficiency does not appear to be involved in the immunode-

iciency associated with these dogs. However, we cannot rule out a transient deficiency during the wasting syndrome because no dogs actively undergoing this syndrome were available for assay. Three dogs that had recovered from the wasting syndrome after treatment with growth hormone were assayed for blood zinc and found to be within normal ranges.

SUMMARY

"Wasting" or "fading" syndromes are common causes of puppy and kitten mortality. Numerous infectious and toxic, metabolic, or nutritional factors could potentially be responsible for wasting and death in young animals. Evidence has been presented that infectious canine hepatitis virus infection, beta-hemolytic streptococcus infection, and feline infectious peritonitis virus infection are responsible for a significant number of deaths due to wasting syndrome. However, many cases of wasting syndrome cannot be attributed to infectious agents or other specific etiologies. The thymus gland warrants special attention when one is evaluating an animal with a wasting syndrome because it is known that, in some species, neonatal thymectomy results in wasting and death. Unfortunately, most reports describing fading syndromes in puppies and kittens do not mention the gross or histologic appearance of the thymus gland at postmortem examination. When examining the thymus gland, one must keep in mind that the thymus may be hypoplastic owing to a congenital or genetic defect in its structure and function or it may be atrophic secondary to whatever is causing the fading syndrome. If a thorough history, clinical examination, and/or postmortem examination do not reveal a cause for the fading syndrome, then defective thymus function should be considered as a possible causative or contributing factor to the fading syndrome. In these cases, therapy designed to replace or improve the defective thymus function should be considered. At least one form of wasting syndrome in puppies (immunodeficient dwarfism) has been found to respond to short-term therapy with a thymus hormone (thymosin fraction 5) or with bovine growth hormone (which is thymotrophic) in limited clinical trials. It is possible that other forms of wasting or fading syndromes would also respond to therapy with thymus hormone or growth hormone. Certain thymus hormones (thymopoietin pentapeptide, thymosin alpha 1, facteur thymique serique, and rabbit thymus acetone powder*) and bovine growth hormone† are commercially available. Before initiating therapy, one should consider that if the cause of the wasting syndrome is genetic, then successful treatment may perpetuate a genetic defect. More research (both basic and clinical) is needed to determine the role of thymus gland dysfunction in fading syndromes of puppies and kittens and if therapy with one or several of the thymus hormones or with growth hormone could reverse the symptoms of wasting.

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