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Canine Hypoadrenocorticism (Canine Addison's Disease): History, Contemporary Diagnosis by Practicing Veterinarians, and Epidemiology

William James Kelch
University of Tennessee - Knoxville

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I am submitting herewith a dissertation written by William James Kelch entitled "Canine Hypoadrenocorticism (Canine Addison's Disease): History, Contemporary Diagnosis by Practicing Veterinarians, and Epidemiology." I have examined the final electronic copy of this dissertation for form and content and recommend that it be accepted in partial fulfillment of the requirements for the degree of Doctor of Philosophy, with a major in Comparative and Experimental Medicine.

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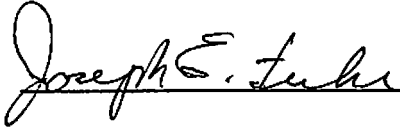Vice Provost and Dean of the Graduate School

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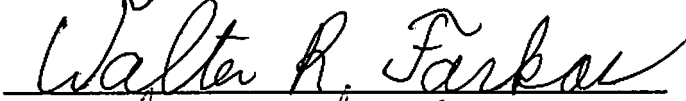
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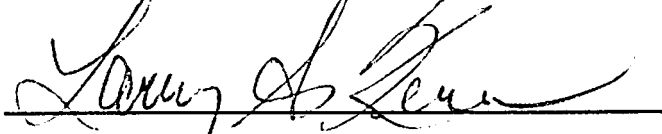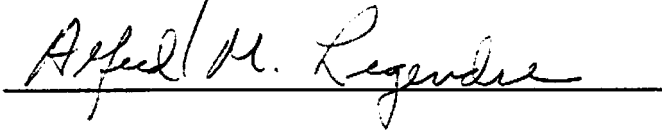
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Associate Vice Chancellor
and Dean of the Graduate School

Canine Hypoadrenocorticism (Canine Addison's Disease): History, Contemporary Diagnosis by Practicing Veterinarians, and Epidemiology

**A Dissertation
Presented for the
Doctor of Philosophy
Degree
The University of Tennessee, Knoxville**

William James Kelch

December 1996

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DEDICATION

This dissertation is dedicated to dogs, creatures whose presence on earth immeasurably enriches the lives of their companion humans. It is dedicated to them in the hope that its content will contribute a tiny bit to the maintenance of their good health.

ACKNOWLEDGMENTS

ABSTRACT

This study of canine hypoadrenocorticism (canine Addison's disease; adrenal insufficiency) used several techniques to determine the incidence and prevalence of the disease and to identify factors associated with its occurrence. These techniques were historical; statistical, including meta-analysis and logistic regression; and epidemiologic, including both case series and case control data. Data were gathered by: extracting the details of cases reported in the veterinary literature, a rudimentary meta-analysis; using data obtained by Ciba Animal Health in the clinical trial of the drug microcrystalline desoxycorticosterone pivalate (DOCP); using data obtained from the Veterinary Medical Data Base (VMDB), a data repository of clinical information from colleges of veterinary medicine in the United States—augmented by directly querying VMDB non-participant colleges of veterinary medicine in the United States and Canada; surveying by mail veterinarians enrolled in the Ciba Animal Health clinical trial of DOCP; and surveying by mail 1,000 practicing small animal veterinarians selected randomly from the mailing list of the American Veterinary Medical Association.

The historical study focused on how humans first recognized the existence of the adrenal glands, next understood they were involved with disease in humans and other animals, and then developed methods for identifying and treating hypoadrenocorticism. The historical study began with Galen in the second century A.D., continued as human understanding expanded over the centuries, ended with

the contemporary understanding of hypoadrenocorticism, and provided a context in which the specific results of the study became meaningful.

Incidence estimates for canine adrenal insufficiency were, depending on the data set used to obtain the estimate, 0.13/1000 dogs/yr, 0.34/1000 dogs/yr, and 0.6/1000 dogs/yr. A point estimate was 0.36/1000 dogs/yr. Prevalence estimates were 3.2/1000 dogs, 1.7/1000 dogs, and 0.6/1000 dogs. A point estimate was 1.8/1000 dogs.

Estimates of the average age (yr) at diagnosis for dogs with hypoadrenocorticism were 4.3, 4.9, and 5.4, again depending on the data set. A point estimate was 4.9. The ages of cases and controls suggested, based on the computation of age-specific odds ratios (OR) and logistic regression, that age was associated with the occurrence of disease and that the probability of disease increased with age.

Female dogs were more likely to be hypoadrenal than males, and neutered dogs of either sex were more likely than intact ones. These conclusions were based on sex-specific incidence estimates, sex-specific OR, and logistic regression. The latter confirmed that sex was a significant factor associated with hypoadrenocorticism in dogs.

Breed was, based on breed-specific OR and logistic regression, a significant factor in whether or not a dog developed adrenal insufficiency. Airedale Terriers, Basset Hounds, Bearded Collies, German Shepherds, German Shorthaired Pointers, Great Danes, Poodles, Saint Bernards, Springer Spaniels, and West

Highland White Terriers were at increased risk of disease. Boston Terriers, Boxers, Cocker Spaniels, Dalmatians, Lhasa Apsos, Pit Bull Terriers, Pomeranians, Shetland Sheepdogs, Shih Tzus, and Yorkshire Terriers were at decreased risk. There was less compelling evidence that Labrador Retrievers and Mixed breed dogs were at decreased risk.

Average body weight (kg) estimates for hypoadrenal dogs were 23.4, 24.5, and 19.7, depending on the data set. A point estimate was 22.5. The body weights of cases and controls suggested, based on age-specific OR and logistic regression, that body weight was associated with disease and that the probability of disease increased with body weight.

Hypoadrenal dogs were characterized by hyponatremia, hyperkalemia, and a decreased ratio of serum sodium to potassium concentrations. Point estimates for serum sodium concentration, serum potassium concentration, and serum sodium to potassium concentration ratio were 132.1 meq/L, 6.6 meq/L, and 21.1, respectively. There was evidence that hypoadrenal dogs were seldom normal for all three diagnostic indicators.

Common clinical findings among hypoadrenal dogs were anorexia, vomiting, depression, weakness, weight loss, azotemia, and diarrhea. Though probably affected by measurement bias, there was evidence that dogs with adrenal insufficiency were more likely than dogs from the general population to have anemia, arthritis, cruciate ligament rupture, diabetes mellitus, hepatitis,

hypothyroidism, keratoconjunctivitis sicca, megaesophagus, myasthenia gravis, nephritis, and thrombocytopenia.

The study concluded that epidemiologic studies of canine hypoadrenocorticism may use the practicing veterinarian's diagnosis as a case definition rather than require a strict case definition based on the adrenocorticotropic hormone stimulation test. This would produce larger numbers of cases, be less complex, more convenient, and less costly.

Logistic regression of data from the mail survey of veterinarians enrolled in the clinical trial of DOCP indicated that age, breed, sex, and body weight were associated with canine hypoadrenocorticism. The probability of disease increased with age and body weight, was greater in females than males, was greater in neutered than intact dogs, and varied with breed. There was model-dependent evidence of higher order interactions, but the exact nature of these interactions could not be determined. Models were prepared which could predict the *relative* probability of hypoadrenocorticism in different dogs. It was emphasized that these models undoubtedly overlooked other unknown variables.

Data from the veterinary literature, VMDB, clinical trial of DOCP, and survey of veterinarians enrolled in the DOCP clinical trial were all useful. The mail survey methodology was valuable, and should be a useful tool in veterinary epidemiologic studies. The mail survey of randomly selected veterinarians was a poor method for studying an uncommon disease; this deficiency might be overcome if larger samples were obtained.

PREFACE

The University of Tennessee (UT) awarded its first Ph.D. degree in 1886 in the field of General. The award of the Ph.D. in General harkens back to the day when one individual could legitimately lay claim to at least a rudimentary grasp of all human knowledge. That grasp, after all, was the whole purpose of the degree.

The Ph.D. in General has sadly disappeared in the short 110 years since 1886. (For time perspective, remember that there is a lady alive in France--this is written in mid-February 1996--who could have attended the 1886 graduation as a small, but sentient, child.) The General degree's disappearance, and its gradual replacement by subsequent generations of ever more specialized degrees, is a natural, unavoidable, and salutary consequence of the logarithmic growth of human knowledge in the last century. No sane person today would claim even the shallowest, most tenuous grasp of all human knowledge, and that is as it should be. A single human brain can comprehend only so much. But the inevitable transition from General to very, very specialized has come at a price, in one sense an unacceptably high price.

It seems that the impossibility today of mastering even a tiny part of human knowledge has become a convenient excuse for avoiding the effort entirely. While mastery is impossible, and failure to do so is not cause for despondency or opprobrium, making the effort is nevertheless worthwhile and essential to meaningful scholarship. While the original goal of the Ph.D. degree, i.e., mastery

of all human knowledge, may be unattainable, the goal's pursuit is not. Those who do not pursue the goal, and particularly those who are contemptuous of its pursuit, show disrespect for the very Ph.D. degree they have or covet.

With the foregoing in mind, I feel very fortunate to be enrolled in the Comparative and Experimental Medicine program, a program specifically defined by its interdisciplinary character. Therefore, while I recognize that this thesis is and should be principally about science, I hope that it is a bit more. I hope I have not been guilty either of "scientific hubris"[a] or the "ignorant barbarism of scientific progress."[b] I have tried to conduct and report good science, but to do so in an historical and interdisciplinary context. I hope that the thesis melds my admittedly limited knowledge of clinical veterinary practice, endocrinology, epidemiology, the philosophy of causality, the mail survey methodology of the social sciences, and statistics. I hope it demonstrates an effort, however inevitably unsuccessful, to achieve the original goal of the Ph.D. degree.

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[a]William F. Buckley, Jr., "Firing Line," November 12, 1995, WSJK Television, Channel 2, Public Broadcasting System, Sneedville, Tennessee.

[b]William Hamilton, "Morning Edition," June 9, 1995, WUOT Radio, 91.9 FM, National Public Radio, Knoxville, Tennessee.

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ACTH	Adrenocorticotropic hormone
DOCA	Desoxycorticosterone acetate
DOCP	Desoxycorticosterone pivalate
o,p'-DDD	2,4'- dichlorodiphenyldichloroethane
OR	Odds ratio
SD	Standard deviation
SEM	Standard error of the mean
VMDB	Veterinary Medical Data Base

CHAPTER 1

A BRIEF HISTORY OF HYPOADRENOCORTICISM

Introduction

Hypoadrenocorticism has almost certainly afflicted humans and other animals since they first evolved, but the disease was not well-defined until about 150 years ago, and the details of its physiology, diagnosis, and therapy were not understood or developed until the 20th century. In fact, definitive therapy was not available until the 1950s.

The following is a brief history through the early 1950s of how understanding of the disease evolved over the decades. The history ends with the early 1950s because, though knowledge about the adrenal glands has certainly advanced substantially since then, the advances can generally be characterized as refinements, such as *improved* synthetic corticosteroids and *improved* clinical case management, rather than altogether new advances.ᶜ The articles reviewed and included in this history, though very numerous and quite comprehensive, do not

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ᶜThe one area in which substantial new contributions have, in fact, been made since the early 1950s is understanding the etiology of hypoadrenocorticism. Its principle cause appears to be immune-mediated destruction of the adrenal cortex,[141] and, since the field of immunology is *so* complex and has progressed *so* much since the 1950s, a discussion of the history of progress in immunology is well beyond the scope of this thesis. Thus it has not been included.

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pretend to be exhaustive--i.e., many, many articles are not included--but the literature reviewed does paint a clear picture of the scientific progress which resulted in our knowledge of the disease today. This chapter focuses on the gradual, stepwise unfolding of knowledge of hypoadrenocorticism, and also, since many other diseases were being similarly characterized during this period, it serves as a model for how "modern medicine" studied disease processes in general.

This chapter does not focus on the disease in dogs since the following chapter is a history of clinical cases in the dog from the first reported cases in 1953 through 1994. Nevertheless, dogs and other animals are frequently mentioned since they were used extensively as laboratory animals, and some information of interest to practicing veterinarians is included if it is not brought out in the next chapter.

Early Period

Galen, in about 177 A.D., while describing the veins which enter the caudal vena cava, referred to "A twig from this not inconsiderable vein [probably the left phrenic] joins and connects with the spongy flesh lying there."[106] The "spongy flesh" is clearly the adrenal gland. Bartolomeo Eustacchio described the adrenal glands in 1563 as "glandulae Renibus incumbentes."[223] His work was first published in 1714 by the Italian clinician Lancisi, who added his own notes.[223]

Edward Tyson (1650-1708[d]), an English physician, stated that "*Glandulae Renales* in Embryos and Infants are greater, at least proportionably, than *in Adultis*."[131] These "*Glandulae Renales*" were, of course, the adrenal glands, and it is interesting to note that Tyson recognized the different proportions of the adrenals in adults and infants—i.e., he recognized that an infant was not simply a miniature adult.[131] This could be viewed as an earlier, admittedly very crude, physiologic observation about the function of the adrenal glands. With regard to domestic animals, August Chauveau (1827-1917) described "The Supra-renal Capsules" in detail.[21] Notably, Chauveau also used the word "*adrenals*" when referring to these organs, and he recognized the difference between "the *cortical* and the *medullary* substance."[21] Two other early veterinary anatomy books also described the gross anatomy of the adrenal glands, both commenting on their ductless nature.[198,241] One of these sources stated, interestingly, but wrongly, that the adrenal glands are "said to be replaced if removed."[241]

First Descriptions of Disease

Thomas Addison, M.D. (1793-1860), an Englishman educated in medicine in Scotland at the University of Edinburgh, was a distinguished physician of his time with very eclectic talents. He worked in surgery, dermatology, toxicology,

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[d]Julian, not Gregorian, calendar.

pathology, anatomy, and physiology. He wrote the first English language book on the actions of poisons on the living body in 1829, was first to use static electricity to treat convulsive disease in 1837, and described appendicitis in 1839. In 1849 he described a pernicious anemia and a disease of the suprarenal capsules (adrenal glands) in a paper to the South London Medical Society. Addison felt that he had indeed described the disease for the first time, although he did so humbly, recognizing that he could be falling prey to the "bias and prejudice inseparable from the hope or vanity of an original discovery." This "Addison's anemia" was described as "a state of general anemia incident to adult males."[e,1]

Six years later, in 1855, Addison published a much more detailed account of the disease which included detailed case reports, autopsy findings, and sketches of patients and their organs. He described clinical hypoadrenocorticism (not the term used then, of course) with remarkable acumen, and (refreshingly) the tone of his writing put the disease in the context of a "philosophic" view of medicine and the pursuit of knowledge, not in a cold, sterile scientific context. Addison prefaced his paper as follows:

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[e]Though now recognized as more often a condition of females, Addison's observation that the disease occurred more often in males may, speculatively, have resulted from chance alone, from males seeking medical attention more often, or from occupational exposure by males, especially since tuberculosis was, though not recognized as such at the time, a principal cause of the disease. Other explanations, of course, are possible.

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If Pathology be to disease what Physiology is to health, it appears reasonable to conclude, that in any given structure or organ, the laws of the former will be as fixed and significant as those of the latter; and that the peculiar characters of any structure or organ may be as certainly recognized in the phenomena of disease as in the phenomena of health. . . . it is as a first and feeble step towards an inquiry into the functions and influence of these organs [the adrenal glands]. . . that I now put forth the following pages.[f,2]

Addison described the condition with incredibly remarkable accuracy:

The leading and characteristic features of the morbid state to which I would direct attention, are, anaemia, general languor and debility, remarkable feebleness of the heart's action, irritability of the stomach, and a peculiar change of colour in the skin, occurring in connexion with a diseased condition of the "supra-renal capsules.". . . Notwithstanding these unequivocal signs of feeble circulation, anaemia, and general prostration, neither the most diligent inquiry, nor the most careful physical examination, tends to throw the slightest gleam of light upon the precise nature of the patient's malady: nor do we succeed in fixing upon any special lesion as the cause of this gradual and extraordinary constitutional change.[2]

Given some updating to a modern-day medical vocabulary, this could easily serve as a contemporary clinical description of hypoadrenocorticism. Addison's careful description of and observations on the 11 clinical cases reported in his article clearly qualify as classics in medical history.

Forty-one years later, in 1896, no lesser personage than William Osler added his imprimatur to Addison's findings. He said, "Recent studies render it very probable that the original view of Addison is correct--namely, that the symptoms of the disease are caused by loss of function of the adrenals."[144] Osler discussed six of his own cases of Addison's disease, and, importantly, put the disease in the

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[f]Whatever happened to prose like this in the scientific literature?

context of other conditions, such as thyroid malfunctions, which underscored "the importance of the ductless glands."[144] Notably, three of Osler's six patients had tuberculosis, and five of the six died, but one was apparently cured by treatment with porcine suprarenal extracts.[144]

During the same era, a veterinary physiology text stated, "The **Renal Capsules** [Bold in original] have been supposed to be connected with the removal of worn-out pigment from the body, but their function is involved in mystery."[199] This points out a prominent hypothesis of the time which was that the adrenal glands were involved in some sort of detoxification. While more than a half-century would pass before a clinical case was reported in the dog,[68] this text recognized that, "In dogs and other animals, the effect of removing these glands has been the production of profound degeneration in the central nervous system, followed by death."[199]

Adrenal Glands Recognized as Essential to Life and
Early Anatomic and Physiologic Studies

Though Addison and Osler, as clinicians, felt that the adrenal glands were essential to life, this had still not been ascertained with scientific certitude. Therefore, researchers studied whether or not these glands were essential, and, if so, why, for about a quarter-century, from roughly 1900 until 1925. The search for definitive answers was made a particularly difficult one because, in addition

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to the crudity of physiologic and surgical studies of the day, the adrenal glands were, of course, comprised of two parts, the cortex and the medulla, with, unbeknownst to the researchers, completely different physiologic roles. Adding further to the complexity were the facts that the cortex itself, again unbeknownst to the researchers, had several different physiologically important products, and that some species, due to the presence of accessory adrenal tissue located elsewhere in the body, could occasionally survive bilateral adrenalectomy.

Many studies demonstrated during this first quarter of the twentieth century that animals which were bilaterally adrenalectomized died.[39,102,132,156-158,210,213,214,243] One study, trying to experimentally mimic Addison's disease, showed that tying the adrenal veins in cats eventually led to death, but death ensued more slowly than in bilaterally adrenalectomized animals.[72] One study demonstrated that bilateral adrenalectomy in the goat was not necessarily fatal,[132] while another indicated that in cats bilateral adrenalectomy "practically always" led to death.[39] These survivals after bilateral adrenalectomy presumably resulted from the presence of accessory adrenal tissue elsewhere in the body, or possibly from incomplete surgical excision of the glands. One report documented the survival of a bilaterally adrenalectomized cat because of the presence of accessory adrenal tissue.[254] In any case, early in this period, the absolute biological requirement for functioning adrenal glands was still in question. By about 1925, however, the issue was pretty well settled, and the conclusion was reached that adrenal glands were indeed necessary to life.[15,82,209,254]

Although it was clearly understood by the end of this quarter-century that the adrenal glands were necessary to life, *why* they were necessary was not understood at all. The hypotheses posited about why they were necessary included that they were related to some vaguely defined "nervous influences" associated with the glands,[214] that the glands were essential to the detoxification of certain substances in the body,[61,118,213,214,243] that they produced a substance necessary to life,[214] that they were involved in some essential way in muscle metabolism,[243] and that they played an active role in antibody production.[61] One quote from this period illustrates just how wrong a statement of scientific certitude can be. It said that the adrenals have two functions: "an antitoxic, protective function accomplished by the internal secretion of cholesterol of cortical origin, and the other the tonic effect of adrenalin of medullary origin."[118] Regardless of this erroneous certainty, the life-maintaining function of the adrenal glands was not defined during this period, and, as illustrated in the preceding quotation, the epinephrin produced by the adrenal medulla caused a good deal of confusion.[g]

The physiologic role of the adrenal glands was extraordinarily bewildering in large part because of the adrenal medulla and its physiologically powerful secretion epinephrin. Researchers, faced with this extremely powerful vasoactive

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[g]Ironically, though the author of the quotation was quite wrong about the life-sustaining role of the adrenal glands, he was prescient in one sense--he did contend that the adrenal cortex and the adrenal medulla had separate functions. In that respect, he stumbled, perhaps accidentally, perhaps not, onto the truth.

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hormone, quite naturally looked for years and years to discover how epinephrin from the adrenal glands was key to life. It was not, of course, so the research community was led astray for a long time. Several papers were published which indicated the (quite predictable and logical) focus on epinephrin.[72,209,211,242] Eventually, researchers, still understanding of course the physiologic power of epinephrin, recognized that adrenal medullary epinephrin was not the key to survival.[103,212] One paper, after reviewing the assertions of others regarding the role of epinephrin in carbohydrate metabolism, said with forthright lucidity:

> Although not one of these statements is true, the theory has possessed a charm from which many have not been able to free themselves, and it has also been productive of work which has shown the matter in its proper light. . . . The theory that epinephrin causes a production of sugar from fat, decreases the power of the organism to oxidize glucose through inhibition of pancreatic function, and stimulates the thyroid so that protein metabolism is increased, is untenable in any of its particulars.[h,103]

Researchers eventually realized that the adrenal cortex, rather than the adrenal medulla, was the part of the adrenal glands essential to life.[i,15,82,212,243,254]

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[h]Another example of the refreshing use of language in a scientific article.

[i]Two fascinating historic notes from this period follow. First, a purportedly pathognomonic diagnostic test for hypoadrenocorticism was described in 1917 which involved tracing a geometric pattern on the abdomen of the patient with a blunt object such as a fountain pen. If a pale white line appeared which became more distinct over a period of about one minute, and then disappeared in one to three minutes more, the patient was hypoadrenal.[191] Second, in 1919 in the wake of the influenza pandemic of 1918, one paper claimed that dysfunctional adrenal glands were involved in influenza and influenzal pneumonia, and that, in fact, the severity of the influenza was proportional to the endocrine dysfunction.[25]

The Fundamentals: Adrenal Cortex,

Anterior Pituitary, and Hypothalamus

Having concluded that the adrenal cortices, not the adrenal medullae, were necessary to sustain life, the research community next tried to determine specifically how the adrenal cortices helped maintain life. An obvious possibility was that some substance required for life was being secreted by the adrenal cortices. Pursuing this hypothesis, a bevy of researchers extracted various fractions from the adrenal glands, and used the extracts to attempt to maintain the lives of bilaterally adrenalectomized animals.[j,73,219] Extracts of tissues other than the adrenal glands such as brain, testes, liver, spleen, and heart were used in attempts to extend the lives of experimental animals with adrenal insufficiency,[16] as were other physiologically active chemicals such as pituitrin, ergotamine, and ephedrine.[16] These extracts and chemicals all failed to sustain life in adrenalectomized animals. One paper, intriguingly, reported that the survival time of four bilaterally adrenalectomized female dogs was significantly extended because they were in heat.[160] This "adrenocortical effect" of the estrogenic hormones gave a hint, apparently unrecognized at the time, of the often

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[j]One quotation from this period illustrates how very crude the surgical techniques being used at that time were: "It is never permissible for an experimenter with an inadequate [surgical] technique to assume that his operations will be of a *uniform degree of badness* [Italics added] in a control set of animals and in a set subjected to a certain procedure, the effect of which is to be tested, so that this factor can be considered as eliminating itself."[161]

overlapping physiologic effects of the steroid hormones. This result led these researchers to use only male dogs in the study of adrenocortical extracts. Another study confirmed that bitches in heat survived adrenalectomy longer than those not in heat, but also showed that luteal extracts did not similarly extend life. This same study demonstrated that in cats, but not in dogs, anterior pituitary extracts extended life in adrenalectomized animals (presumably, based on present-day knowledge, because of the presence of some accessory adrenocortical tissue), and that, in rats, growth hormone from the anterior pituitary did not.[216] This began to show an acknowledgment of the interplay between the anterior pituitary and the adrenal cortices. Another study found that progesterone would maintain adrenalectomized ferrets in "excellent health."[62] This contradicted (unless one posits a species difference) at least one other study which showed that progesterone did not extend the life of adrenalectomized cats.[216] The authors suggested that this apparent discrepancy probably resulted from the use of different dosages of progesterone.[62] In any case, this clearly illustrated again that researchers were gradually realizing the often overlapping physiologic effects of the steroid hormones.

Having established that adrenocortical extracts of one sort or another would sustain the life of adrenalectomized animals, the researchers naturally turned to the next issue, which was *what specifically* in the extracts sustained life. Several

papers discussed the isolation and efficacy of compounds isolated from adrenocortical extracts or their synthetic analogs.[122,196,207,228] These extracts or synthetics were then, of course, used to treat humans with adrenal insufficiency, sometimes successfully and sometimes not, and to maintain the life of adrenalectomized experimental animals.[22,48,94,126,197,227,236]

By 1940, as pointed out in a review article discussing the diagnosis and treatment of adrenal insufficiency, the synthetic crystalline corticosteroid desoxycorticosterone acetate (DOCA) was the most sophisticated therapeutic agent of the day. It was efficacious and available in large quantities at reasonable cost.[224] The DOCA could be injected intramuscularly or implanted subcutaneously as pellets.[7,230] Successful sublingual administration of DOCA dissolved in propylene glycol and alcohol was also reported.[8]

Advances in knowledge in this area were fascinating. First, the determination that the adrenal cortices were required for life; second, the determination that extracts from the adrenal cortices and their synthetic analogs could sustain life in adrenalectomized animals; third, the purification in crystalline form of components of the extracts; and, last, the preparation of synthetic DOCA in large quantities at reasonable cost. While use was made of both the purified adrenal extracts and synthetic DOCA, as time went on more of the latter was used to treat human Addison's disease.

Despite these rapid advances in understanding and treating hypoadrenocorticism, therapeutic results were still not entirely satisfactory. Though DOCA, often combined with the administration of sodium chloride to help alleviate sodium loss,[k] was reasonably effective therapy, there were continuing problems related to an ill-defined failure in their "carbohydrate-regulating capability,"[226,235] and some required treatment with cortical extracts in addition to DOCA.[172] Although unknown at the time, this resulted from the powerful mineralocorticoid effect, but very weak glucocorticoid effect, of DOCA. (The words "mineralocorticoid" and "glucocorticoid" were not, of course, in use during this period.) Gradually, however, researchers began to realize that the adrenal cortices produced two distinctly different types of corticosteroids, one with an electrolyte-regulating function (later to be known as mineralocorticoids), and a second with a carbohydrate-regulating one (later to be known as glucocorticoids). A study in 1940 showed that Addison's disease patients with low normal fasting blood glucose values, an increased tolerance for hypoglycemia, and a low normal basic metabolic rate were non-responsive to DOCA, but responsive to 17-hydroxy-11-dehydrocorticosterone and corticosterone.[238] Another study demonstrated the effects on carbohydrate metabolism in adrenalectomized dogs of crystalline 17-

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[k]Use of this exogenous sodium chloride sometimes led to hypertension, edema, and even heart failure. These problems were occasionally attributed to the concomitant use of DOCA since the now well-known connection between hypertension and high salt intake was not well understood at the time.[247]

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hydroxy-11-dehydrocorticosterone isolated from an adrenal cortical extract.[96] These studies presaged the distinction between mineralocorticoids and glucocorticoids. By 1946 it was reasonably clear that both glucocorticoid and mineralocorticoid treatment (though, again, these words were still not in use) provided the best therapy for Addison's disease. Specifically, one article stated,

> In most patients [11-dehydrocorticosterone] therapy alone . . . failed to effect a significant change in the clinical condition. When . . . [11-dehydrocorticosterone] was added to . . . desoxycorticosterone acetate . . ., a striking improvement over and above that observed with desoxycorticosterone acetate alone was observed.[57]

By 1949 the idea that treatment should consist of cortical extract for its glucocorticoid effect and DOCA for its mineralocorticoid effect had found its way into a medical textbook.[206] Notably, this textbook also indicated the need for sodium chloride therapy[l] as well, and commented that 11-dehydrocorticosterone (described as a "carbohydrate-active hormone") could also be used, but that there was still no source of it for general clinical use. This textbook also recognized that Addison's disease could sometimes be part of a multiglandular disease involving the pituitary, thyroid, gonads, pancreas, thymus, and, perhaps, parathyroid. The relationship between Addison's disease and other endocrinopathies had been

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[l]Sodium chloride could be given in normal food, per os as a supplement, intravenously, and even *per rectum*. One paper stated that "In a *typical* [Italics added] case of Addison's disease, the symptoms of severe adrenal insufficiency were relieved by treatment consisting of the administration of NaCl by mouth and by rectum.[101]

reported earlier. One report of a man with concomitant Addison's disease and diabetes mellitus noted that these diseases had often been reported simultaneously in the same patient.[225]

The present-day terms glucocorticoid and mineralocorticoid were in use by 1950. One review article of that year used both these terms, and also made several other important points.[181] It said that, although the exact active natural adrenocorticoids had still not been defined chemically, their physiologic roles, such as glucocorticoid and mineralocorticoid, had been. Further, the article said that, though the exact roles of the zona glomerulosa, zona fasciculata, and zona reticularis had not yet been defined, they might have distinctly different roles. This paper also recognized the physiologic interplay between the anterior hypophysis and the adrenal cortices. The idea that the adrenal cortices produced at least two distinctly different kinds of hormones, glucocorticoids and mineralocorticoids, was controversial. Some believed that only one corticosteroid, 17-hydroxycorticosterone, was required. But a further study discussed the secretion of a salt-retaining hormone by the adrenal cortex.[195]

So, by the end of the 1940s, the idea was established that the adrenal cortices regulated electrolyte, carbohydrate, protein, and fat metabolism. The recognition by researchers and physicians of this functional duality was reflected in several publications.[66,231,232,234] One article even specifically identified the zona glomerulosa of the adrenal cortex as the source of desoxycorticosteroids which regulated fluid

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and electrolyte balance, and the zona fasciculata as the source of 11-oxy-corticosteroids which regulated gluconeogenesis.[66] Papers emphasized the physiologic effects of the "carbohydrate-regulating" corticosteroids[5,85,229] and the effects of "electrolyte-regulating" ones.[17,23,47,125,151,229,237] During the decade of the 1940s, some elucidation of the physiologic interplay between the anterior pituitary and the adrenal cortices occurred.

Two papers in 1943 described the isolation of pure adrenocorticotropic hormone (ACTH), one isolation from the anterior hypophyses of sheep,[97] and another from pigs.[182] The physiologic and therapeutic effects in humans of ACTH included those on blood and blood constituents,[58,76] electrolytes,[58] metabolism,[58] androgens,[58] and urine,[58] as well as those on normal humans and those afflicted with Addison's disease, Cushing's disease, and hypothyroidism.[154] By the early 1950s, adrenal cortical insufficiency had been clearly classified into primary and secondary disease. Thorn's article in 1951 reported, "Adrenal cortical insufficiency may occur as a result of disease of the adrenal gland itself (primary) or as a consequence of inadequate secretion of ACTH due to anterior pituitary or hypothalamic disease (secondary)."[233] Therefore, by the early 1950s, hypoadrenocorticism was understood as a disease related directly to the adrenal cortices or indirectly to the anterior pituitary or hypothalamus. The control mechanism for the adrenocorticoids was shown, however, to be more complicated

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than a simple feedback loop between the anterior hypophysis and the adrenal cortices.

Steinbeck described three major mechanisms regulating ACTH and, hence, adrenocorticoid secretion.[208] The three were negative feedback from adrenocorticoids, circadian rhythm, and stress; the latter two, significantly, were mediated through the hypothalamus. The hypothalamus released corticotropin-releasing hormone which stimulated the anterior pituitary to release ACTH, the ACTH stimulated the release of adrenocorticoids from the adrenal cortices, and these adrenocorticoids then controlled further secretions by the hypothalamus and the anterior pituitary.[150] This relationship between the central nervous system and the adrenal cortices is one mechanism whereby altered emotional and psychologic states are translated into altered physiologic function.[223] Stresses such as pain, trauma, and anxiety could lead to this stimulation of adrenocorticoid release by the central nervous system.[37]

The historical treatment of Addison's disease[138] pointed out that cortisol had been shown to be a major product of the adrenal cortex in man and dog,[139,140] that aldosterone was a major salt-retaining hormone secreted by the adrenal cortex,[195] and that the adrenal gland produced androgenic substances.[60] Consequently, "the three major types of adrenal hormones produced were [by 1952] represented by specific hormones: glucocorticoids-cortisol, mineralocorticoids-aldosterone, and the androgens, androstenedione and dehydroepiandrosterone, which are converted

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to testosterone to produce their androgenic effects."[138] By the early 1950s, the fundamental physiology and control of the adrenal cortices were understood. It involved the secretion of glucocorticoids, mineralocorticoids, and androgens by the adrenal cortices under the control of the anterior pituitary and the hypothalamus. Interestingly, just as these fundamentals were first clearly understood, the veterinary profession reported the first three clinical cases of canine hypoadrenocorticism.[68]

CHAPTER 2

REVIEW OF 244 CASES OF NATURALLY OCCURRING CANINE HYPOADRENOCORTICISM REPORTED BETWEEN 1953 AND 1994

Introduction

Hypoadrenocorticism (Addison's disease, adrenal insufficiency, adrenocortical hypofunction) was first described in the dog in 1953.[68] It is thought to be an uncommon disease.[41,43] Clinical signs of disease include vomiting, anorexia, weakness, depression, weight loss, diarrhea, and dehydration. These signs result from a deficiency of mineralocorticoids, glucocorticoids, or both. Hypoadrenocorticism can be classified as primary or secondary. In primary hypoadrenocorticism, the adrenal glands fail to produce enough glucocorticoids, mineralocorticoids, or both. It may be caused by granulomatous diseases such as histoplasmosis and blastomycosis, hemorrhagic infarctions, cancer metastases, amyloidosis of the adrenals, intoxication, and treatment for hyperadrenocorticism with the adrenocorticolytic drug 2,4'-dichlorodiphenyldichloroethane (o,p'-DDD).[41] Immune-mediated destruction of the adrenal glands occurs in human beings, and, though it has not been definitively demonstrated, it may also occur in dogs.[41] The cause of adrenal failure is usually not identified, so it is classified as idiopathic.[41] In secondary hypoadrenocorticism, decreased secretion of adrenocorticotropic

hormone (ACTH) by the pituitary or corticotropin releasing hormone by the hypothalamus leads to decreased glucocorticoid production.[41] It can be associated with neoplasia, inflammation, and trauma.[41]

The diagnosis of hypoadrenocorticism is based on histopathology,[9,13,27,36,59,68,83,92,133,134,163,171,176,184,194,222,246] either high serum potassium concentration or low serum sodium concentration or both,[10,11,14,26,27,42,43,59,70,75,86,87,104,105,119,134,135,142,152,153,193,222,244,246] and a low plasma cortisol response to ACTH stimulation.[12,20,28,42,45,46,95,104,105,127,152,155,171,183,184,244,246] Definitive diagnosis is demonstrated by a lack of adequate plasma cortisol or aldosterone response to ACTH stimulation.[95,104,105] Treatment consists of administration of glucocorticoids and mineralocorticoids as required to reestablish physiologic homeostasis.

This chapter reviews 244 naturally occurring (non-iatrogenic) cases of canine hypoadrenocorticism reported in English language journals between 1953 and 1994.

Methods

Forty-six reports (Table 2.1) in the English language of naturally occurring canine hypoadrenocorticism were reviewed for ages, sexes, breeds, diagnostic methods, serum potassium and sodium concentrations, and clinical findings. One report was excluded from the review because the cases reported were biased by selection of only hypercalcemic cases from a larger pool of cases.[147] Thirty-five of 48 cases were excluded from another report because they were reportedly of

Table 2.1. Number of Cases Reported, Average Ages, Sexes, Breeds, Diagnostic Methods, and Mean Serum Sodium (Na+) and Potassium (K+) Concentrations of 244 Reported Cases of Naturally Occurring Canine Hypoadrenocorticism

ACTH stim = ACTH stimulation test	MC = male-castrated
EKG = electrocardiogram	Na+/K+ = diagnosis by serum sodium or potassium concentration,
F = female-intact	or the ratio of sodium to potassium
FS = female-spayed	NR = not reported
M = male-intact	Path = gross and/or microscopic pathology

Year of report	Author of report*	No. of cases reported	Average ages (yr)	Sexes (number)	Breeds (number)	Diagnostic methods (number)	Mean Na+ (meq/L)	Mean K+ (meq/L)
1953	Hadlow[68]	3	3.2	FS(2),M(1)	NR (3)	Path (3)	NR	NR
1960	Annis[9]	2	4	F(1)	Welsh Corgi (1)	Eosinophilia(1);Na+/K+(1); urinary steroids(1)	120	8.5
1960	Marshak et al.[119]	1	3.1	FS(2)	Cocker Spaniel (1); Mixed (1)	Path (2)	NR	NR
1961	Ditchfield et al.[36]	1	4	FS(1)	German Shepherd (1)	Path (1)	NR	NR
1962	Howell et al.[83]	1	6	M(1)	Cocker Spaniel (1)	Path (1)	NR	NR
1965	Kelly[92]	1	6	F(1)	Boxer (1)	Path (1)	NR	NR
1966	Rothenbacher et al.[169]	1	12	M(1)	Mixed (1)	Path(1)	NR	NR
1967	Siegel et al.[194]	1	3	F(1)	Beagle (1)	Path(1)	NR	NR
1968	Nimmons et al.[142]	1	3	M(1)	West Highland White Terrier(1)	Na+/K+(1); urinary chloride(1)	136	7.0
1968	Siegel[193]	1	5.5	M(1)	Mixed (1)	Na+/K+(1); path(1); urinary steroids (1)	NR	NR
1968	Theran[222]	1	2	M(1)	Saint Bernard (1)	EKG (1); NA+/K+ (1); path (1)	130.5	8.2
1970	Morales et al.[133]	2	2.5	F(1),FS(1)	German Shepherd (1); Gordon Setter (1)	Path (2)	NR	NR
1971	Bonneau et al.[16]	1	2	F(1)	Poodle (1)	Na+/K+ (1)	126	7.2
1971	Mulnix[134]	8	4.6	F(2),FS(5), MC(1)	Beagle (1); Irish Terrier (1); Manchester Terrier (1); Mixed (1); Springer Spaniel (2); Poodle (1); West Highland White Terrier (1)	EKG (3); Na+/K+ (8); path (3)	132.6	7.1
1972	Keeton et al.[77]	5	3.2	F(3),FS(1),M(1)	German Shepherd (1); Labrador Retriever (1); Mixed (1); Poodle (1); Saint Bernard (1)	EKG (2); hemogram (3); Na+/K+ (5)	119.3	6.7
1972	de Lahunta[27]	1	3	F(1)	Mixed (1)	EKG (1); Na+/K+ (1); path (1)	139	8.0

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Table 2.1 (continued)

Year of report	Author of report[*]	No. of cases reported	Average ages (yr)	Sexes (number)	Breeds (number)	Diagnostic methods (number)	Mean Na+ (meq/L)	Mean K+ (meq/L)
1973	Fox et al.[59]	2	4.3	FS(2)	Brittany (1); Dalmatian (1)	Eosinophilia (2); Na+/K+ (1); path (1); urinary steroids (1)	130.5	7.1
1974	Sanger et al.[176]	1	2.5	M(1)	German Shepherd (1)	Path (1)	NR	NR
1975	Musselman[136]	1	3	F(1)	Mixed (1)	EKG (1); urinary steroids (1); water-loading test (1)	NR	NR
1975	O'Rourke[143]	2	4.5	FS(2)	Mixed(2)	Na+/K+ (2)	127	7.5
1976	Harlton[70]	1	4	M(1)	Poodle (1)	Na+/K+ (1)	114	6.0
1977	Feldman et al.[45]	11	4.3	F(3),FS(4),M(4)	German Shepherd (1); Golden Retriever (2); Great Dane (2); Mixed (1); Poodle (3); Samoyed (1); Schnauzer (1)	ACTH stim (11)	133.1†	6.8†
1977	Feldman et al.[42]	1	4	FS(1)	Australian Terrier (1)	ACTH stim (1); EKG (1); Na+/K+ (1); plasma ACTH (1)	119	8.6
1978	Bath et al.[13]	3	4.4	F(1),FS(2)	Mixed (2); Welsh Corgi (1)	Hypoglycemia (1); Na+/K+ (3); path (1); uremia (1)	121.3	7.2
1978	Feldman et al.[46]	8	4.1	F(1),FS(4),M(3)	German Shepherd (1); Golden Retriever (1); Great Dane (1); Irish Setter (1); Mixed (2); Poodle (1); Samoyed (1)	ACTH stim (8)	NR	NR
1978	Reimers et al.[153]	2	8.5	F(1),FS(1)	Cockapoo (1); Poodle (1)	EKG (2); NA+/K+ (2)	120	8.8
1979	Atwell et al.[10]	1	7	M(1)	Mixed (1)	EKG (1); eosinophilia (1); hemogram (1); NA+/K+ (1); uremia (1)	132	9.3
1979	Crenshaw[26]	1	6	FS(1)	Mixed (1)	Na+/K+ (1); uremia (1)	133	7.4
1979	Hill[75]	5	4.5	F(1),FS(3),M(1)	Kelpie (1); Mixed (3); Welsh Corgi (1)	Na+/K+ (5)	121.6	7.4
1980	DiBartola[28]	3	3.7	F(1),FS(1),M(1)	Mixed (1); Poodle (1); Weimaraner (1)	EKG (3); ACTH stim (1)	122	9.5
1980	Murrell[133]	1	5	F(1)	Mixed (1)	NA+/K+ (1)	124	6.4
1980	Willard[244]	1	6	FS(1)	Mixed (1)	ACTH stim (1); Na+/K+ (1)	126	5.0
1981	Rogers et al.[155]	3	6.7	FS(1),M(2)	Poodle (1); Pointer (1); Wheaten Terrier (1)	ACTH stim (3)	144.7	4.6

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Table 2.1 (continued)

Year of report	Author of report[*]	No. of cases reported	Average ages (yr)	Sexes (number)	Breeds (number)	Diagnostic methods (number)	Mean Na+ (meq/L)	Mean K+ (meq/L)
1982	Willard et al.[245]	37	4.2	F(6),FS(19), M(7),MC(5)	NR (37)	ACTH stim (16); Na+/K+ (17); path (4)	129	7.4
1983	Schaer et al.[193]	13	4.5	F(3),FS(3),M(7)	Boston Terrier (1); Cocker Spaniel (1); Dachshund (1); Doberman Pinscher (3); German Shorthaired Pointer (1); Irish Setter (1); Mixed (1); Poodle (2); Schnauzer (1); Whippet (1)	ACTH stim (13)	140.4	6.2
1984	Rakich et al.[152]	23	4.1	F(4),FS(12), M(4), MC(3)	Mixed (5); NR (18)	ACTH stim (18); Na+/K+ (17)	131	7.0
1985	Auge[11]	1	5	M(1)	Poodle (1)	EKG (1); Na+/K+ (1)	116	8.4
1985	Ruben et al.[171]	1	0.2	F(1)	Lhasa Apso (1)	ACTH stim (1); path (1)	NR	NR
1986	Schaer et al.[194]	3	3.9	FS(1),M(1),MC (1)	Dachshund (1); Shar Pei (1); Weimaraner (1)	ACTH stim (3); path (1)	114.5	6.6
1987	Burrows[30]	1	0.8	M(1)	Shar Pei (1)	ACTH stim (1)	123	6.4
1989	Joseph[95]	1	6	FS(1)	Collie (1)	Na+/K+ (1)	128	10.8
1991	Lynn et al.[104]‡	21	4.1	F(1),FS(11), M(2), MC(7)	Airedale Terrier (1); Cocker Spaniel (1); Dalmatian (1); German Shepherd (3); Golden Retriever (1); Kuvasz (1); Labrador Retriever (3); Maltese (1); Mixed (1); Poodle (3); Rat Terrier (1); Rottweiler (2); Scottish Terrier (1); Welsh Corgi (1)	ACTH stim (21); Na+/K+ (21)	131.2	7.3
1992	Bartges et al.[12]	1	5	FS(1)	Poodle (1)	ACTH stim (1); eosinophilia (1)	150	4.8

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Table 2.1 (continued)

Year of report	Author of report[*]	No. of cases reported	Average ages (yr)	Sexes (number)	Breeds (number)	Diagnostic methods (number)	Mean Na+ (meq/L)	Mean K+ (meq/L)
1993	Lynn et al.[105]‡	60	4.6	F(3),FS(34), M(8), MC(15)	Alaskan Malamute (1); Basset Hound (2); Brittany (1); Cairn Terrier (1); Collie (1); Dachshund (2); Doberman Pinscher (4); German Shepherd (4); German Shorthaired Pointer (3); Golden Retriever (1); Great Pyrennes (1); Labrador Retriever (9); Mastiff (1); Mixed (11); Poodle (6); Pointer (1); Portuguese Water Dog (2); Rottweiler (3); Samoyed (1); Welsh Corgi (1); West Highland White Terrier (3); Yorkshire Terrier (1)	ACTH stim (60); Na+/K+ (60); plasma ACTH (14)	128.3	7.2
1993	Medinger et al.[127]	3	4	F(1),FS(2)	Chesapeake Bay Retriever (1); Fox Terrier (1); Great Pyrennes (1)	ACTH stim (3)	123.3	6.4
1994	Levy[95]	1	6	F(1)	Poodle (1)	ACTH stim (1)	135	7.5

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Table 2.1 (continued)

Year of report	Author of report*	No. of cases reported	Average ages (yr)	Sexes (number)	Breeds (number)	Diagnostic methods (number)	Mean Na+ (meq/L)	Mean K+ (meq/L)
Total		244	4.3	F(41),FS(119), M(52),MC(32)	Airedale Terrier (1); Alaskan Malamute (1); Australian Terrier (1); Basset Hound (2); Beagle (2); Boston Terrier (1); Boxer (1); Brittany (2); Cairn Terrier (1); Chesapeake Bay Retriever (1); Cockapoo (1); Cocker Spaniel (4); Collie (2); Dachshund (4); Dalmatian (2); Doberman Pinscher (7); Fox Terrier (1); German Shepherd (13); German Shorthaired Pointer (4); Golden Retriever (5); Gordon Setter (1); Great Dane (3); Great Pyrennes (2); Irish Setter (2); Irish Terrier (1); Kelpie (1); Kuvasz (1); Labrador Retriever (13); Lhasa Apso (1); Maltese (1); Manchester Terrier (1); Mastiff (1); Mixed (40); NR (58); Pointer (2); Poodle (25); Portuguese Water Dog (2); Rat Terrier (1); Rottweiler (5); Saint Bernard (2); Samoyed (3); Schnauzer(2); Scottish Terrier (1); Shar Pei (2); Springer Spaniel (2); Weimaraner (2); Welsh Corgi (5); West Highland White Terrier (5); Wheaten Terrier (1); Whippet (1); Yorkshire Terrier (1)	ACTH stim (163); EKG (16); eosinophilia (5); hemogram (4); hypoglycemia (1); Na+/K+ (155); path (27); plasma ACTH (15); plasma corticoids (2); uremia (3); urinary chloride (1); urinary steroids (5); water-loading test (1)	129.4f	7.2f

* Superscript indicates reference number.
† Mean of 10 cases.
‡ Some breed information obtained by direct communication with the authors.
f Mean of 220 cases; normal sodium 136.0-150.0 meq/L;[41,43] normal potassium 3.5-5.0 meq/L.[41,43]

iatrogenic origin, seven due to treatment with o,p'-DDD and 28 due to treatment with glucocorticoids.[183] Similarly, three iatrogenic cases were excluded from another report.[45] One report was excluded because the cases all came from the same family of Standard Poodles.[192] Another was excluded because the endocrine characteristics of the reported case were confounded with those of canine distemper.[24]

Sex of the dog was classified as female, female-spayed, male, or male-castrated. If an individual dog was reported as being "male," it was considered to be uncastrated. Similarly, "female" was considered to be unspayed. Two reports, Willard et al. (1982) and Rakich et al. (1984), reported 37 and 23 dogs, respectively, as all being either male or female. Since any group of 37 or 23 clinically ill dogs is likely to have at least a few castrated or spayed individuals, it was assumed that these authors did not distinguish in their report between altered and intact patients. Therefore, these studies were not included in calculations regarding sex.

One report was not included in the clinical findings data since it reported no clinical findings.[46] Another report did not separate clinical findings between naturally-occurring and iatrogenic cases, so the assumption was made that the number of cases with a particular clinical finding was distributed proportionally between naturally-occurring and iatrogenic cases.[45]

Since the reports generally did not distinguish among Toy, Miniature, and Standard Poodles, all Poodles have been reported as one breed. Similarly, since

the reports did not distinguish among Miniature, Standard, and Giant Schnauzers, all Schnauzers have been reported as one breed. Clinical signs and response to therapy were not included as methods of diagnosis because they were presumed to always be consistent with the diagnosis.

Results, Discussion, and Conclusions

Cases

The year the report was published, author, number of cases reported, average ages, sexes, breeds, diagnostic methods, mean serum sodium concentration, and mean serum potassium concentrations are included in Table 2.1. Two hundred forty-four cases from 46 reports were reviewed. Thirty-eight (82.6%) of the 46 reports described five or fewer cases each, for a total of 63 (25.8%) of the 244 total cases.[9-14,20,26-28,36,42,43,59,68,70,75,83,86,87,92,95,119,127,133,135,136,142,153,155,163,171,176,184,193,194,222,244] Eight of the reports accounted for the remaining 181 (74.2%) cases.[45,46,104,105,134,152,183,246] One hundred sixty-nine (69.3%) cases were reported after 1980.

Ages

The average age was 4.3 yr for all dogs. The range of average ages for the 46 studies was 0.2 yr to 12.0 yr, with a mean of 4.3 yr. This suggested that canine hypoadrenocorticism can occur in dogs of any age, with an average age between 4 and 5 yr.

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Sexes

Sex was reported for 184 (75.4%) of the cases with 41 (22.3%) male-intact, 24 (13.0%) male-castrated, 31 (16.8%) female-intact, and 88 (47.8%) female-spayed (Table 2.2). However, without data about the sex distribution in the entire dog population, the assertion that canine hypoadrenocorticism is typically a disease of the female dog[41,43,189] remains to be proved. One report, which did include controls representing the entire dog population, concluded that females were more likely to develop this disease.[148]

Breeds

Breed was reported for 186 (76.2%) of the cases, and 50 breeds were represented (Table 2.3). The most frequently reported purebreds (%) were Poodle (13.4), German Shepherd (7.0), Labrador Retriever (7.0), Doberman Pinscher (3.8), Golden Retriever (2.7), Rottweiler (2.7), Welsh Corgi (2.7), and West Highland White Terrier (2.7). The breed data established that canine hypoadrenocorticism can occur in many different breeds. As with sex, however, without data about the proportion of each of these breeds in the entire dog population, any conclusions about breed predispositions need to be proved.

Table 2.2. Sexes of 184 Reported Cases of Naturally Occurring Canine Hypoadrenocorticism*

Sex	Number	Percent
Female-intact	31	16.8
Female-spayed	88	47.8
All females	119	64.7
Male-intact	41	22.3
Male-castrated	24	13.0
All males	65	35.3
All dogs	184	100.0

*Two reports[152,246] were excluded because they apparently did not distinguish neutered from intact dogs.

Table 2.3. Breeds of 186 Reported Cases of Naturally Occurring Canine Hypoadrenocorticism*

Breed	Number	Percent
Airedale Terrier	1	0.5
Alaskan Malamute	1	0.5
Australian Terrier	1	0.5
Basset Hound	2	1.1
Beagle	2	1.1
Boston Terrier	1	0.5
Boxer	1	0.5
Brittany	2	1.1
Cairn Terrier	1	0.5
Chesapeake Bay Retriever	1	0.5
Cockapoo	1	0.5
Cocker Spaniel	4	2.2
Collie	2	1.1
Dachshund	4	2.2
Dalmatian	2	1.1
Doberman Pinscher	7	3.8
Fox Terrier	1	0.5
German Shepherd	13	7.0
German Shorthaired Pointer	4	2.2
Golden Retriever	5	2.7
Gordon Setter	1	0.5
Great Dane	3	1.6
Great Pyrennes	2	1.1
Irish Setter	2	1.1
Irish Terrier	1	0.5
Kelpie	1	0.5
Kuvasz	1	0.5
Labrador Retriever	13	7.0
Lhasa Apso	1	0.5
Maltese	1	0.5
Manchester Terrier	1	0.5
Mastiff	1	0.5
Mixed	40	21.5
Pointer	2	1.1
Poodle	25	13.4
Portuguese Water Dog	2	1.1
Rat Terrier	1	0.5
Rottweiler	5	2.7

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Table 2.3 (continued)

Breed	Number	Percent
Saint Bernard	2	1.1
Samoyed	3	1.6
Schnauzer	2	1.1
Scottish Terrier	1	0.5
Shar Pei	2	1.1
Springer Spaniel	2	1.1
Weimaraner	2	1.1
Welsh Corgi	5	2.7
West Highland White Terrier	5	2.7
Wheaten Terrier	1	0.5
Whippet	1	0.5
Yorkshire Terrier	1	0.5

*Breed was not reported for 58 of the 244 cases.

Diagnostic Methods

Thirteen different diagnostic methods (in addition to clinical signs and response to therapy) were used to diagnose canine hypoadrenocorticism (Table 2.4). The antemortem diagnostic acumen of veterinary practitioners who reported their results to professional publications, as well as the availability and accessibility of laboratory tests, has apparently improved with time. Diagnosis of the earliest reported cases was based largely on necropsy findings. With few exceptions,[11,86,152,246] all cases reported after 1980 were diagnosed using the ACTH stimulation test, the definitive test.[95,104,105]

Serum Sodium and Potassium Concentrations

The mean sodium concentration was 129.4 meq/L with range from 114.0-150.0 meq/L, and the mean potassium concentration was 7.2 meq/L with range from 4.6-10.8 meq/L. The mean sodium to potassium ratio (obtained by dividing 129.4 by 7.2) was 18.0, well below the published diagnostic criterion of 27.0 or less suggested by two references,[43,189] and also below the diagnostic criterion of 25.0 or less suggested by another.[129] So sodium to potassium ratio seemed a useful, though not definitive, diagnostic criterion. Other conditions such as chylothorax[245] and gastrointestinal disease[29] can produce hyponatremia and hyperkalemia.

Table 2.4. Methods Used to Diagnose 244 Reported Cases of Naturally Occurring Canine Hypoadrenocorticism*

Method	Number	Percent
ACTH stimulation test	163	66.8
Electrocardiogram	16	6.6
Eosinophilia	5	2.0
Hemogram	4	1.6
Hypoglycemia	1	0.4
Na+/K+**	155	63.5
Path***	27	11.1
Plasma ACTH	15	6.1
Plasma corticoids	2	0.8
Uremia	3	1.2
Urinary chloride	1	0.4
Urinary steroids	5	2.0
Water loading test	1	0.4

*Excluding "clinical signs" and "response to therapy."

**Na+/K+ = Diagnosis by serum sodium or potassium concentration, or the ratio of sodium to potassium.

***Path = Gross and/or microscopic pathology.

Clinical Findings

Clinical findings frequently reported are tabulated in Table 2.5. The seven most frequently reported (%) were anorexia (73.7), vomiting (64.0), depression (61.0), weakness (54.2), weight loss (36.9), azotemia (25.8), and diarrhea (25.0). Other less frequently observed clinical findings included changes in skin and hair, microcardia, muscle atrophy, limb stiffness, panting, and hematuria. Table 2.5 should be useful to the veterinary clinician since it provides a picture of what clinical findings to expect from a hypoadrenal dog.

Treatment

Treatment may be on an emergency basis to deal with a hypoadrenal crisis, and maintenance to correct mineralocorticoid and glucocorticoid deficits on a long-term basis. The following is a composite treatment plan gleaned from the review of the canine hypoadrenocorticism literature.

Emergency treatment must be tailored to each individually evaluated patient. It generally consists of isotonic intravenous saline solution to correct hyponatremia, hyperkalemia, and hypovolemia, and the immediate initiation of glucocorticoid and mineralocorticoid therapy.[86] Intravenous sodium bicarbonate may be used to correct metabolic acidosis and to lower serum potassium levels.[28] A simple lead II electrocardiogram can be used to monitor the patient's response to treatment for hyperkalemia.[28,86] As hyperkalemia is reduced, peaked T waves become less

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Table 2.5. Clinical Findings for 236 Reported Cases of Naturally Occurring Canine Hypoadrenocorticism*

Clinical finding	Number	Percent
Anorexia	174	73.7
Vomiting	151	64.0
Depression	144	61.0
Weakness	128	54.2
Weight loss	87	36.9
Azotemia	61	25.8
Diarrhea	59	25.0
Dehydration	51	21.6
Polyuria or polydipsia	34	14.4
Shock or collapse	34	14.4
Bradycardia or arrhythmia	31	13.1
Shaking or trembling	25	10.6
Ataxia or seizures	13	5.5
Gastroenteritis or abdominal pain	12	5.1

*Includes only 236 of 244 reported cases because one report[46] of eight cases did not report any clinical findings.

apparent, the amplitude of P and R waves will increase, the PR and QT intervals will decrease, and bradycardia, if present, will subside.[28] Intravenous 2.5 or 5.0% dextrose solution can carefully be used in the hypoglycemic patient, recognizing that the use of hypertonic solutions may cause or exacerbate dehydration.[86,95]

Maintenance therapy requires that the glucocorticoid and mineralocorticoid deficits be corrected. Mineralocorticoid activity may be obtained by administering fludrocortisone acetate orally daily or microcrystalline desoxycorticosterone pivalate (DOCP) intramuscularly about once a month.[28,95] The oral and parenteral routes each have obvious advantages and disadvantages to the clinician and client. Either drug may require additional glucocorticoid supplementation, such as prednisone, though fludrocortisone acetate has greater glucocorticoid activity.[95] Some dogs do not respond adequately to fludrocortisone acetate and should be treated with DOCP,[95] which has near universal efficacy.[104,105] Maintenance therapy should be tailored to the individual patient's response, both general health and serum sodium and potassium concentrations, and to the convenience of the clinician and client.

CHAPTER 3

DESCRIPTION OF CASES OF CANINE HYPOADRENOCORTICISM ENROLLED IN THE CLINICAL TRIAL OF MICROCRYSTALLINE DESOXYCORTICOSTERONE PIVALATE

Introduction

This chapter has two purposes. First, it will review cases of canine hypoadrenocorticism which were enrolled in a clinical trial of microcrystalline desoxycorticosterone pivalate (DOCP), a mineralocorticoid drug used to treat the disease. This review will provide descriptive data about ages at diagnosis, breeds, sexes, body weights, serum sodium and potassium concentrations, and clinical findings for the hypoadrenal dogs in the clinical trial. Second, this chapter will compare two different case definitions, one which required a definitive adrenocorticotropic hormone (ACTH) stimulation test to confirm the diagnosis of hypoadrenocorticism, and a second unconfirmed diagnosis which required only that the veterinarian diagnosed the disease regardless of the diagnostic method. This chapter will examine the question whether for epidemiologic studies of canine hypoadrenocorticism it was necessary to use the definitive, confirmed, ACTH

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stimulation test[m] as a case definition, or whether the less exacting, unconfirmed case definition using only the veterinarian's judgment was satisfactory. If the results were different or equivocal, depending on the definition, then clearly the confirmed ACTH stimulation test definition must be used, despite its expense, inconvenience, and fewer case numbers. If, on the other hand, the results were the same, or nearly so, regardless of case definition, then the unconfirmed definition using only the veterinarian's judgment could be used, thereby gaining in cost-effectiveness, convenience, and the number of cases available for study.

Methods

Data on 506 cases of naturally occurring canine hypoadrenocorticism were compiled between April 18, 1989, and December 31, 1991, in a clinical trial conducted by Ciba Animal Health to test the efficacy of DOCP. Three hundred ninety-four investigating veterinarians from 367 veterinary hospitals and clinics in the United States and Canada participated in the clinical trial. Veterinarians were enrolled if they requested DOCP to treat a patient from Ciba Animal Health, and were willing to participate in the clinical trial. The veterinarian's diagnosis of hypoadrenocorticism, regardless of the basis for the diagnosis, was satisfactory for entry in the clinical trial. Most of the diagnoses were made using either the ACTH

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[m]Demonstrating a lack of cortisol response to ACTH stimulation.

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stimulation test or diagnostic serum sodium and potassium concentrations. The drug could not be obtained without enrollment in the clinical trial. Patient information obtained during the trial included age at diagnosis, sex, breed, diagnostic method, serum sodium and potassium concentrations, ACTH stimulation test results, and clinical findings.

A subset of 262 (51.7%) of these 506 cases had confirmed diagnoses using the ACTH stimulation test. These cases came from 239 investigating veterinarians from 200 veterinary hospitals and clinics in 39 different states in the United States. A subset of 244 (48.2%) of these 506 cases were unconfirmed by the ACTH stimulation test, and the diagnosis was therefore based on the veterinarian's judgment. These cases came from 203 investigating veterinarians from 198 veterinary hospitals and clinics in 42 different states in the United States and one province of Canada. All the data came from the clinical records of practicing veterinarians, and were therefore dependent on the accuracy of these records.

Since veterinarians often did not distinguish among different Poodle (Toy, Miniature, or Standard) or Schnauzer (Miniature, Standard, or Giant) breeds, Poodles and Schnauzers are each reported as one breed.

Results

General

The following results (and the discussion that follows), except as noted, were for the 262 cases which had confirmed diagnoses using the ACTH stimulation test.

Ages at Diagnosis

The average age at diagnosis (Figure 3.1) was 4.9 yr (SD 3.0) (SEM[a] 0.2) (Range 0.3 – 13.0).

Breeds

The breeds of the 262 dogs (Table 3.1) demonstrated that canine hypoadrenocorticism can occur in many breeds. The seven most frequently represented breeds (%) were Mixed (12.2), Poodle (11.8), German Shepherd (8.4), Labrador Retriever (8.0), West Highland White Terrier (6.5), Golden Retriever (3.8), and Great Dane (3.8).

Sexes

The sexes (%) (Table 3.2) of the 262 dogs were 16 (6.1) female-intact, 162 (61.8) female-spayed, 34 (13.0) male-intact, and 50 (19.1) male-castrated.

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[a]Standard error of the mean (SEM) equals the standard deviation (SD) divided by the square root of the sample size.

Age (yr) at Diagnosis of Dogs
Mean (All Dogs) 4.9 yr (SD 3.0) (SEM 0.2) (Range 0.3-13.0)
***Age at diagnosis was unavailable for 30 of the 262 cases.**
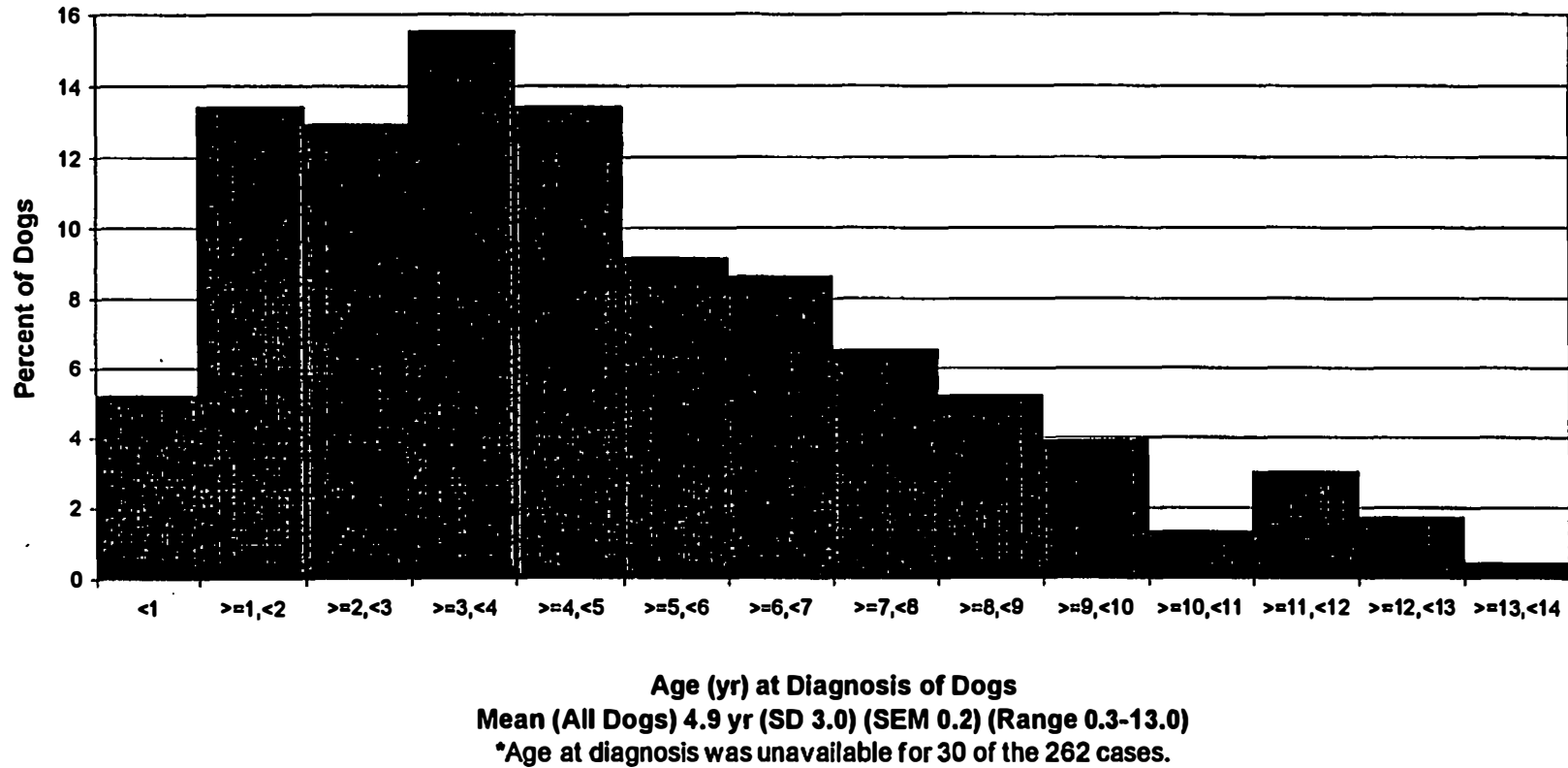
Figure 3.1. Ages at Diagnosis of 232* Dogs with Canine Hypoadrenocorticism Enrolled in Clinical Trial

Table 3.1. Breeds of 262 Dogs with Canine Hypoadrenocorticism Enrolled in Clinical Trial by Breed Group

Breed	Number	Percent
Poodles (Toy, Miniature, and Standard)	31	11.8
Schnauzers (Miniature, Standard, and Giant)	3	1.1
Toy breeds		
Chihuahua	2	0.8
Shih Tzu	3	1.1
Bichon Frise	2	0.8
Maltese	1	0.4
Pomeranian	1	0.4
All toy breeds	9	3.4
Sporting breeds		
Labrador Retriever	21	8.0
Golden Retriever	10	3.8
Springer Spaniel	6	2.3
Cocker Spaniel	8	3.1
German Shorthaired Pointer	5	1.9
Chesapeake Bay Retriever	1	0.4
Irish Setter	1	0.4
English Setter	1	0.4
Nova Scotian Duck Tolling Retriever	1	0.4
Pointer	1	0.4
Portuguese Water Dog	1	0.4
Vizsla	1	0.4
All sporting breeds	57	21.8
Hound breeds		
Dachshund	8	3.1
Beagle	4	1.5
Basset Hound	6	2.3
Afghan Hound	1	0.4
Norwegian Elkhound	1	0.4
Rhodesian Ridgeback	1	0.4
Saluki	1	0.4
All hound breeds	22	8.4
Non-sporting breeds		
Chow Chow	2	0.8
Shar Pei	3	1.1
Keeshond	1	0.4
Lhasa Apso	1	0.4

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Table 3.1 (continued)

All non-sporting breeds	7	2.7
Herding breeds		
German Shepherd	22	8.4
Collie	3	1.1
Australian Shepherd	2	0.8
Welsh Corgi	1	0.4
Bouvier des Flanders	1	0.4
Old English Sheepdog	1	0.4
All herding breeds	30	11.5
Working breeds		
Great Dane	10	3.8
Doberman Pinscher	7	2.7
Rottweiler	6	2.3
Siberian Husky	4	1.5
Alaskan Malamute	3	1.1
Akita	4	1.5
Saint Bernard	2	0.8
All working breeds	36	13.7
Terrier breeds		
West Highland White Terrier	17	6.5
Airedale Terrier	4	1.5
Scottish Terrier	2	0.8
Bull Terrier	1	0.4
Fox Terrier	1	0.4
Pit Bull Terrier	1	0.4
Wheaten Terrier	1	0.4
All terrier breeds	27	10.3
Miscellaneous breeds		
Bearded Collie	5	1.9
Border Collie	3	1.1
All miscellaneous breeds	8	3.1
Mixed	32	12.2
Total dogs	262	100.0

Table 3.2. Sexes of 262 Cases of Canine Hypoadrenocorticism Enrolled in Clinical Trial

Sex	Number	Percent
Female-intact	16	6.1
Female-spayed	162	61.8
All females	178	67.9
Male-intact	34	13.0
Male-castrated	50	19.1
All males	84	32.1
All dogs	262	100.0

Body Weights

Body weights (Figure 3.2) averaged 23.4 kg (SD 13.6) (SEM 0.8) (Range 2.7 - 72.7).

Serum Sodium and Potassium Concentrations

Two hundred forty-nine (95.0%) of the 262 cases had their serum sodium and potassium concentrations determined. Table 3.3 presents these results with the sodium to potassium ratio. The mean sodium concentration was 131.8 meq/L (SD 9.4) (SEM 0.6) (Range 104.0 - 174.0) (Normal 136.0 - 150.0[41,43]), the mean potassium concentration was 6.8 meq/L (SD 1.3) (SEM 0.1) (Range 3.2 - 12.8) (Normal 3.5 - 5.0[41,43]), and the mean sodium to potassium ratio was 20.2 (SD 4.8) (SEM 0.3) (Range 10.5 - 38.8) (Normal ≥ 27.0[41,43,189] or ≥ 25.0[129]).

Clinical Findings

Clinical findings were tabulated for the 262 cases and are displayed in Table 3.4. The seven most frequently reported, in order of decreasing frequency, were vomiting (28.2%), anorexia (19.5%), depression (18.3%), weakness (14.1%), weight loss (11.1%), diarrhea (9.2%), and bradycardia or arrhythmia (6.5%).

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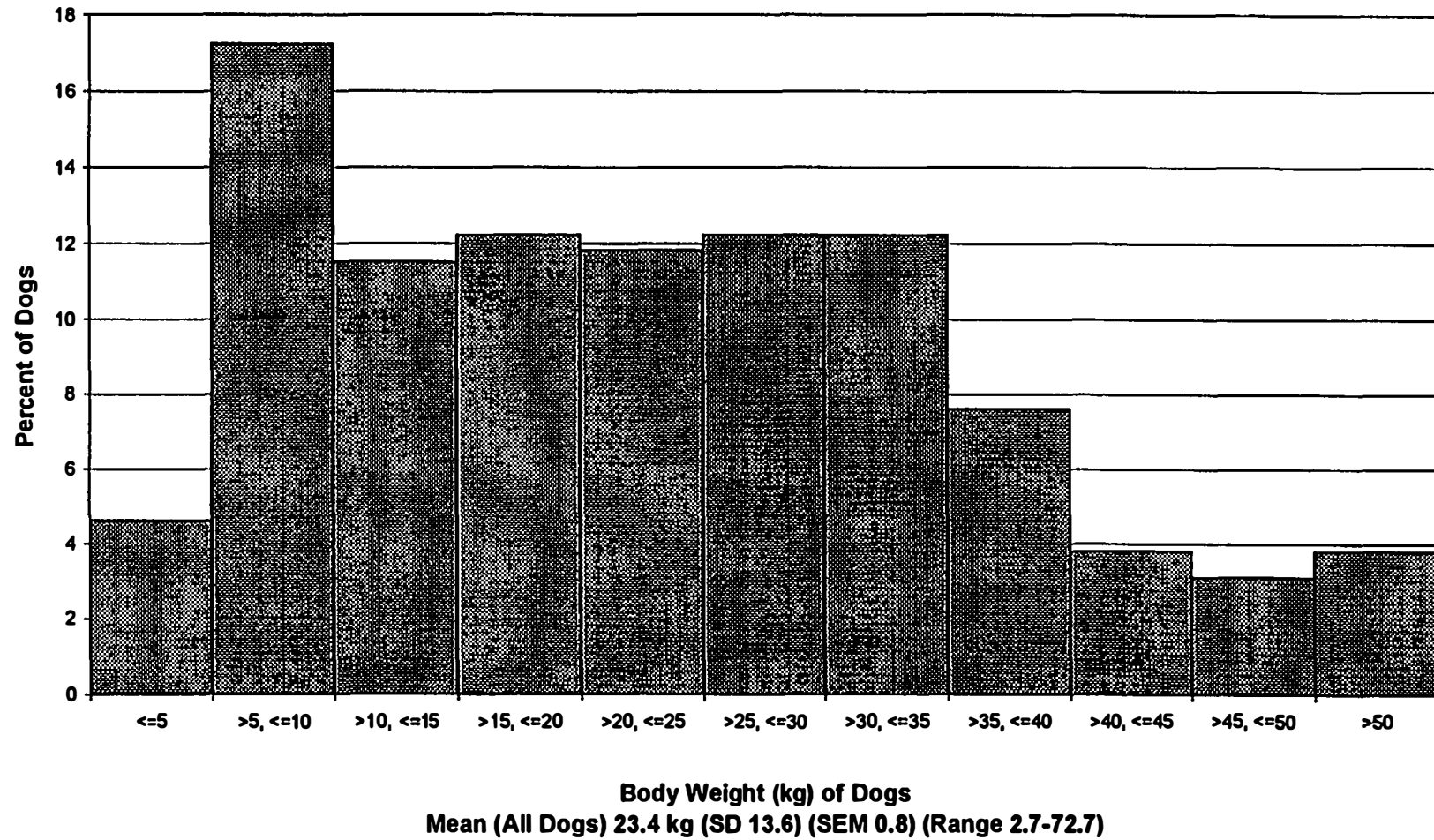
Figure 3.2. Body Weights of 262 Dogs with Canine Hypoadrenocorticism Enrolled in Clinical Trial

Table 3.3. Serum Sodium and Potassium Concentrations and Sodium/Potassium Ratios for 249* Dogs wit Canine Hypoadrenocorticism Enrolled in Clinical Trial

Sodium (meq/L)	Number	Percent	Potassium (meq/L)	Number	Percent	Sodium potassium ratio**	Number	Percent
> 100, ≤ 110	6	2.4	> 3, ≤ 4	5	2.0	10.1 - 15.0	21	8.4
> 110, ≤ 120	18	7.2	> 4, ≤ 5	15	6.0	15.1 - 20.0	123	49.4
> 120, ≤ 130	79	31.7	> 5, ≤ 6	47	18.9	20.1 - 25.0	76	30.5
> 130, ≤ 140	106	42.6	> 6, ≤ 7	85	34.1	25.1 - 30.0	15	6.0
> 140, ≤ 150	36	14.5	> 7, ≤ 8	56	22.5	30.1 - 35.0	10	4.0
< 150	4	1.6	> 8, ≤ 9	29	11.6	35.1 - 40.0	4	1.6
			> 9, ≤ 10	11	4.4			
			> 10	1	0.4			

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Mean 131.8
SD 9.4
SEM 0.6
Range 104.0 - 174.0
Normal 136.0 - 150.0[41,43]
    Number below normal 171 (68.7%)
    Number normal 74 (29.7%)
    Number above normal 4 (1.6%)

Mean 6.8
SD 1.3
SEM 0.1
Range 3.2 - 12.8
Normal 3.5 - 5.0[41,43]
    Number below normal 1 (0.4%)
    Number normal 19 (7.6%)
    Number above normal 229 (92.0%)

Mean 20.2
SD 4.8
SEM 0.3
Range 10.5 - 38.8
Normal ≥ 27.0[41,43,189] or ≥ 25.0[129]
    Number below normal 228 (91.6%)***; 219 (88.0%)****
    Number normal 21 (8.4%)***; 30 (12.0%)****

*Serum sodium and potassium concentrations were not reported for 13 of the 262 cases.

**Twenty-one (8.4%) of t e sodium/potassium ratios exceeded 27.0. A ratio below 27.0 is sometimes considered diagnostic of canine hypoadrenocorticism.[41,43,189] Twenty-nine (11.6%) of t e ratios exceeded 25.0, t e diagnostic criterion suggested by a commonly used reference.[129]

***A sodium to potassium ratio ≥ 27.0 was considered normal.[41,43,189]

****A sodium to potassium ratio ≥ 25.0 was considered normal.[129]

Table 3.4. Clinical Findings* for 262 Cases of Canine Hypoadrenocorticism Enrolled in Clinical Trial

Clinical finding	Number	Percent
Vomiting	74	28.2
Anorexia	51	19.5
Depression	48	18.3
Weakness	37	14.1
Weight loss	29	11.1
Diarrhea	24	9.2
Bradycardia or arrhythmia	17	6.5
Shock or collapse	15	5.7
Shaking or trembling	11	4.2
Azotemia	10	3.8
Gastroenteritis or abdominal pain	10	3.8
Polyuria or polydipsia	9	3.4
Dehydration	8	3.1

*Includes those clinical findings reported for five or more cases.

Efficacy of Microcrystalline Desoxycorticosterone Pivalate

When simply asked whether or not DOCP was effective, veterinarians responded yes for 260 (99.2%) of the 262 cases.

Discussion

Ages at Diagnosis

The average age at diagnosis was 4.9 yr (SD 3.0) (SEM 0.2) (Range 0.3 - 13.0) (Figure 3.1). These results suggested that the average age at diagnosis for canine hypoadrenocorticism was about five years, but, notably, could vary from very young to very old dogs. This was consistent with the estimate provided in a well-known veterinary reference.[43]

Breeds

The seven most frequently reported breeds afflicted with canine hypoadrenocorticism were, in order of frequency from most to least frequent: Mixed, Poodle, German Shepherd, Labrador Retriever, West Highland White Terrier, Golden Retriever, and Great Dane (Table 3.1). These results demonstrated that canine hypoadrenocorticism can occur in many different breeds. Without data about breed distribution in the entire dog population, whether or not these breeds are predisposed to adrenal insufficiency cannot be determined.

Sexes

The sexes of dogs (percent) were female-intact (6.1), female-spayed (61.8), male-intact (13.0), and male-castrated (19.1) (Table 3.2). Thus females, both intact and spayed, made up about 70% of the hypoadrenal patients. This was consistent with two veterinary references which found that 70%[43] and 76%[41] were female. However, without data about sex distribution in the entire dog population, the assertion that canine hypoadrenocorticism is typically a disease of the female dog[41,43] remains to be proved. One report, which did consider the sex distribution in the entire dog population, concluded that females were more likely to develop this disease.[148] (This will be discussed at some length in succeeding chapters.)

Body Weights

Body weights averaged 23.4 kg (SD 13.6) (SEM 0.8) (Range 2.7 - 72.7). (Figure 3.2). This established pretty convincingly that canine hypoadrenocorticism occurs in all sizes of dogs, and confirmed the previously reported assertion that the disease can affect dogs of any size.[41,43]

Serum Sodium and Potassium Concentrations

The sodium, potassium, and sodium to potassium ratio were, respectively, 131.8 (SD 9.4) (SEM 0.6) (Range 104.0-174.0), 6.8 (SD 1.3) (SEM 0.1) (Range 3.2 - 12.8), and 20.2 (SD 4.8) (SEM 0.3) (Range 10.5 - 38.8) (Table 3.3). The normal values for sodium, potassium, and sodium to potassium ratio are,

respectively, 136.0 - 150.0,[41,43] 3.5 - 5.0,[41,43] and ≥27.0[41,43,189] or ≥25.0.[129] So, the means of these diagnostic indicators were consistent with the hyponatremia and hyperkalemia expected in the hypoadrenal patient.[41,43,129] However, it is important to note that 74 (29.7%) of the patients had normal sodium concentrations, 19 (7.6%) had normal potassium concentrations, and 29 (11.6%) (using diagnostic criterion ≥25.0) or 21 (8.4%) (using diagnostic criterion ≥27.0) had normal sodium to potassium ratios. These results suggested that normal sodium and potassium values in a clinical patient *do not* eliminate the possibility that the dog suffers from an adrenal insufficiency. They also raised the interesting question as to how many dogs had normal electrolyte values for all three diagnostic indicators- -sodium concentration, potassium concentration, and sodium to potassium ratio. The answer was 13 (5.2%) of 249[o] were normal for all three diagnostic indicators,[p] suggesting that a veterinarian pondering a list of differential diagnoses can usually eliminate hypoadrenocorticism based on normal sodium and potassium results. It is important to recognize that the truth of the converse is unknown based on these data; i.e., abnormal sodium and potassium results which are consistent with hypoadrenocorticism do not necessarily make the diagnosis.

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[o]Of the 262 cases with valid ACTH stimulation test results, 249 also had sodium and potassium concentrations determined; therefore, 13/249 = 0.052 = 5.2% is the meaningful datum.

[p]Using either the ≥25.0 or the ≥27.0 diagnostic criterion.

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Clinical Findings

The six most frequently reported clinical findings were vomiting, anorexia, depression, weakness, weight loss, and diarrhea (Table 3.4). Others included bradycardia or arrhythmia, shock or collapse, shaking or trembling, azotemia, gastroenteritis or abdominal pain, polyuria or polydipsia, and dehydration (Table 3.4). This provided a reasonably comprehensive list of the clinical findings associated with adrenal insufficiency in the dog when compared to other accounts of the disease.[44]

Efficacy of Microcrystalline Desoxycorticosterone Pivalate

Since the veterinarians concluded that DOCP was effective in 99.2% of these cases, it seemed clear that the drug was efficacious. This has been reported before, but in much smaller groups of dogs.[104,105]

Case Definition in Epidemiologic Studies of Canine Hypoadrenocorticism

To help answer the question if, for epidemiologic studies of canine hypoadrenocorticism, it matters whether the ACTH stimulation test (confirmed diagnosis) or the veterinarian's judgment (unconfirmed diagnosis) was used as a case definition, a side-by-side comparison of ages at diagnosis, breeds, sexes, body weights, serum sodium and potassium concentrations, and clinical findings is made in Table 3.5. An examination of Table 3.5 revealed that the results were virtually identical regardless of which definition was chosen. Age at diagnosis (yr) was 5.1

Table 3.5. Comparison of Results Using Two Different Case Definitions for Cases of Canine Hypoadrenocorticism Enrolled in Clinical Trial

Result	Unconfirmed diagnosis* (n=244)	Confirmed diagnosis** (n=262)
Average age at diagnosis (yr)	5.1*** (SD 2.9) (SEM 0.2) (Range 0.2 - 15.5)	4.9*** (SD 3.0) (SEM 0.2) (Range 0.3 - 13.0)
Seven most frequently reported breeds (%)	Poodle (22.5) Mixed (14.8) Labrador Retriever (10.2) Golden Retriever (6.6) West Highland White Terrier (6.1) German Shepherd (4.5) Springer Spaniel (4.1)	Mixed (12.2) Poodle (11.8) German Shepherd (8.4) Labrador Retriever (8.0) West Highland White Terrier (6.5) Golden Retriever (3.8) Great Dane (3.8)
Sexes (%)	Female-intact (7.8) Female-spayed (67.6) All females (75.4) Male-intact (8.6) Male-cast ated (16.0) All males (24.6)	Female-intact (6.1) Female-spayed (61.8) All females (67.9) Male-intact (13.0) Male-cast ated (19.1) All males (32.1)
Body weight (kg)	21.4 (SD 13.3) (SEM 0.9) (Range 2.7 - 75.0)	23.4 (SD 13.6) (SEM 0.8) (Range 2.7 - 72.7)
Serum concentrations ****	Sodium (meq/L) 129.2 (SD 9.9) (SEM 0.7) (Range 104.0 - 159.0) Potassium (meq/L) 7.0 (SD 1.3) (SEM 0.1) (Range 4.0 - 11.0) Sodium/potassium ratio 19.1 (SD 4.3) (SEM 0.3) (Range 11.6 - 38.8)	131.8 (SD 9.4) (SEM 0.6) (Range 104.0 - 174.0) 6.8 (SD 1.3) (SEM 0.1) (Range 3.2 - 12.8) 20.2 (SD 4.8) (SEM 0.3) (Range 10.5 - 38.8)
Seven most frequently reported clinical findings (%)	Vomiting (32.0) Weakness (24.2) Anorexia (22.5) Depression (18.9) Diarrhea (12.3) Bradycardia or ar hythmia (6.6) Shaking or trembling (6.1)	Vomiting (28.2) Ano exia (19.5) Depression (18.3) Weakness (14.1) Weight loss (11.1) Diar hea (9.2) Bradycardia or arrhythmia (6.5)

*A case was defined as a dog which the veterinarian, for whatever reason, said had hypoadrenocorticism.
**A case was defined as a dog which was diagnosed using the ACTH stimulation test.
***Not significantly different at p=0.05.
****Normal: sodium 136.0-150.0 meq/L;[41,43] potassium 3.5-5.0 meq/L;[41,43] sodium to potassium ratio ≥ 27.0[41,43,189] or ≥ 25.0.[129]

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using the unconfirmed diagnosis, and 4.9 using the confirmed one; standard deviations, standard errors of the mean, and ranges were almost indistinguishable. Six of the seven most frequently afflicted breeds were the same. The sex distributions were very similar, and the sexes ranked from most to least frequently reported were identical for the unconfirmed and confirmed diagnosis: female-spayed, male-castrated, male-intact, and female-intact. Average body weight (kg) differed by only two units, 23.4 using the confirmed diagnosis compared to 21.4 using the unconfirmed one; again, the standard deviations, standard errors of the mean, and ranges were virtually identical. Similarly, the results for serum sodium and potassium concentrations were, for all intents and purposes, the same. As with breeds, six of the seven most frequently reported clinical findings were the same, and the percentages of each clinical finding were quite consistent between the two definitions. Though the only way to definitively determine whether the veterinarians' diagnoses were accurate would be to test each dog individually with the ACTH stimulation test, these results suggested that, despite the probable presence of an inconsequential number of misdiagnoses when a less rigorous case definition is used, for epidemiologic studies of canine hypoadrenocorticism a rigorous case definition may be unnecessary. A less rigorous case definition would generally be more convenient and less costly. This recommendation cannot be generalized to other diseases.

Conclusions

The following conclusions were based on all the cases reported, both confirmed and unconfirmed.

1. <u>Ages at Diagnosis</u>. An estimated average age at diagnosis for hypoadrenal dogs was 5 yr, but the disease can occur in dogs of any age.

2. <u>Breeds</u>. Poodle, Mixed, Labrador Retriever, German Shepherd, West Highland White Terrier, and Golden Retriever breeds seemed to have a propensity for developing hypoadrenocorticism. However, without data about the proportion of each of these breeds in the entire dog population, any conclusions about breed predispositions remain to be proved. (This issue will be explored in subsequent chapters.)

3. <u>Sexes</u>. Females made up about 70% of hypoadrenal patients, and, of all females, about 90% of them were spayed. This was, again, consistent with the estimates that 70%[43] or 76%[41] of hypoadrenal patients are female, and with assertions that canine hypoadrenocorticism is typically a disease of the female dog.[41,43,93,148] Again, however, without data about the sex distribution in the entire dog population, these conclusions remain to be proved. (This issue will also be addressed in subsequent chapters.)

4. <u>Body Weights</u>. An estimated average body weight for dogs with canine hypoadrenocorticism was 23 kg, but the disease can occur in dogs of any size.

5. <u>Serum Sodium and Potassium Concentrations</u>. Estimated average serum sodium and potassium concentrations (meq/L) were 130 and 7, respectively. An estimated average serum sodium to potassium ratio was 20. Nevertheless, hypoadrenal patients had abnormally low, normal, and abnormally high values for all three of these diagnostic indicators. Therefore, no single electrolyte indicator should be used for diagnosis. However, only about 5% of hypoadrenal patients were normal for all three diagnostic criteria, so a dog normal for all three is unlikely to be hypoadrenal. Conversely, sodium and potassium results consistent with adrenal insufficiency do not necessarily make the diagnosis.

6. <u>Clinical Findings</u>. The most common clinical findings in hypoadrenal dogs were vomiting, anorexia, weakness, depression, diarrhea, weight loss, shaking or trembling, and bradycardia or arrhythmia.

7. <u>Efficacy of Microcrystalline Desoxycorticosterone Pivalate</u>. Based on reports from veterinarians, DOCP was very effective in the treatment of canine hypoadrenocorticism.

8. <u>Case Definition in Epidemiologic Studies of Canine Hypoadrenocorticism</u>. Epidemiologic studies of canine hypoadrenocorticism may be conducted using the case definition that, if the veterinarian says a dog has adrenal insufficiency, then the diagnosis is made and the case definition satisfied. This will increase the number of cases included in epidemiologic studies, and make them less complicated, more convenient, and less costly.

CHAPTER 4

THREE HUNDRED SEVENTY-SIX CASES DIAGNOSED
BY VETERINARY COLLEGES AND A REFERRAL INSTITUTION

Introduction

Colleges of veterinary medicine and other veterinary referral hospitals typically maintain detailed case records. About two thirds of the colleges of veterinary medicine in the United States and Canada contribute case data to the Veterinary Medical Data Base (VMDB) at Purdue University, West Lafayette, Indiana. The remaining third of the colleges and the referral hospitals maintain their case data independently. These data are a rich source of information about canine hypoadrenocorticism, and this source was used to estimate the incidence and prevalence of canine hypoadrenocorticism; to describe the patients afflicted with the disease as to ages at diagnosis, sexes, breeds, serum sodium and potassium concentrations, and treatment; and to identify factors associated with the disease.

Methods

The VMDB was queried for all the data on hypoadrenal dogs submitted by participating universities during 1989, 1990, and 1991. The data available included

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university, patient identification number, discharge date, length of hospitalization, clinician, patient sex, species, breed, age, weight, diagnoses, and surgical procedures. Since information not available from the VMDB was needed, a collection form (Case Data Abstract Form, Appendix A1) was developed. Additional data obtained using this form included adrenocorticotropic hormone (ACTH) stimulation test results, serum sodium and potassium concentrations, other diagnoses, and whether the dogs had been treated with fludrocortisone acetate or microcrystalline desoxycorticosterone pivalate (DOCP). These forms were sent with a cover letter explaining the purpose of the request to the 20 universities in the United States and Canada known to have submitted cases of canine hypoadrenocorticism to the VMDB in 1989, 1990, or 1991.

Six universities and two veterinary referral hospitals which did not submit data to the VMDB during the years of interest were also queried. A Population Data Abstract Form (Appendix A2) and a modified Case Data Abstract Form (Appendix A3) were developed to obtain the data. Data requested included number of dogs seen during 1989, 1990, and 1991 by sex and breed if available, date of diagnosis, age at diagnosis, sex, breed, ACTH stimulation test results, other diagnoses, and whether or not the dogs had been treated with fludrocortisone acetate or DOCP. These forms were sent with a cover letter explaining the purpose of the request.

Only data from institutions responding with data forms were included in the study. Non-responders were included for incidence and prevalence calculations if they had contributed valid case and population data to the VMDB, but failed to return data forms.

Confidence intervals for odds ratios (OR) were calculated using Cornfield's approximation.[49] If Cornfield confidence limits were inexact, exact confidence limits were calculated.[128] Uncorrected chi-square statistics were reported.[40] Fisher exact probability calculations for the 2x2 contingency tables were calculated when the expected value of a cell was less than five (Appendix B).[162]

The selected clinical findings were chosen either because of their anecdotal association with canine hypoadrenocorticism (they seemed from clinical experience to be associated with canine hypoadrenocorticism), or, since canine hypoadrenocorticism may be an autoimmune disease,[41] because of their putative autoimmune etiology. They were selected to investigate whether or not they were actually associated with hypoadrenocorticism in the dog. The list of selected clinical findings requested was not exhaustive.

The VMDB coded ages into eight categories, zero through seven, rather than the specific age of each patient. Each category represented an age range. The midpoint of each range (yr) was used as the dog's age for this study. Table 4.1 includes the VMDB age codes, age code ranges, and the midrange ages used for this study.

Table 4.1. Veterinary Medical Data Base (VMDB) Age Codes and Corresponding Midrange Ages Used in Veterinary College and Referral Institution Study of Canine Hypoadrenocorticism

VMDB age code	Age code range	Midrange age used in study (yr)
0	0 - 2 wk	0.019
1	2 wk - 2 mo	0.103
2	2 - 6 mo	0.333
3	6 - 12 mo	0.750
4	1 - 2 yr	1.500
5	2 - 4 yr	3.000
6	4 - 7 yr	5.500
7	7 - 10 yr	8.500
8	10 - 15 yr	12.500
9	15 yr and older	15.000

Although the VMDB data distinguished among Toy, Miniature, and Standard Poodles, and among Miniature, Standard, and Giant Schnauzers, other data sets reported in subsequent chapters did not. Dogs were, for example, frequently reported as simply "Poodle" or "Schnauzer" without size specification. Therefore, to maintain consistency among data sets, all Poodles in each data set have been reported as one breed, and all Schnauzers have been reported as one breed.

The VMDB was queried a second time for the years 1989, 1990, and 1991 to gather data on seven diseases or other reasons for being taken to veterinary referral hospitals in dogs both with and without hypoadrenocorticism (natural or iatrogenic). These seven--cataracts, dental tartar, fleas, heartworm infection, mitral insufficiency, rabies vaccination, and squamous cell carcinoma--were specifically chosen because they were, in the judgment of several veterinarians, probably *not* associated with hypoadrenocorticism. The data were collected as a check on methodology, since, hypothetically, these seven reasons for presentation of dogs should not have been related to hypoadrenocorticism.

Results

General

Unless noted otherwise, all results are for naturally occurring cases (as opposed to iatrogenic).

Institutional Participants

Nineteen of the 20 universities (Table 4.2) which submitted canine hypoadrenocorticism case data to the VMDB for 1989, 1990, or 1991 returned Case Data Abstract Forms. All six universities (Table 4.2) which did not submit data to the VMDB for 1989, 1990, or 1991 provided Case Data Abstract Forms, and five provided Population Data Abstract Forms. The Angell Memorial Animal Hospital provided Case Data Abstract Forms, but not a Population Data Abstract Form. Therefore, all English-speaking colleges of veterinary medicine in the United States and Canada, except one, which reported cases of canine hypoadrenocorticism in 1989, 1990, or 1991, submitted data.

Cases

Three hundred seventy-six cases of canine hypoadrenocorticism were reported (Table 4.2). Two hundred ninety-one (77.4%) were from universities participating in the VMDB, and 85 (22.6%) were from non-participants. The total number of canine patients seen at each institution during 1989, 1990, and 1991, were available for 346 of the 376 cases. Three hundred forty-one of the cases were naturally occurring hypoadrenocorticism. Thirty-five were iatrogenically produced cases, virtually all of which were produced by treating hyperadrenocorticism (Cushing's disease) with 2,4'-dichlorodiphenyldichloroethane (o,p'-DDD).

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Table 4.2. Universities and Veterinary Referral Hospitals in the United States and Canada Responding with Canine Hypoadrenocorticism Case Data for 1989-1991 and Number of Cases Contributed*

Participants in the Veterinary Medical Data Base	Number of cases contributed
Auburn University	8
Colorado State University	19
Florida, University of	9
Georgia, University of	35
Illinois, University of	21
Iowa State University	7
Kansas State University	10
Michigan State University	25
Minnesota, University of	24
Missouri, University of	12
Ohio State University	2
Ontario Veterinary College	15
Pennsylvania, University of	35
Purdue University	15
Saskatchewan, University of	5
Tennessee, University of	10
Texas A&M University	15
Virginia Tech and University of Maryland	7
Wisconsin, University of	17
Subtotal	291
Non-participants in the Veterinary Medical Data Base	**Number of cases contributed**
Angell Memorial Animal Hospital	16
California, University of	23
Mississippi State University	4
North Carolina State University	23
Prince Edward Island, University of	2
Tufts University	14
Washington State University	3
Subtotal	85
Total	376

*Non-responders: Cornell University; Animal Medical Center, New York

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Incidence and Prevalence Estimates

Incidence and prevalence were estimated because measures of disease frequency are fundamental to the study of any disease, and because Ciba Animal Health requested the estimates in return for project support. Since incidence can only be determined prospectively, and since a prospective study of canine hypoadrenocorticism would be too costly, incidence was estimated retrospectively. Because the date of initial diagnosis could be easily retrieved from the VMDB, the strategy was to estimate incidence and then estimate prevalence using the incidence estimate and an estimate of average disease duration. Underlying the estimates is the understanding that the focus is on the population of dogs seen by veterinarians, not all dogs. The estimates are also based on the assumption that a dog with hypoadrenocorticism will be presented to a veterinarian since it will not recover spontaneously.

Incidence was estimated using the total number of dogs initially diagnosed with hypoadrenocorticism during 1989, 1990, and 1991 divided by the total number of dogs seen by all the institutions in 1989, 1990, and 1991. Institutions which responded with case data, but not population data, were excluded. Cornell University, which had 39 cases but did not respond with data forms, was included in this computation because its number of cases and underlying population were

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reported to VMDB. Since the VMDB does not distinguish between natural and iatrogenic cases, the assumption was made that the 39 Cornell cases were divided between natural and iatrogenic in the same proportions, 90.2% and 9.8%, respectively, as were the rest of the cases. This led to the computations below.

Incidence estimate (natural cases) =

Number of cases diagnosed   + Number of cases diagnosed
(all institutions except   (Cornell University)
Cornell University)

───

Total dogs seen in 1989, 1990, 1991 (all institutions)

$$= \frac{312 + (.902)(39)}{207,388} = 0.001674 = 0.1674\%$$

$\doteq$ 1.7 cases/1,000 dogs/3 yr

Adding iatrogenic cases yielded an incidence estimate (natural and iatrogenic cases) of 1.9 cases/1000 dogs/3 yr.

These incidence estimates were used with an estimate of average disease duration of 4.9 yr (see Chapter 5 for computation of this estimate). Prevalence estimates were computed using the following formula:

Prevalence = (Incidence) (Average disease duration)

This formula is well established in the epidemiologic literature as a method for estimating the prevalence of diseases which have a low prevalence and a stable

endemic rate of occurrence.[3,98,120,123,168,200,215,239] This led to the computation below.

Prevalence estimate (natural cases) =

[Incidence estimate (natural cases)] [Average disease duration]

= (1.7 cases/1000 dogs/3 yr) (4.9 yr)

= 2.8 cases /1000 dogs

The prevalence estimate (natural and iatrogenic cases) was 3.1 cases/1000 dogs.

Sex-specific incidence estimates were calculated for naturally occurring cases. These incidence estimates were (number of cases of the particular sex/1000 dogs of that sex/3 yr) female-intact 1.0, female-spayed 3.0, all females 2.1, male-intact 0.7, male-castrated 1.9, and all males 1.1 (Table 4.3). The computation for female-intact follows to illustrate the computation method.

Female-intact incidence estimate =

$$\frac{\text{Number of female-intact cases diagnosed}}{\text{Total female-intact dogs seen in 1989, 1990, 1991 (all institutions)}}$$

$$= \frac{43}{43,249} = 0.000994 = 0.0994\%$$

$\doteq$ 1.0 case/1000 female-intact dogs/ 3 yr

Table 4.3. Sex-Specific Incidence Estimates of Naturally Occurring Canine Hypoadrenocorticism Seen in Veterinary Referral Hospitals in 1989-1991, United States and Canada

Sex	Number of cases	Sex-specific incidence estimate*
Female-intact	43	1.0
Female-spayed	159	3.0
All females	202	2.1
Male-intact	40	0.7
Male-castrated	55	1.9
All males	95	1.1

*Expressed as number of cases of the particular sex with hypoadrenocorticism/ 1000 dogs of that sex/3 yr.

Breed-specific incidence estimates were calculated for naturally occurring cases reported by 19 institutions which participated in the VMDB. These incidence estimates were calculated for the seven breeds most frequently affected with canine hypoadrenocorticism (see Breeds section which follows). Incidence estimates were (number of diseased dogs of the particular breed/1000 dogs of that breed/3 yr), in decreasing order, West Highland White Terrier 12.0, Great Dane 7.6, Poodle 4.9, Rottweiler 2.2, Mixed 1.7, German Shepherd 1.2, and Labrador Retriever 0.9; the incidence estimate for all other breeds combined was 1.4 (Table 4.4).

Ages at Diagnosis

Age at diagnosis (yr) was reported for 329 (96.5%) of the 341 naturally occurring cases. It averaged 5.4 (SD 3.2) (SEM[q] 0.2) (Range 0.1 - 15.0). Age is stratified by sex in Table 4.5.

Age-specific OR were calculated for age at diagnosis (Table 4.6). These OR are based on all the cases submitted to the VMDB, except those from Cornell University, during 1989, 1990, and 1991.

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[q]Standard error of the mean (SEM) equals the standard deviation (SD) divided by the square root of the sample size.

Table 4.4. Breed-Specific Incidence Estimates of Naturally Occurring Canine Hypoadrenocorticism Seen in Veterinary Referral Hospitals in 1989-1991, United States and Canada

Breed	Number of cases	Breed-specific incidence estimate*
German Shepherd	9	1.2
Great Dane	10	7.6
Labrador Retriever	9	0.9
Mixed	58	1.7
Poodle	35	4.9
Rottweiler	7	2.2
West Highland White Terrier	12	12.0
All other breeds	118	1.4

*Expressed as number of cases of a particular breed with hypoadrenocorticism/ 1000 dogs of that breed/3 yr.

Table 4.5. Average Age at Diagnosis for 329 Naturally Occurring Cases of Canine Hypoadrenocorticism Seen in Veterinary Referral Hospitals in 1989-1991, United States and Canada

Sexes of cases	Number of cases	Average age at diagnosis (yr) (SD) (SEM) (Range)
Female-intact	46	3.9 (2.5) (0.4) (0.1 - 10.2)
Female-spayed	176	5.9 (3.2) (0.2) (1.3 - 15.0)
All females	222	5.4 (3.2) (0.2) (0.1 - 15.0)
Male-intact	40	5.2 (3.6) (0.6) (0.8 - 15.0)
Male-castrated	62	5.3 (3.1) (0.4) (0.7 - 12.5)
All males	102	5.2 (3.3) (0.3) (0.7 - 15.0)
All sexes*	329	5.4 (3.2) (0.2) (0.1 - 15.0)

*Includes five dogs of unknown sex.

Table 4.6. Age-Specific Odds Ratios (OR) for Age at Diagnosis of Dogs with Naturally Occurring and Iatrogenic Hypoadrenocorticism Seen in Veterinary Referral Hospitals in 1989-1991, United States and Canada

Age interval (yr)*	Number of cases n=330	Total number of dogs n=147,037	OR	95% confidence interval for OR[49]	χ^2 statistic (p value) Uncorrected[40]
0 < age < 1	11	32,790	0.12	0.06 - 0.22	68.45 (< 0.0001)
1 ≤ age < 4	92	40,829	1.01	0.78 - 1.29	0.00 (0.9641)
4 ≤ age < 7	101	27,688	1.90	1.49 - 2.42	29.84 (< 0.0001)
7 ≤ age < 10	73	23,238	1.51	1.16 - 1.98	9.87 (0.0017)
age ≥ 10	53	22,492	1.06	0.78 - 1.43	0.15 (0.7002)

* The comparison group is all other dogs.

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Sexes

Sex was reported for 329 (96.5%) of the 341 naturally occurring cases. The number (%) of each sex is reported in Table 4.7, and sex-specific OR in Table 4.8.

Breeds

Breed was reported for 333 (97.7%) of the 341 naturally occurring cases (Table 4.9). The seven most frequently reported breeds with number (%) were: Mixed 68 (20.4); Poodle 46 (13.8); Labrador Retriever 16 (4.8); German Shepherd 15 (4.5); Great Dane 12 (3.6); Rottweiler 12 (3.6); and West Highland White Terrier 12 (3.6). Breed-specific OR were calculated for these seven breeds (Table 4.10).

Serum Sodium and Potassium Concentrations

Serum sodium and potassium concentrations were reported for 250 (75.1%) of the 341 naturally occurring cases (Figures 4.1 and 4.2, respectively). The sodium to potassium ratios are reported in Figure 4.3. One hundred forty (56.0%) of the ratios were 25.0 or less, the diagnostic indicator suggested by one reference,[129] and 151 (60.4%) were 27.0 or less, the diagnostic indicator suggested by two others.[43,189]

Table 4.7. Sexes of 329 Naturally Occurring Cases of Canine Hypoadrenocorticism Seen in Veterinary Referral Hospitals in 1989-1991, United States and Canada

Sexes	Number	Percent
Female-intact	46	14.0
Female-spayed	177	53.8
All females	223	67.8
Male-intact	43	13.1
Male-castrated	63	19.1
All males	106	32.2
All sexes	329	100.0

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Table 4.8. Sex-Specific Odds Ratios (OR) for Dogs with Naturally Occurring Hypoadrenocorticism Seen in Veterinary Referral Hospitals in 1989-1991, United States and Canada

Sex*	Number of cases $n = 297$	Total number of dogs $n = 185,026$	OR	95% confidence interval for OR[49]	χ^2 statistic (p value) Uncorrected[40]
Female-intact	43	43,206	0.56	0.40 - 0.78	13.05 (0.0003)
Female-spayed	159	52,839	2.88	2.28 - 3.64	90.60 (< 0.0001)
Female-spayed**	159	52,839	3.02	2.13 - 4.30	45.75 (< 0.0001)
Female (intact and spayed)	202	96,045	1.97	1.53 - 2.53	30.81 (< 0.0001)
Male-intact	40	60,484	0.32	0.23 - 0.45	49.81 (< 0.0001)
Male-castrated	55	28,497	1.25	0.92 - 1.69	2.21 (0.1371)
Male-castrated***	55	28,497	2.92	1.91 - 4.47	29.16 (< 0.0001)
Neutered (either sex)	214	81,336	3.29	2.53 - 4.27	94.99 (< 0.0001)

* Except as noted, the comparison group is all other dogs.

** Female-spayed compared to female-intact.

*** Male-castrated compared to male-intact.

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Table 4.9. Breeds of 333 Naturally Occurring Cases of Canine Hypoadrenocorticism Seen in Veterinary Referral Hospitals in 1989-1991, United States and Canada

Breed	Number	Percent
Afghan Hound	1	0.3
Airedale Terrier	3	0.9
Alaskan Malamute	1	0.3
American Foxhound	1	0.3
Australian Heeler	1	0.3
Australian Shepherd	4	1.2
Australian Terrier	1	0.3
Basset Hound	9	2.7
Beagle	3	0.9
Bearded Collie	3	0.9
Bedlington Terrier	1	0.3
Bichon Frise	2	0.6
Border Collie	3	0.9
Boston Terrier	1	0.3
Bouvier des Flandres	1	0.3
Brittany	1	0.3
Bull Terrier	1	0.3
Cairn Terrier	3	0.9
Chesapeake Bay Retriever	2	0.6
Chihuahua	4	1.2
Chow Chow	2	0.6
Cocker Spaniel	6	1.8
Collie	1	0.3
Dachshund	5	1.5
Dandie Dinmont Terrier	1	0.3
Doberman Pinscher	8	2.4
English Bulldog	1	0.3
English Setter	1	0.3
Fox Terrier	2	0.6
French Bulldog	1	0.3
German Shepherd	15	4.5
German Shorthaired Pointer	2	0.6
Golden Retriever	8	2.4
Gordon Setter	1	0.3

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Table 4.9 (continued)

Breed	Number	Percent
Great Dane	12	3.6
Great Pyrennes	2	0.6
Greyhound	1	0.3
Irish Setter	1	0.3
Irish Wolfhound	1	0.3
Keeshond	1	0.3
Kuvasz	1	0.3
Labrador Retriever	16	4.8
Mixed	68	20.4
Newfoundland	2	0.6
Nova Scotian Duck Tolling Retriever	1	0.3
Pit Bull Terrier	4	1.2
Pointer	4	1.2
Pomeranian	1	0.3
Poodle	46	13.8
Rottweiler	12	3.6
Saint Bernard	2	0.6
Samoyed	4	1.2
Schipperke	1	0.3
Schnauzer	7	2.1
Scottish Terrier	3	0.9
Shar Pei	2	0.6
Shetland Sheepdog	2	0.6
Shih Tzu	2	0.6
Siberian Husky	3	0.9
Silky Terrier	1	0.3
Springer Spaniel	9	2.7
Vizsla	2	0.6
Weimaraner	1	0.3
Welsh Corgi	2	0.6
Welsh Terrier	1	0.3
West Highland White Terrier	12	3.6
Wheaten Terrier	3	0.9
Whippet	2	0.6
Yorkshire Terrier	1	0.3

Table 4.10. Selected Breed-Specific Odds Ratios (OR) for Dogs with Naturally Occurring Hypoadrenocorticism Seen in Veterinary Referral Hospitals in 1989-1991, United States and Canada

Breed*	Number of cases n=258	Number of controls n=149,208	OR	95% confidence interval for OR[49]	χ^2 statistic (p value) Uncorrected[40]	Fisher exact (2-tailed p value)**[162]
Mixed	58	34,697	0.96	0.71 - 1.29	0.09 (0.7689)	
Poodle	35	7,045	3.17	2.18 - 4.58	44.65 (< 0.0001)	
Labrador Retriever	9	10,255	0.49	0.24 - 0.98	4.61 (0.0317)	
German Shepherd	9	7,229	0.71	0.34 - 1.42	1.03 (0.3105)	
Great Dane	10	1,309	4.56	2.28 - 8.83	26.48 (< 0.0001)	0.0001
Rottweiler	7	3,154	1.29	0.56 - 2.83***	0.45 (0.5038)	
West Highland White Terrier	12	986	7.33	3.90 - 13.46	61.83 (< 0.0001)	< 0.0001

* The comparison group is all other dogs.

** Calculated only if an expected cell value is < 5; the preferred p value for this OR.

*** Inaccurate; exact calculation of confidence interval beyond computing ability.

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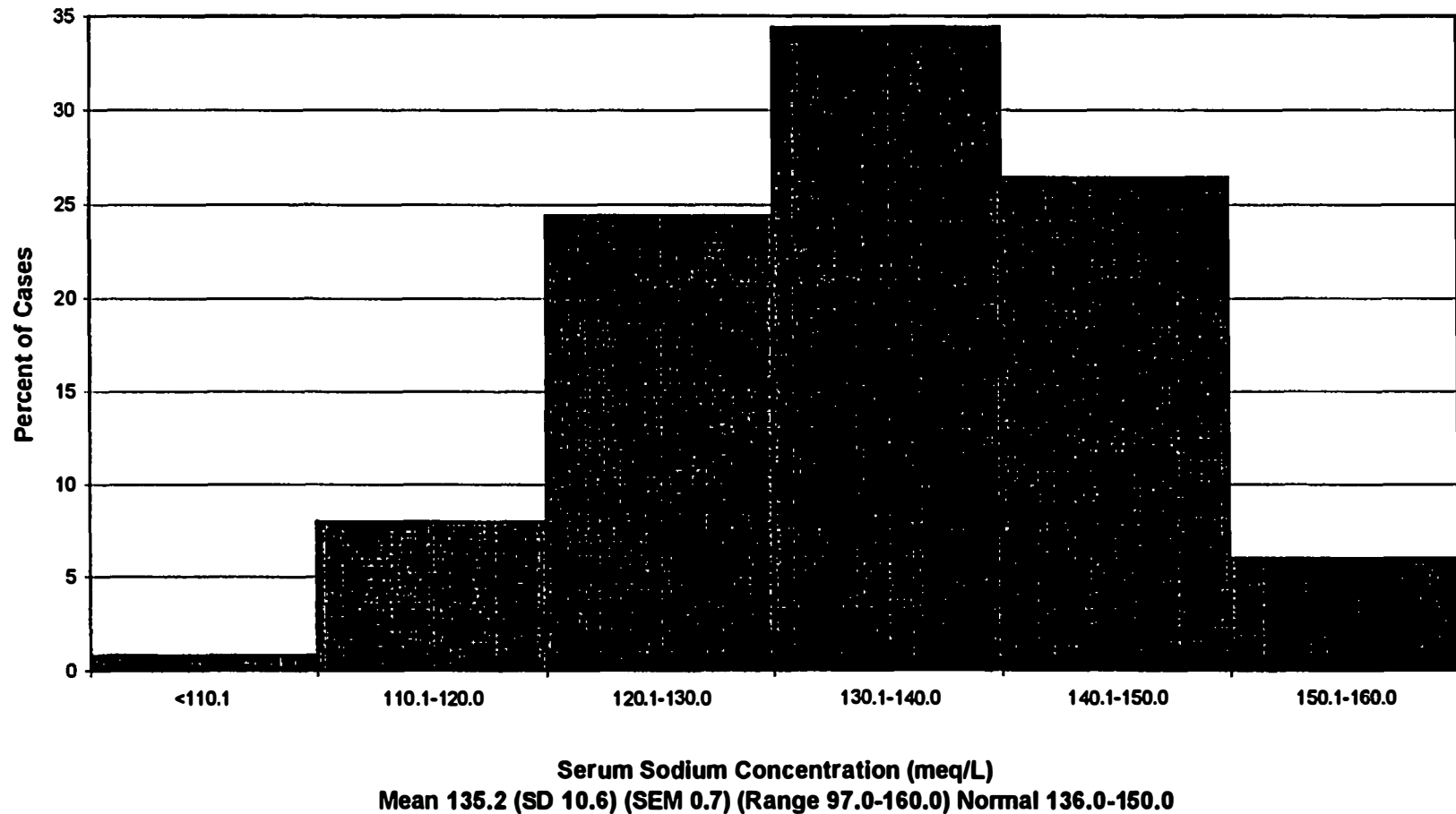
Figure 4.1. Serum Sodium Concentrations for 250 Naturally Occurring Cases of Canine Hypoadrenocorticism Seen in Veterinary Referral Hospitals in 1989-1991, United States and Canada

Serum Potassium Concentration (meq/L)
Mean 5.9 (SD 1.7) (SEM 0.1) (Range 2.9-11.7)
Normal 3.5-5.0
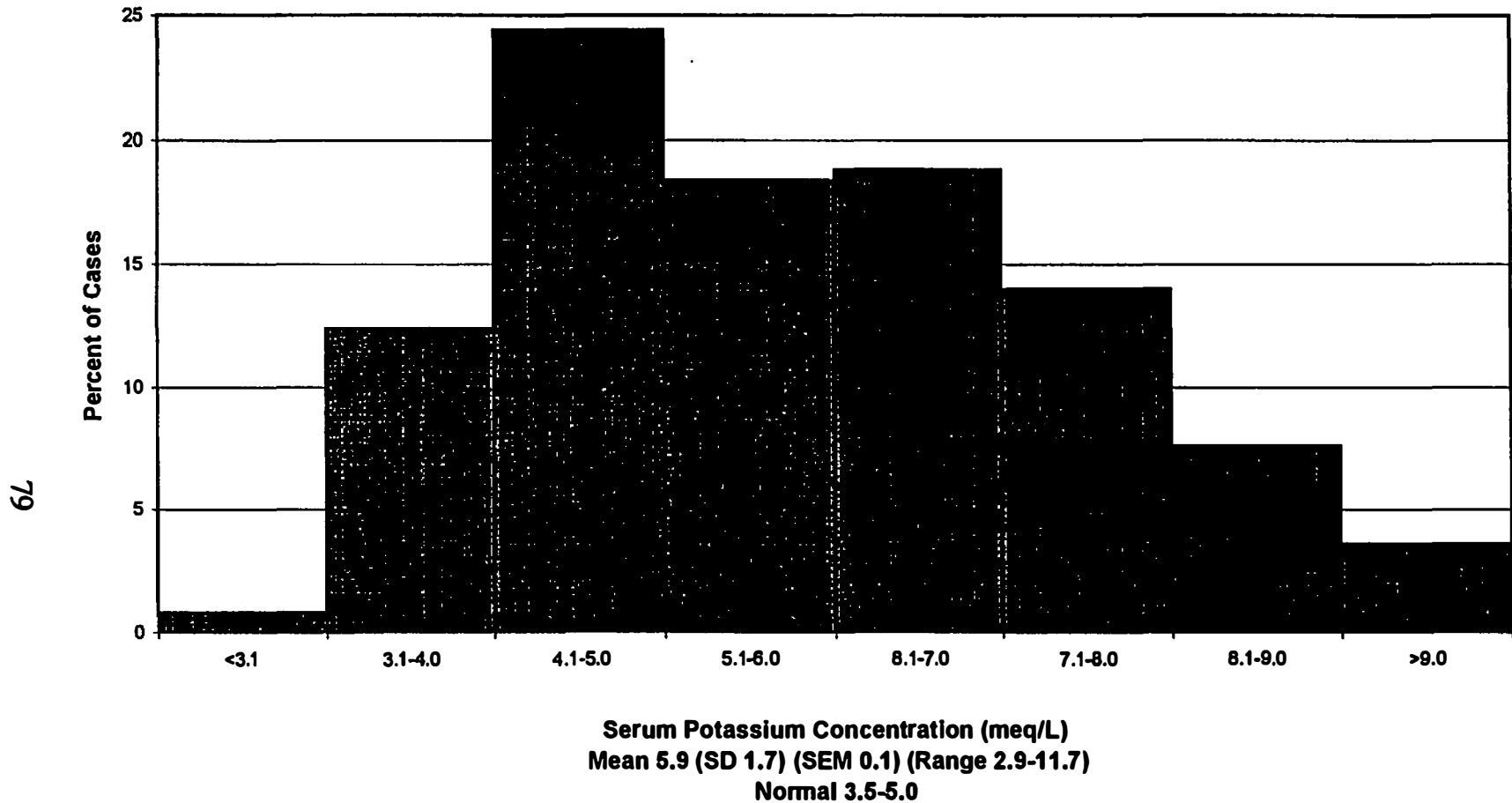
Figure 4.2. Serum Potassium Concentrations for 250 Naturally Occurring Cases of Canine Hypoadrenocorticism Seen in Veterinary Referral Hospitals in 1989-1991, United States and Canada
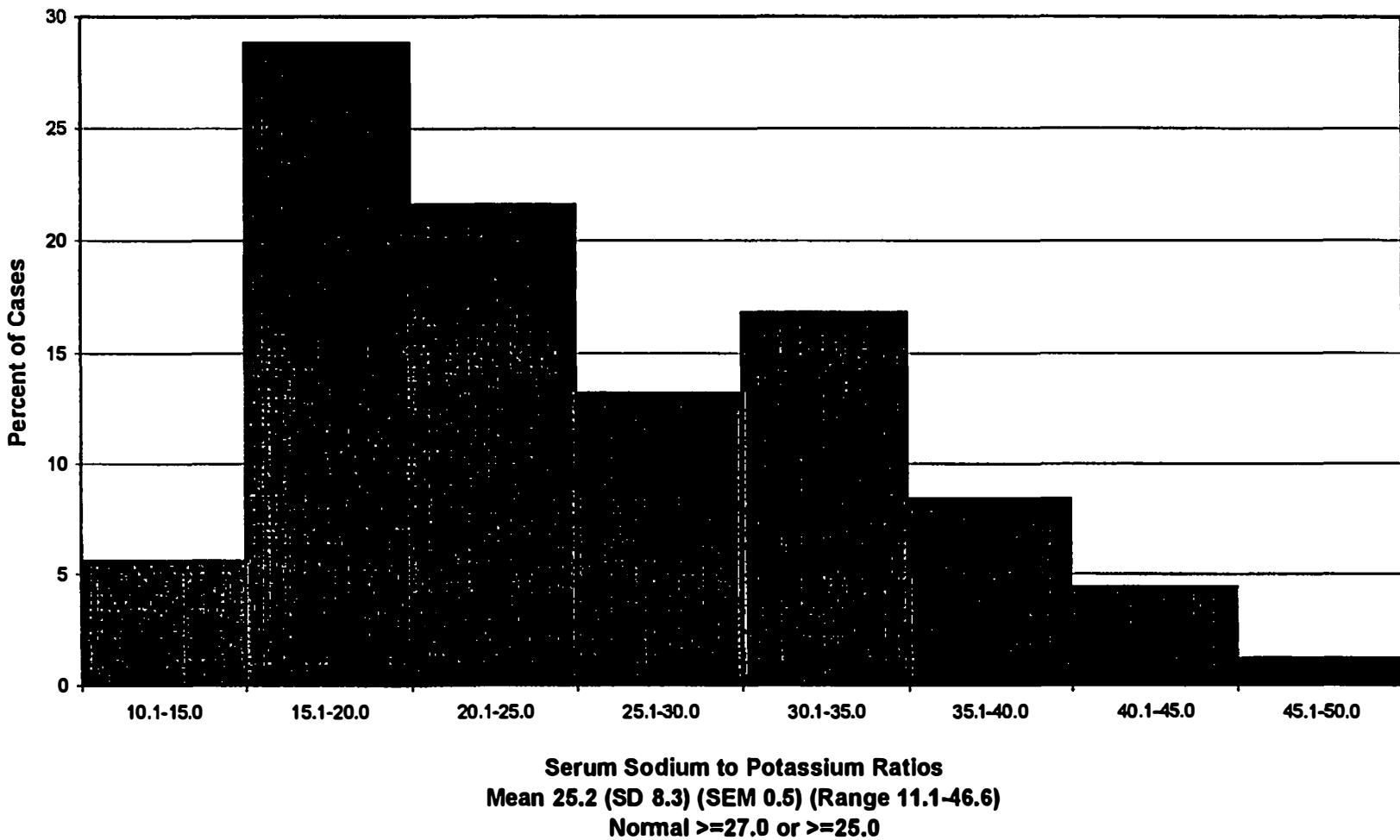
Figure 4.3. Serum Sodium to Potassium Ratios for 250 Naturally Occurring Cases of Canine Hypoadrenocorticism Seen in Veterinary Referral Hospitals in 1989-1991, United States and Canada

One hundred fifteen (46.0%) of the sodium results were normal. Eighty-four (33.6%) of the potassium results were normal. Fifty-eight (23.2%) were normal for both sodium and potassium. Forty-four percent were normal using the diagnostic criterion for disease of a sodium to potassium ratio of 25.0 or less, and 39.6% were normal using the 27.0 or less criterion. No case was normal for sodium, potassium, and sodium to potassium ratio (using either the 25.0 or the 27.0 criterion).

Occurrence of Selected Clinical Findings

The most frequently reported (%) of the selected clinical findings among the 341 naturally occurring cases were anemia (6.7), hypothyroidism (5.9), thrombocytopenia (3.5), and megaesophagus (2.9). A complete list of frequencies is included as Table 4.11.

Treatment

Of the reports for the 341 naturally occurring cases, 312 indicated whether or not fludrocortisone acetate was used to treat the disease, and 285 indicated whether DOCP was used. Of those, 235 (75.3%) and 36 (12.6%) used, respectively, fludrocortisone acetate and DOCP (Table 4.12).

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Table 4.11. Frequency of Occurrence of Selected Clinical Findings* for 341 Naturally Occurring Cases of Canine Hypoadrenocorticism Seen in Veterinary Referral Hospitals in 1989-1991, United States and Canada

Clinical finding	Number	Percent
Anemia	23	6.7
Arthritis	3	0.9
Cruciate ligament rupture	2	0.6
Diabetes mellitus	2	0.6
Hepatitis	4	1.2
Hypothyroidism	20	5.9
Keratoconjunctivitis sicca	4	1.2
Megaesophagus	10	2.9
Myasthenia gravis	4	1.2
Nephritis	3	0.9
Thrombocytopenia	12	3.5

*Clinical findings were chosen either because of their anecdotal association with canine hypoadrenocorticism, or their putative autoimmune etiology.

Table 4.12. Treatment of 341 Naturally Occurring Cases of Canine Hypoadrenocorticism Seen in Veterinary Referral Hospitals in 1989-1991, United States and Canada

Treatment	Total number of dogs*	Number of dogs treated with drug	Percent
Desoxycorticosterone pivalate	285	36	12.6
Fludrocortisone acetate	312	235	75.3

*Indicates the number of dogs of the 341 naturally occurring cases where reports indicated whether or not the drug was used for treatment.

Odds Ratios for Diseases (or Other Reasons for Presentation of Dogs to Veterinary Referral Hospitals) Hypothetically Not Associated with Hypoadrenocorticism

The OR for these diseases are included in Table 4.13. When case information was requested the second time from the VMDB, information on 434 cases was received. This number of cases differed from the 376 reported earlier for two reasons. First, the VMDB is constantly being updated. Second, to be included in the 376, a Case Data Abstract Form had to be provided by the institution. In contrast, diseases or other reasons for presentation that were coincident with cases of canine hypoadrenocorticism could be extracted directly from the VMDB.

Discussion

Institutional Participants

Virtually all the colleges of veterinary medicine in the United States and Canada submitted data, and data were very complete. A weakness of the study was that colleges of veterinary medicine are referral hospitals which do not represent all veterinary hospitals. A corollary was that colleges of veterinary medicine are a particular kind of referral hospital which do not necessarily represent all veterinary referral hospitals.

Table 4.13. Odds Ratios (OR) for Diseases or Other Reasons for Presentation to Veterinary Referral Hospitals for Dogs with Naturally Occurring or Iatrogenic Hypoadrenocorticism in 1989-1991, United States and Canada

Disease or reason for presentation*	Number of cases n=434	Number of controls n=189,909	OR	95% confidence interval for OR[49]	χ^2 statistic (p value) Uncorrected[40]	Fisher exact (2-tailed p value)**[162]
Cataracts	6	5,615	0.46	0.19-1.06***	3.74 (0.0530)	
Dental tartar	20	4,284	2.09	1.30-3.34	10.84 (0.0010)	
Fleas	5	2,428	0.90	0.33-2.25***	0.05 (0.8148)	
Heartworm infection	0	1,472	0.00	0.00-1.42***	3.39 (0.0656)	0.0881
Mitral insufficiency	7	1,394	2.22	0.96-4.83***	4.58 (0.0324)	0.0435
Rabies vaccination	24	25,447	0.38	0.24-0.58	23.14 (< 0.0001)	
Squamous cell carcinoma	0	653	0.00	0.00-3.21***	1.50 (0.2211)	0.4127

*   The comparison group is all other dogs.

**   Calculated only if an expected cell value is < 5; the preferred p value for this OR.

***   Inaccurate; exact calculation of confidence interval beyond computing ability.

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Cases

The large numbers of cases, 341 naturally occurring and 35 iatrogenically produced, provided, at least for summary calculations for the entire population, reasonable confidence in the results. This confidence diminished as the overall population was subdivided by variables such as sex and breed.

Incidence and Prevalence Estimates

A discussion of the incidence and prevalence estimates must be prefaced with an understanding of the method underlying their calculation. Most fundamental are the definitions of incidence and prevalence. Incidence was defined as the number of *new cases* diagnosed during this time period divided by the population at risk. This definition is consistent with several textbook definitions of incidence.[50,123,188,190] The population at risk was defined as all dogs (individual dogs, *not* dog visits) which were presented to veterinary referral hospitals during these years for any reason. Since all dogs can develop hypoadrenocorticism, the only dogs which should have been excluded from the population at risk were those which already had the disease. But, since the disease is so uncommon, these cases were ignored; i.e., the denominator would not change substantially whether or not they were included.

The incidence estimates of 1.7 cases/1000 dogs/3 yr (0.6 cases/1000 dogs/yr) for naturally occurring disease provide useful information to veterinary

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practitioners who need to know roughly how many cases they might expect to see in their practices. For example, if a practice sees 5,000 dogs a year, it would expect to see (5000) (0.6) = 3 dogs with hypoadrenocorticism. Chance will dictate a good deal of variation among practices, but if the practice did not diagnose *any* cases (or, conversely, diagnosed two dozen), the veterinarians in the practice might want to reevaluate their approach to hypoadrenocorticism. Similarly, with the prevalence estimates of 2.8 cases/1000 dogs for naturally occurring disease, the veterinarians might look askance at their diagnostic acumen if they had 10,000 patient records and *no* cases of hypoadrenocorticism (or, conversely, 100 cases). So, both the incidence and prevalence estimates should be useful to the veterinarian. This logic must be cautiously considered since the data extant came from veterinary referral hospitals and the interpretation has been extended to private veterinary practitioners. Since veterinarians may be more likely to refer cases of canine hypoadrenocorticism, this logic is more sound for veterinarians in referral hospitals than for those in private practice.

The prevalence estimate for naturally occurring and iatrogenically produced canine hypoadrenocorticism should be useful to producers of drugs used to treat the disease. The prevalence estimate would help the producers plan for the manufacture, marketing, and distribution of their drugs as illustrated below.

Microcrystalline DOCP is used as a mineralocorticoid to treat hypoadrenal dogs. The dosage of the drug used therapeutically varies among dogs, but averages about 1 mg/4.5kg/25da. Using an estimate of the United States dog population of 52.5 million,[6] and an estimate of 22.4 kg for the average weight of a hypoadrenal dog (see Chapter 3), the following computation is straightforward.

Potential amount of DOCP (mg) which could be used in one yr in United States = Dog population (dogs) • Prevalence (diseased dogs)/(dogs) • Average weight (kg)/diseased dog •

dose (mg/kg/da) • $\frac{365 \text{ da}}{\text{yr}}$ = 52,500,000 total dogs • $\frac{3.1 \text{ diseased dogs}}{1000 \text{ dogs}}$ • $\frac{22.4 \text{ kg}}{\text{diseased dog}}$ •

1 mg/4.5 kg/25 da • $\frac{365 \text{ da}}{\text{yr}}$ ≐ 11,830,000 mg/yr

This computation assumes that DOCP is the only drug used to treat canine hypoadrenocorticism, which it is not. The computation does, however, indicate the potential market for the drug, and can be adapted to accommodate a market penetration of whatever percent seems reasonable. For example, a 20% market penetration would require 20% of the above amount of DOCP per yr.

The sex-specific incidence estimates (Table 4.3) suggested that female dogs are more likely to be hypoadrenal than males. This was indicated by the incidence estimate of 0.7 case/1000 female dogs/yr compared to 0.4 case/1000 male dogs/yr.

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The data also suggested the possibility that neutering either a female or a male leads to an increased probability of disease. The incidence estimate for female-spayed was 1.0 case/1000 female-spayed dogs/yr, three times the incidence estimate for female-intact dogs, which was 0.3 case/1000 female-intact dogs/yr. Similarly, the incidence estimate for male-castrated dogs was 0.6 case/1000 male-castrated dogs/yr, compared to the incidence estimate for male-intact of 0.2 case/1000 male-intact dogs/yr. There may be variables such as age which mitigate this seeming predilection of the neutered dog for hypoadrenocorticism. Increased age (Table 4.6) and neutering (Table 4.8) led to a predilection for the disease. This possibility will be explored by stratified data analysis in Chapter 5.

The breed-specific incidence estimates (Table 4.4) suggested that Great Danes (7.6 cases/1000 dogs/3 yr), Poodles (4.9 cases/1000 dogs/3 yr), and West Highland White Terriers (12.0 cases/1000 dogs/3 yr) were at increased risk. Other variables may account for this effect, but none is an obvious possibility.

Using 1989, 1990, and 1991 registration statistics for the American Kennel Club,[115-117] the same years included in this study, Great Danes comprised 0.7% of total registrations, Poodles 5.9%, and West Highland White Terriers 0.9%. In this

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study (using Table 4.9 and calculating breed percentages of pure-bred dogs only, i.e., excluding Mixed dogs), Great Danes comprised 4.5% of total cases, Poodles 17.4%, and West Highland White Terriers 4.5%. These percentages were all substantially higher than for the general population. Recognizing that American Kennel Club registrations do not represent all pure-bred dogs, this was further evidence that these breeds were more likely to be hypoadrenal.[r]

Ages at Diagnosis

The average ages at diagnosis (Table 4.5) were unremarkable with the possible exception of the difference between the average age for female-intact dogs of 3.9 yr compared to female-spayed dogs of 5.9 yr. Older dogs may be more likely to be spayed than younger ones, but a similar disparity might be expected between male-intact and male-castrated. But this difference did not exist between the 5.2 yr and 5.3 yr ages of male-intact and male-castrated dogs, respectively. Perhaps owners who eventually spay their females delay the procedure for some reason, while owners who castrate their males are less likely to delay. (Data on

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[r] To ensure that the 1989, 1990, and 1991 American Kennel Club registrations represented American Kennel Club registrations over a longer time period, and that the percentages of these breeds in the general population were relatively stable over time; percentages of total registrations for Great Danes, Poodles, and West Highland White Terriers were calculated for the years 1981 through 1988. These were: Great Danes 1.0%, Poodles 7.9%, and West Highland White Terriers 0.8%. These were all consistent with the percentages for 1989, 1990, and 1991, and supported the conclusion that these breeds were more likely to be hypoadrenal.[107-114]

average age at the time of spaying or castrating, as well as proportion of males and females neutered, would be useful in addressing this issue.) In any case, the age disparity between female-intact and female-spayed was interesting, but unexplained.

Regarding age-specific OR in Table 4.6, dogs in the 0-1 yr age range were less likely to be diseased (OR = 0.12), though dogs as young as 0.1 yr were diagnosed. Dogs in the 1-4 yr age range had neither an increased nor decreased probability of disease (OR = 1.01), but age beyond 4 yr seemed to predispose to disease. Significant OR for the 4-7 yr and 7-10 yr age groups were 1.90 and 1.51, respectively. Variables other than age were possibly involved, but an age effect seemed clear. The age effect seemed to disappear in very elderly dogs--the OR for the over 10 yr age group was not significant. Nevertheless, three 15 yr old dogs were diagnosed as hypoadrenal. While recognizing the necessarily arbitrary selection of the age categories above, the probability of onset of hypoadrenocorticism in dogs increased with age, significantly between 4 and 10 yr.

Sexes

Females (intact and spayed) made up 51.9% of dogs in the 1989, 1990, and 1991 VMDB data base; males (intact and castrated) made up the remaining 48.1%. Among the hypoadrenal dogs, 67.8% were females (intact and spayed) and 32.2%

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were males (intact and castrated) (Table 4.7). The predisposition of females to the disease has been reported previously.[41,43,93,148,189] This study confirmed this effect by the sex-specific incidence of hypoadrenocorticism among females (intact and spayed) of 2.1 cases/1000 female dogs/3 yr compared to 1.1 cases/1000 dogs/3 yr for males (intact and castrated) (Table 4.3).

Since female-spayed comprised 53.8% (Table 4.7) of all the hypoadrenal patients in this study, it seemed that female-spayeds were at increased risk of having adrenal insufficiency. This could have resulted from an overrepresentation of female-spayeds in the overall population. However, the overall population of dogs reported to the VMDB in 1989, 1990, and 1991 included only 27.7% female-spayed dogs. Though other variables may be at work, it seemed likely that the large percentage of female-spayeds in the diseased population resulted from a real predisposition of female-spayeds to the disease. This was consistent with the discussion above of sex-specific incidence estimates.

Interestingly, female-intact dogs comprised 14.0% of the hypoadrenal patients, and 24.3% of the general VMDB population. This suggested that an unspayed female may be less likely to be hypoadrenal. This was consistent with the sex-specific incidence estimates. It was inconsistent, however, with one report that female-intacts had a higher risk than female-spayeds.[148]

Male-castrates were 15.1% of the overall population, but were 19.1% of the diseased group. This suggested that being neutered might increase the likelihood

of disease. This was consistent with the sex-specific incidence estimates since male-castrates had a substantially higher incidence of disease than male-intact dogs. However, the overall incidence estimate for male-castrates (Table 4.3) was exactly the same as the incidence estimate for all dogs of all sexes of 1.9 cases/1000 dogs (all sexes)/3 yr.

The results for male-intact dogs were striking. They comprised 33.0% of the general VMDB population, but only 13.1% of the diseased population. This suggested that male-intact dogs were less likely to be hypoadrenal than castrated ones, and this was supported by the sex-specific incidence estimate of 0.7 case/1000 male-intact dogs/3 yr compared to the incidence estimate for all dogs of all sexes of 1.9 cases/1000 dogs (all sexes)/3 yr.

The sex-specific OR reported in Table 4.8 reinforced these conclusions. Females (intact and spayed) were more likely to be diseased than males (intact and castrated). Female-spayeds were more likely to be hypoadrenal compared to all other dogs and female-intact dogs. Male-castrates were (OR 1.25 compared to all other dogs, and OR 2.92 compared to male-intact dogs) more likely to be diseased.[s] Female-intact dogs (OR 0.56) and male-intact dogs (OR 0.32) were less likely to be affected.

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[s]All the OR reported here were highly significant (p < 0.001) except the OR 1.25 (p ≐ 0.15) for male-castrates compared to all other dogs.

Since female-spayed and male-castrated dogs seem predisposed to hypoadrenocorticism, a neutering effect may be at work. This was reinforced by the OR of 3.29 (p < 0.0001) for neutered animals of either sex compared to intact animals of either sex (Table 4.8). This may have been affected to some extent by the age effects discussed above.

Breeds

Sixty-nine breeds were reported among the 333 naturally occurring cases which reported breed (Table 4.9). This established that hypoadrenocorticism can occur in many breeds.

The OR for the seven most frequently reported breeds (Table 4.10) indicated a predisposition for hypoadrenocorticism among the following breeds: Poodle (OR 3.17, p < 0.0001); Great Dane (OR 4.56, p = 0.0001); and West Highland White Terrier (OR 7.33, p < 0.0001). Another paper reported breed predilections in the Standard Poodle, Great Dane, and West Highland White Terrier.[148] The OR for the Labrador Retriever was 0.49 (p < 0.05), indicating that Labrador Retrievers were less likely to be diseased. Possible familial predispositions for hypoadrenocorticism have been reported in this breed.[69]

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Serum Sodium and Potassium Concentrations

Of the 250 naturally occurring cases for which serum sodium and potassium concentrations were available, 115 (46.0%) had normal sodium concentrations, 84 (33.6%) had normal potassium concentrations, and 58 (23.2%) had both normal sodium and potassium concentrations. These results differed from others which showed that only 18.7% and 4.4% of hypoadrenal dogs had normal serum sodium and potassium concentrations, respectively.[148] Forty-four percent had normal sodium to potassium ratios using the 25.0 or less diagnostic criterion,[129] and 39.6% had normal ratios using the 27.0 or less criterion.[43,189] The remarkable result was that *no* one case of the 250 was normal for all three diagnostic criteria--sodium concentration, potassium concentration, and sodium to potassium ratio (regardless of whether the less than 25.0 or the less than 27.0 criterion was used). This suggested that a dog diagnosed with hypoadrenocorticism will usually have an electrolyte abnormality. This could mean that most veterinarians are already not diagnosing hypoadrenocorticism in dogs normal by all three criteria. If they are not, it means they should seldom go to the time, trouble, and expense of the ACTH stimulation test.

Occurrence of Selected Clinical Findings

The frequency (%) of occurrence of anemia (6.7), hypothyroidism (5.9), thrombocytopenia (3.5), and megaesophagus (2.9) suggested that these conditions

were associated with canine hypoadrenocorticism (Table 4.11). However, since this study contained no data about the frequency of these clinical findings in the entire study population, these results must be viewed as anecdotal.

Treatment

Fludrocortisone acetate and DOCP were used in 75.3% and 12.6% of the patients, respectively. The more common use of fludrocortisone acetate may result from its advantages: oral administration, glucocorticoid and mineralocorticoid activity,[69] and its easy availability since it is currently approved by the United States Food and Drug Administration (FDA). It has some disadvantages as well: cost in large dogs, difficulty of use in animals resistant to taking oral medication, large doses sometimes required,[69] occurrence of significant polyuria and polydipsia in some patients,[69] and the failure of some dogs to respond to it.[69] Microcrystalline DOCP has the advantages of nearly universally favorable response in dogs, and its use obviates the need for daily administration since it is given by intramuscular injection about every 25 da. Its disadvantages are: the need to visit the veterinarian for an injection every 3 to 4 wk; it often requires supplemental administration of glucocorticoids;[69] and it is more difficult to obtain since it is not approved by the FDA. Though both drugs will have therapeutic niches, the test of which drug is

preferred by owners and veterinarians will have to wait until both drugs are readily available to the veterinary practitioner.

Odds Ratios for Diseases (or Other Reasons for Presentation of Dogs to Veterinary Referral Hospitals) Hypothetically Not Associated with Hypoadrenocorticism

Data on seven diseases not believed to be associated with canine hypoadrenocorticism were obtained from the VMDB as a methodology check. Of the seven items included in Table 4.13, four--cataracts, fleas, heartworm infection, and squamous cell carcinoma--were not statistically related to hypoadrenocorticism. This was expected since these diseases were intuitively not related to hypoadrenocorticism.

Two of the items--dental tartar and rabies vaccination--were positively and negatively associated, respectively, with hypoadrenocorticism. These results were unexplained, but dental tartar and hypoadrenocorticism may have been associated because each was associated with older age. Conversely, younger dogs may have had a lesser tendency to be hypoadrenal and a greater tendency to be vaccinated for rabies; therefore, adrenal insufficiency and rabies vaccination were negatively associated.

The results for mitral insufficiency were equivocal in that the Cornfield's approximate 95% confidence interval included one, but the 2-tailed Fisher exact

p value was 0.0435. Since the Cornfield's approximation could be considered inaccurate in this case, and an exact computation of the confidence interval was beyond the computer's capability, the 2-tailed Fisher exact p value should be considered definitive, thus leading to the conclusion that mitral insufficiency and hypoadrenocorticism were positively associated. If so, they may have been associated through age, as may be the case with hypoadrenocorticism and dental tartar.

Conclusions

1. <u>Incidence and Prevalence Estimates</u>. The incidence (0.6 case/1000 dogs/yr for naturally occurring, and 0.6 case/1000 dogs/yr for naturally occurring and iatrogenic) and prevalence (2.8 cases/1000 dogs for naturally occurring and 3.2 cases/1000 dogs for naturally occurring and iatrogenic) estimates from this study can serve as baselines for the expected caseload of canine hypoadrenocorticism for referral hospitals. They could be used by pharmaceutical companies for marketing decisions.

2. <u>Sex-Specific Incidence Estimates and Sex Predispositions</u>. Sex-specific incidence estimates suggested that female dogs were more likely than males to develop hypoadrenocorticism. Further, the data suggested that neutering either females or males increased the incidence of disease. This effect may have been exacerbated by other variables, possibly age.

The overrepresentation of females, particularly female-spayeds, in the diseased population compared to the entire VMDB population suggested that females, especially those spayed, were at increased risk for hypoadrenocorticism. It also appeared that intact animals of either sex were less likely to develop disease than their neutered counterparts. These conclusions were supported by both sex-specific OR and incidence rates.

3. <u>Breed-Specific Incidence Estimates and Breed Predispositions</u>. Breed-specific incidence estimates suggested that Great Danes, Poodles, and West Highland White Terriers were at increased risk of developing hypoadrenocorticism. Other variables may be involved. These breed predispositions were supported by a pronounced overrepresentation of these breeds in the study population of diseased dogs compared to American Kennel Club breed registrations for the same years. Labrador Retrievers were less likely to have the disease.

4. <u>Age-Specific Odds Ratios</u>. Age-specific OR indicated that increasing age was associated with an increased risk of developing disease. This effect was particularly profound between the ages of 4 and 10 yr.

5. <u>Serum Sodium and Potassium Concentrations</u>. No dog with hypoadrenocorticism was normal for serum concentrations of sodium and potassium and the sodium to potassium ratio. This suggested that dogs with this disease seldom are normal for all three diagnostic criteria. As a practical matter,

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this means that veterinarians considering hypoadrenocorticism in a canine patient can usually remove hypoadrenocorticism from the list of differential diagnoses if all three diagnostic tests are within normal limits.

6.   Associated Conditions. Anemia, hypothyroidism, thrombocytopenia, and megaesophagus were positively associated with canine hypoadrenocorticism. This conclusion was based on anecdotal data, and must be viewed skeptically. These associations warrant further investigation.

7.   Treatment. Fludrocortisone acetate was much more frequently used than DOCP to treat hypoadrenocorticism. This probably resulted from several factors, but the principal reason was probably that fludrocortisone acetate was more easily available to veterinarians.

CHAPTER 5

CASE CONTROL STUDY USING PATIENTS OF VETERINARIANS ENROLLED IN THE CLINICAL TRIAL OF MICROCRYSTALLINE DESOXYCORTICOSTERONE PIVALATE

Introduction

To this point the study has focused almost exclusively on cases of hypoadrenocorticism: cases from the literature (Chapter 2), cases enrolled in the clinical trial of microcrystalline desoxycorticosterone pivalate (DOCP) (Chapter 3), and cases from veterinary referral hospitals (Chapter 4). The cases have, with a few exceptions for data gathered from veterinary referral hospitals, been without controls. This limits the utility of any result. For example, if a certain percent of cases are Poodles, and the percent seems to be inordinately high, does this represent a breed predisposition for hypoadrenocorticism or not? Therefore, controls needed to be obtained with cases as described in this chapter.

Methods

The veterinarians enrolled in the Ciba Animal Health clinical trial of DOCP provided an ideal source of controls to compare with the hypoadrenal dogs.

Detailed information was already known about the veterinarians and their patients, and the veterinarians were accustomed to providing data. Therefore, a case control study was designed using these veterinarians as respondents. The cases were the dogs enrolled in the clinical trial. The two controls for each case were the next dog in the veterinarian's patient record file which was owned by a different client, and the fifth dog owned by a different client after the first control dog (see Appendices A6 and A7). Whether the control dogs were sick or well was not considered.

A questionnaire (Appendices A4 and A5) with instructions (Appendices A6 and A7) was designed and used to query veterinarians enrolled in the clinical trial. Veterinary hospitals known by Ciba Animal Health personnel to be referral hospitals were not queried. The method of Dillman,[35] slightly abbreviated, was used for the mail survey. This involved mailing the questionnaire with instructions and cover letter to 571 veterinarians who had diagnosed 767 cases of canine hypoadrenocorticism. A follow-up reminder letter was sent to all the veterinarians approximately 1 wk after the initial mailing, and subsequent mailings with additional questionnaires and cover letters were made to those not known to have responded approximately 4 and 7 wk after the initial mailing.

The questionnaire requested the number of dogs (not dog visits) seen in the veterinary practice in 1993, and the age, breed, sex, body weight, and other

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diseases diagnosed for cases and controls selected randomly from the hospital's patient files. These data were used to calculate odds ratios (OR).

Confidence intervals for OR were calculated using Cornfield's approximation.[49] If Cornfield confidence limits were inexact, exact confidence limits were calculated.[128] Uncorrected chi-square statistics were reported.[40] Fisher exact probability calculations for the 2x2 contingency tables were calculated when the expected value of a cell was less than five.[162] Appendix B contains further details regarding these calculations. Body weights for cases and controls were compared using a technique for comparing means of unequal variances.[130]

Logistic regression was done using JMP® statistical software.[177] Breeds were specifically included in the logistic regression if they met two sequential criteria. First, if the breed was represented in the study by either five cases or five controls, an OR was calculated for the breed. Second, if the 95% confidence interval for the breed's OR did not include one, the breed was included in the logistic regression. If the breed had neither five cases nor five controls in the study, or if the 95% confidence interval for its OR did include one, then it was categorized as "Other" in the logistic regression. Sexes were categorized as female-intact, female-spayed, male-intact, and male-castrated. The units were yr for age and kg for body weight.

Logistic regression models were developed generally using the method advocated by Hosmer and Lemeshow.[80] This method calls for variable selection

first by a univariate analysis of each variable; second, by the selection from the univariate analysis of variables to be included in a multivariate analysis; third, by a verification of the importance of each variable included in the multivariate model; and, last, by consideration of whether or not to include variable interaction terms in the model. This was done with the following admonition about the purpose of logistic regression:

> Before beginning a study of logistic regression it is important to understand that the goal of an analysis using this method is the same as that of any model-building technique used in statistics: To find the best fitting and most parsimonious, yet biologically reasonable model to describe the relationship between an outcome (dependent or response variable) and a set of independent (predictor or explanatory) variables.[78]

Dogs were frequently reported as simply "Poodle" or "Schnauzer" without size specification. Therefore, all Poodles (Standard, Miniature, and Toy) have been reported as one breed, and all Schnauzers (Giant, Standard, and Toy) have, similarly, been reported as one breed.

The selected clinical findings were chosen for inclusion in the questionnaire either because of their anecdotal association with canine hypoadrenocorticism, or their putative autoimmune etiology. The list of selected clinical findings is not exhaustive.

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Results

Questionnaire Responses and Description of Veterinary Clinics

Five hundred nineteen (90.9%) of the 571 veterinarians from 494 separate veterinary clinics in the United States returned questionnaires on 720 cases and 1,192 controls. One case was not included in the computations in this chapter (except for Figure 5.1) because the computations were completed before the response was received. The first response was received 7 da after the first mailing, and the last response was received 240 da after. Figure 5.1 graphs number of responses received vs. time after initial mailing.

Four hundred fifty-nine veterinarians reported a total of 1,208 full-time veterinarians in the 459 clinics for an average of 2.6 per clinic (SD 1.7) (SEM[t] 0.1) (Range 1.0 - 13.0). Figure 5.2 plots the number of full-time veterinarians in the clinics vs. the percent of clinics employing that number of veterinarians.

Four hundred two of the veterinary clinics reported the number of dogs diagnosed with canine hypoadrenocorticism in 1993 and the estimated number of active dog patients[u] seen in the practice in 1993. The estimated number of dogs diagnosed for 1993 was 495.5 by the 402 veterinary clinics for a mean of 1.23

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[t]Standard error of the mean (SEM) equals the standard deviation (SD) divided by the square root of the sample size.

[u]An active dog patient was a dog seen in the practice in 1993. Dogs were counted only once, even if several visits to the hospital were made in 1993.
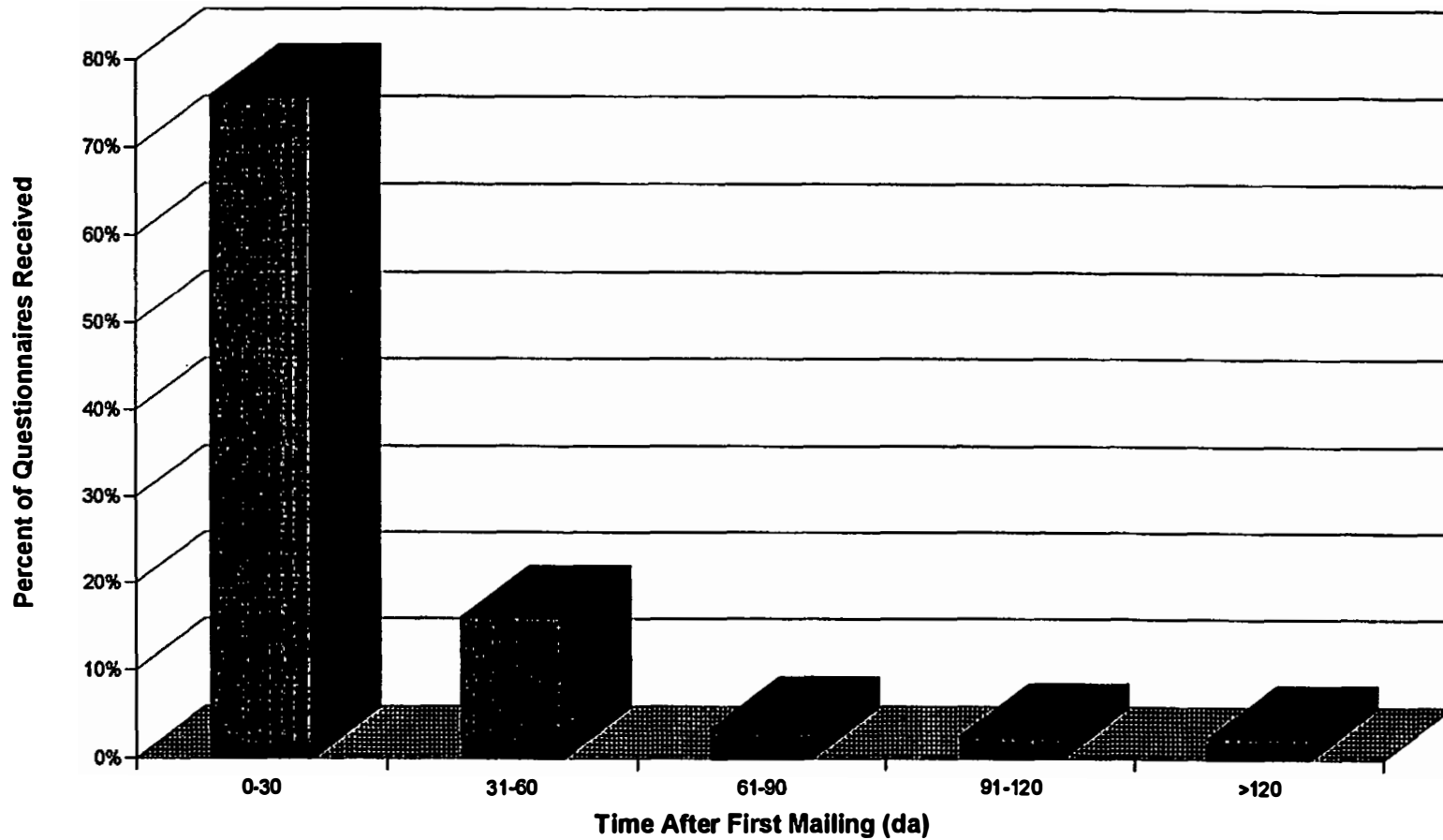
Figure 5.1. Time Questionnaires Received After First Mailing from 1994 Survey in the United States of Veterinarians Enrolled in Clinical Trial
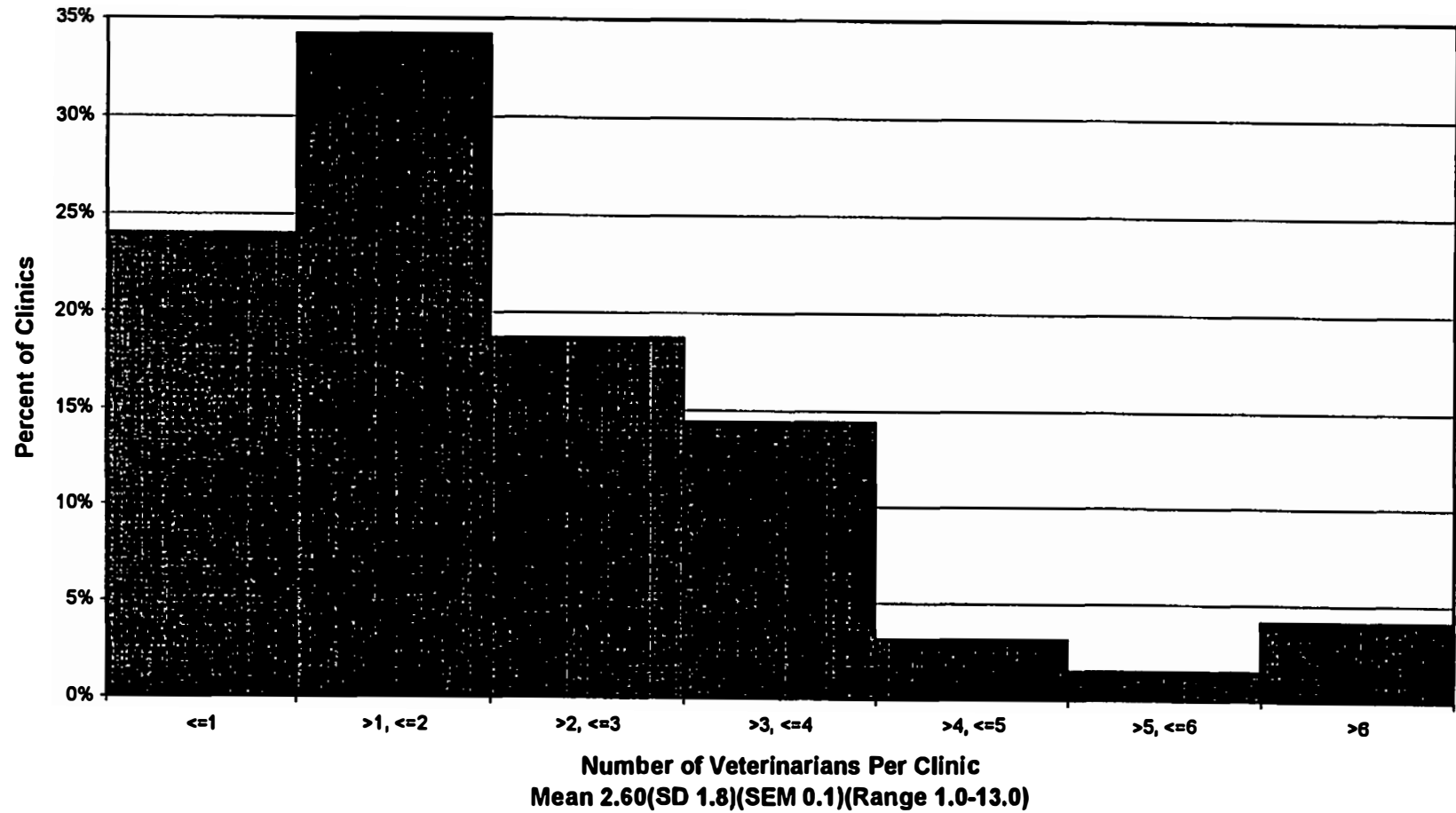
Figure 5.2. Number of Veterinarians Per Clinic from 1994 Survey in the United States of Veterinarians Enrolled in Clinical Trial

dogs newly diagnosed per clinic (SD 1.9) (SEM 0.1) (Range 0.0 - 21.0). These 402 clinics estimated that they saw 1,472,081 active dog patients during 1993. Four hundred one clinics reported the number of dogs diagnosed in 1993 and the number of full-time veterinarians employed in these clinics. The average annual number of dogs diagnosed per full-time veterinarian was 0.53 (SD 0.92) (SEM 0.05) (Range 0.00 - 10.50). Four hundred six clinics reported the number of active dog patients seen in the practice in 1993 and the number of full-time veterinarians employed in these clinics. The average annual number of active dog patients seen per full-time veterinarian was 1504.7[v] (SD 929.5) (SEM 46.1) (Range 86.0 - 7000.0).

Incidence and Prevalence Estimates

Incidence was estimated at 0.34 case/1000 dogs/yr by dividing 495.5 estimated cases in 1993 by 1,472,081 estimated dogs seen in practices in 1993. This incidence estimate led to a prevalence estimate of 1.7 cases/1000 dogs by multiplying the incidence estimate by the average disease duration estimate of 4.9 yr (see Ages below).[3,98,120,123,168,200,215,239]

$$\text{Prevalence} = (\text{Incidence})(\text{Average disease duration})$$

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[v]This was similar to the estimate of 1,600 dogs seen per veterinarian per yr obtained on July 29, 1996 from personal communication with Dr. J. Karl Wise, Center for Information Management, American Veterinary Medical Association.

Ages

The ages reported in this survey were current age *or* age at death *or* age when lost to follow-up, depending on which age applied to the particular patient. This was a different definition of age from the ages at diagnosis reported in Chapter 4, and was used so that the ages of cases and controls could be compared.

There were 666 (92.6%) of the 719 hypoadrenal cases which reported age. The mean age was 8.7 yr (SD 3.2) (SEM 0.1) (Range 1.0 - 18.0). These ages are displayed in Figure 5.3. Of these 666 cases, 405 (60.8%) were alive, 231 (34.7%) were dead, 20 (3.0%) were lost to follow-up, and 10 (1.5%) were of unknown status. The average current age was 8.1 yr (SD 3.0) (SEM 0.1) (Range 1.5 - 18.0) compared to average age at death of 9.8 yr (SD 3.4) (SEM 0.2) (Range 1.0 - 17.2), and average age when lost to follow-up of 8.6 yr (SD 3.1) (SEM 0.7) (Range 4.0 - 13.0). These data were combined and displayed in Figure 5.3.

Age was reported for 1,163 (97.6%) of the 1,192 controls. The mean age was 6.2 yr (SD 4.1) (SEM 0.1) (Range 0.1 - 19.0) as displayed in Figure 5.4. Of these 1,163 controls, 954 (82.0%) were alive, 44 (3.8%) were dead, 98 (8.4%) were lost to follow-up, and 67 (5.8%) were of unknown status. The average age of the live dogs was 6.1 yr (SD 3.9) (SEM 0.1) (Range 0.1 - 19.0). The average age at death of the dead dogs was 10.2 yr (SD 5.2) (SEM 0.8) (Range 0.3 - 17.0).

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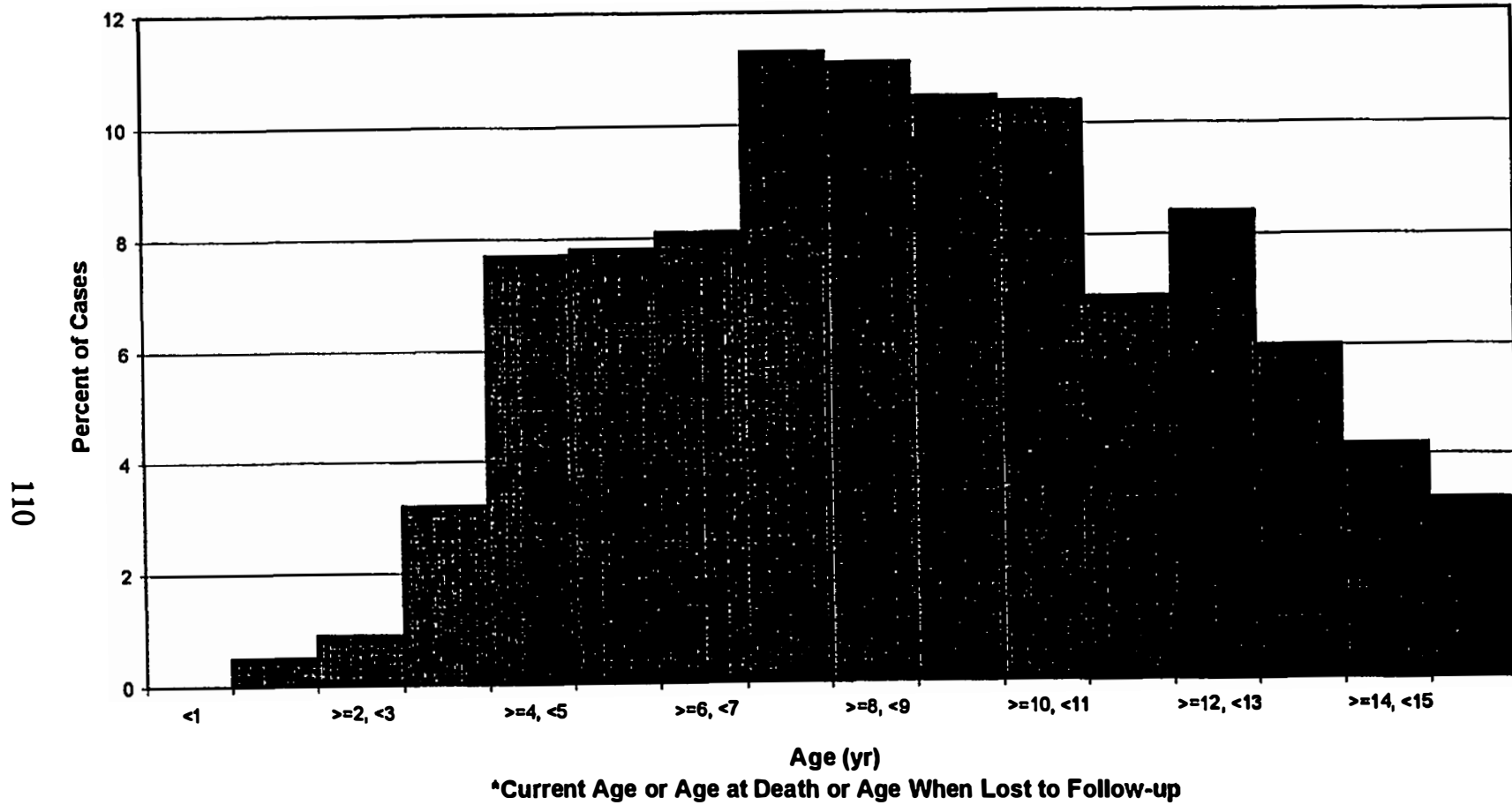
Figure 5.3. Ages* of 666 Dogs with Hypoadrenocorticism from 1994 Survey in the United States of Veterinarians Enrolled in Clinical Trial
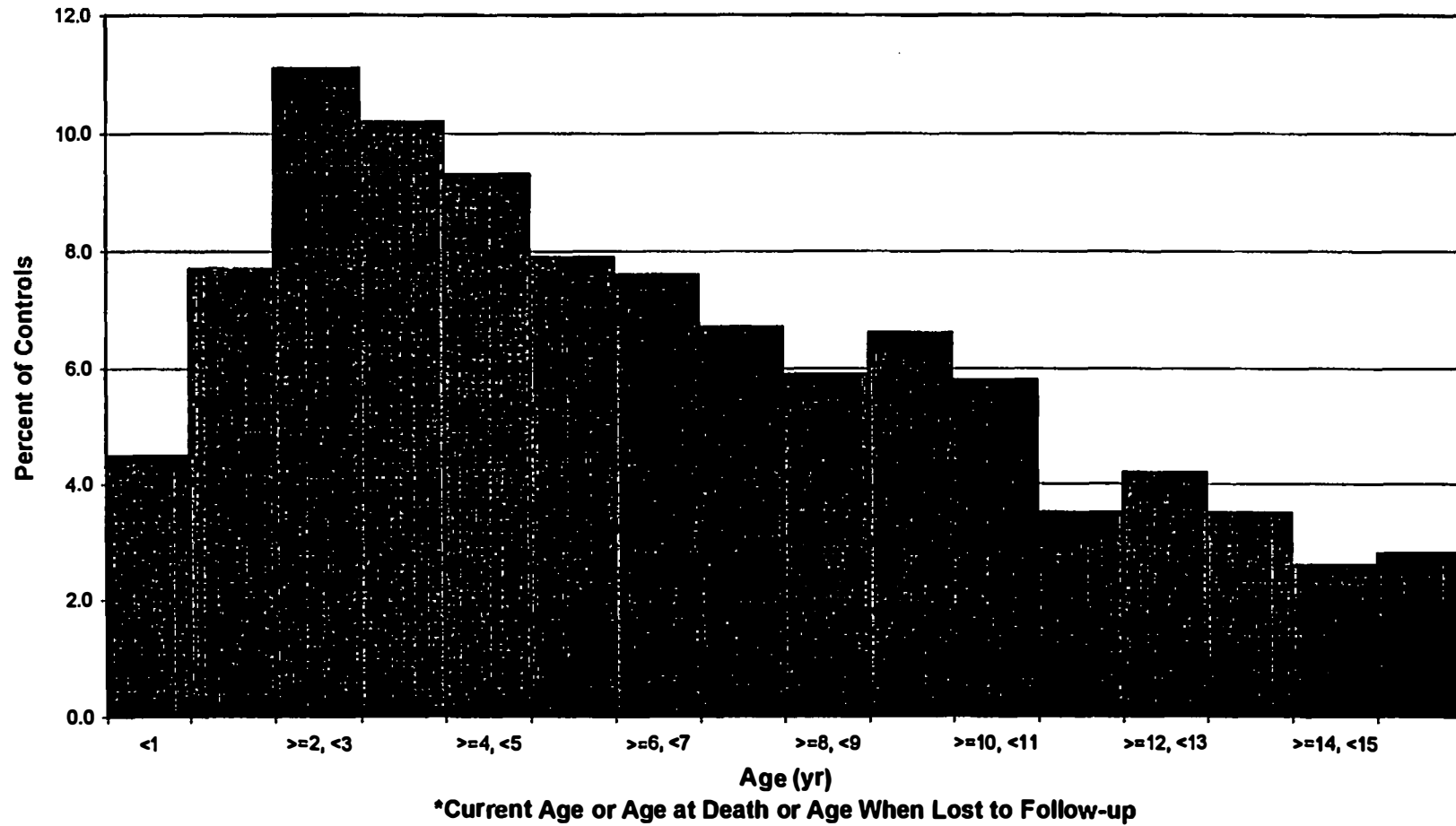
Figure 5.4. Ages* of 1,163 Control Dogs from 1994 Survey in the United States of Veterinarians Enrolled in Clinical Trial

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The average age of the dogs lost to follow-up was 5.7 yr (SD 4.3) (SEM 0.4) (Range 0.2 - 16.0).

Age-specific OR and relevant statistics are presented in Table 5.1.

Average disease duration was estimated as 4.9 yr by subtracting the estimated average age at diagnosis (4.9 yr) from the average age at death (9.8 yr). Average age at death was likely influenced by euthanasia of dogs whose owners chose not to treat their dog. This average age at diagnosis was estimated with a weighted average of 4.3 yr for 244 literature review cases (Chapter 2), 4.9 yr for 232 cases enrolled in the clinical trial of DOCP (Chapter 3), and 5.4 yr for 329 cases from veterinary referral hospitals (Chapter 4).

Sexes

Sex was reported for 711 (98.9%) of the 719 cases and 1,152 (96.6%) of the 1,192 controls (Table 5.2). Sex-specific OR are presented in Table 5.3. Age stratified sex-specific OR were calculated for the age intervals (yr) $0 < age < 5$, $5 \leq age < 10$, and $age \geq 10$ (Tables 5.4 - 5.6).

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Table 5.1. Age*-Specific Odds Ratios (OR) for Dogs with Hypoadrenocorticism from 1994 Survey in the United States of Veterinarians Enrolled in Clinical Trial

Age interval (yr)**	Number of cases n=666	Number of controls n=1,163	OR	95% confidence interval for OR[49]	χ^2 statistic (p value) Uncorrected[40]
0 < age < 1	0	52	0.00	0.00 - 0.12***	30.65 (< 0.0001)
1 ≤ age < 2	3	89	0.05	0.01 - 0.17***	45.98 (< 0.0001)
2 ≤ age < 3	6	129	0.07	0.03 - 0.16***	64.34 (< 0.0001)
3 ≤ age < 4	21	119	0.29	0.17 - 0.47	30.02 (<0.0001)
4 ≤ age < 5	51	108	0.81	0.56 - 1.16	1.42 (0.2342)
5 ≤ age < 6	52	92	0.99	0.68 - 1.42	0.01 (0.9374)
6 ≤ age < 7	54	88	1.08	0.75 - 1.56	0.17 (0.6771)
7 ≤ age < 8	75	78	1.77	1.25 - 2.49	11.46 (0.0007)
8 ≤ age < 9	74	69	1.98	1.39 - 2.83	15.76 (0.0001)
9 ≤ age < 10	70	77	1.66	1.16 - 2.36	8.67 (0.0032)
10 ≤ age < 11	69	68	1.86	1.29 - 2.68	12.45 (0.0004)
11 ≤ age < 12	46	41	2.03	1.29 - 3.20	10.69 (0.0011)
12 ≤ age < 13	56	49	2.09	1.38 - 3.16	13.77 (0.0002)
13 ≤ age < 14	40	41	1.75	1.09 - 2.80	6.16 (0.0131)
14 ≤ age < 15	28	30	1.66	0.95 - 2.88	3.64 (0.0564)
age ≥ 15	21	33	1.11	0.62 - 2.01	0.15 (0.7012)

* Current age *or* age at death *or* age when lost to follow-up.
** The comparison group is all other dogs.
*** Exact confidence limits.[128]

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Table 5.2. Sexes of 711 Cases of Canine Hypoadrenocorticism and 1,152 Controls from 1994 Survey in the United States of Veterinarians Enrolled in Clinical Trial

Sexes	Cases		Controls	
	Number	**Percent**	**Number**	**Percent**
Female-intact	37	5.2	157	13.6
Female-spayed	454	63.9	474	41.1
All females	491	69.1	631	54.8
Male-intact	73	10.3	272	23.6
Male-castrated	147	20.7	249	21.6
All males	220	30.9	521	45.2
All sexes	711	100.0	1,152	100.0

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Table 5.3. Sex-Specific Odds Ratios (OR) for Dogs with Hypoadrenocorticism from 1994 Survey in the United States of Veterinarians Enrolled in Clinical Trial

Sex*	Number of cases n=711	Number of controls n=1,152	OR	95% confidence interval for OR[49]	χ² statistic (p value) Uncorrected[40]
Female-intact	37	157	0.35	0.24 - 0.51	33.45 (< 0.0001)
Female-spayed	454	474	2.52	2.07 - 3.08	90.68 (< 0.0001)
Female-spayed**	454	474	4.06	2.74 - 6.06	57.88 (< 0.0001)
Female (intact and spayed)	491	631	1.84	1.51 - 2.25	37.18 (< 0.0001)
Male-intact	73	272	0.37	0.28 - 0.49	51.70 (< 0.0001)
Male-castrated	147	249	0.95	0.75 - 1.20	0.22 (0.6410)
Male-castrated***	147	249	2.20	1.56 - 3.10	22.50 (< 0.0001)
Neutered (either sex)	601	723	3.24	2.54 - 4.13	101.00 (< 0.0001)

* Except as noted, the comparison group is all other dogs.

** Female-spayed compared to female-intact.

*** Male-castrated compared to male-intact.

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Table 5.4. Sex-Specific Odds Ratios (OR) for Dogs (0 yr < Age < 5 yr) with Hypoadrenocorticism from 1994 Survey in the United States of Veterinarians Enrolled in Clinical Trial

Sex*	Number of cases n=81	Number of controls n=478	OR	95% confidence interval for OR[49]	χ^2 statistic (p value) Uncorrected[40]
Female-intact	6	108	0.26	0.09 - 0.65**	9.84 (0.0017)
Female-spayed	38	134	2.27	1.37 - 3.77	11.59 (0.0007)
Female-spayed***	38	134	5.10	2.03 - 15.26**	14.92 (0.0001)
Female (intact and spayed)	44	242	1.16	0.70 - 1.91	0.38 (0.5386)
Male-intact	11	141	0.38	0.18 - 0.76	8.86 (0.0029)
Male-castrated	26	95	1.91	1.10 - 3.29	6.10 (0.0135)
Male-castrated****	26	95	3.51	1.57 - 7.97	11.68 (0.0006)
Neutered (either sex)	64	229	4.09	2.26 - 7.50	26.87 (< 0.0001)

* Except as noted, the comparison group is all other dogs.

** Exact confidence limits. [128]

*** Female-spayed compared to female-intact.

**** Male-castrated compared to male-intact.

Table 5.5. Sex-Specific Odds Ratios (OR) for Dogs (5 yr $\leq$ Age < 10 yr) with Hypoadrenocorticism from 1994 Survey in the United States of Veterinarians Enrolled in Clinical Trial

Sex*	Number of cases n=323	Number of controls n=393	OR	95% confidence interval for OR[49]	χ^2 statistic (p value) Uncorrected[40]
Female-intact	15	32	0.55	0.28 - 1.07	3.54 (0.0600)
Female-spayed	202	190	1.78	1.31 - 2.44	14.41 (0.0001)
Female-spayed**	202	190	2.27	1.14 - 4.55	6.46 (0.0110)
Female (intact and spayed)	217	222	1.58	1.15 - 2.17	8.55 (0.0035)
Male-intact	36	73	0.55	0.35 - 0.86	7.58 (0.0059)
Male-castrated	70	98	0.83	0.58 - 1.20	1.05 (0.3050)
Male-castrated***	70	98	1.45	0.85 - 2.47	2.09 (0.1484)
Neutered (either sex)	272	288	1.94	1.32 - 2.87	12.42 (0.0004)

* Except as noted, the comparison group is all other dogs.

** Female-spayed compared to female-intact.

*** Male-castrated compared to male-intact.

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Table 5.6. Sex-Specific Odds Ratios (OR) for Dogs (Age ≥ 10 yr) with Hypoadrenocorticism from 1994 Survey in the United States of Veterinarians Enrolled in Clinical Trial

Sex*	Number of cases n=259	Number of controls n=255	OR	95% confidence interval for OR[49]	χ^2 statistic (p value) Uncorrected[40]
Female-intact	11	15	0.71	0.30 - 1.68	0.72 (0.3976)
Female-spayed	183	140	1.98	1.35 - 2.89	13.66 (0.0002)
Female-spayed**	183	140	1.78	0.74 - 4.30	2.01 (0.1566)
Female (intact and spayed)	194	155	1.93	1.30 - 2.86	11.75 (0.0006)
Male-intact	21	48	0.38	0.21 - 0.68	12.69 (0.0004)
Male-castrated	44	52	0.80	0.50 - 1.28	0.98 (0.3222)
Male-castrated***	44	52	1.93	0.96 - 3.91	3.99 (0.0459)
Neutered (either sex)	227	192	2.33	1.42 - 3.81	13.01 (0.0003)

* Except as noted, the comparison group is all other dogs.

** Female-spayed compared to female-intact.

*** Male-castrated compared to male-intact.

Breeds

Breeds were reported for 714 (99.3%) of the 719 cases (Table 5.7). The seven most frequently reported case breeds with number (%) were: Poodle 122 (17.1); Mixed 72 (10.1); Labrador Retriever 71 (9.9); German Shepherd 40 (5.6); Golden Retriever 32 (4.5); West Highland White Terrier 31 (4.3); and Rottweiler 24 (3.4).

Breeds were reported for 1,184 (99.3%) of the 1,192 controls (Table 5.7). The seven most frequently reported control breeds with number (%) were: Mixed 152 (12.8); Labrador Retriever 118 (10.0); German Shepherd 86 (7.3); Golden Retriever 68 (5.7); Cocker Spaniel 67 (5.7); Poodle 65 (5.5); and Shetland Sheepdog 33 (2.8). The number (%) of the seven most frequently reported case breeds among controls was (in the same order as listed above for cases): Poodle 65 (5.5); Mixed 152 (12.8); Labrador Retriever 118 (10.0); German Shepherd 86 (7.3); Golden Retriever 68 (5.7); West Highland White Terrier 9 (0.8); and Rottweiler 32 (2.7).

Breed-specific OR were calculated for all breeds for which there were at least five cases or five controls of the breed reported in the survey (Table 5.8).

Table 5.7. Breeds of 714 Cases of Hypoadrenocorticism and 1,184 Controls from 1994 Survey in the United States of Veterinarians Enrolled in Clinical Trial*

	Cases		Controls	
Breed	Number	Percent	Number	Percent
Airedale Terrier	14	2.0	9	0.8
Akita	5	0.7	4	0.3
Alaskan Malamute	7	1.0	6	0.5
Australian Shepherd	7	1.0	20	1.7
Basset Hound	20	2.8	10	0.8
Beagle	11	1.5	30	2.5
Bearded Collie	10	1.4	4	0.3
Bichon Frise	3	0.4	9	0.8
Border Collie	7	1.0	6	0.5
Boston Terrier	0	0.0	7	0.6
Boxer	1	0.1	14	1.2
Brittany	4	0.6	7	0.6
Chihuahua	5	0.7	10	0.8
Chow Chow	7	1.0	22	1.9
Cocker Spaniel	21	2.9	67	5.7
Collie	10	1.4	19	1.6
Dachshund	11	1.5	23	1.9
Dalmatian	0	0.0	14	1.2
Doberman Pinscher	8	1.1	25	2.1
English Bulldog	0	0.0	6	0.5
German Shepherd	40	5.6	86	7.3
German Shorthaired Pointer	15	2.1	10	0.8
Golden Retriever	32	4.5	68	5.7
Great Dane	18	2.5	4	0.3
Irish Setter	4	0.6	7	0.6
Jack Russell Terrier	0	0.0	5	0.4
Labrador Retriever	71	9.9	118	10.0
Lhasa Apso	3	0.4	22	1.9

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Table 5.7 (continued)

Breed	Cases		Controls	
	Number	Percent	Number	Percent
Maltese	5	0.7	19	1.6
Mixed	72	10.1	152	12.8
Pekingese	3	0.4	7	0.6
Pit Bull Terrier	0	0.0	9	0.8
Pomeranian	1	0.1	14	1.2
Poodle	122	17.1	65	5.5
Pug	0	0.0	6	0.5
Rottweiler	24	3.4	32	2.7
Saint Bernard	5	0.7	0	0.0
Schnauzer	11	1.5	25	2.1
Scottish Terrier	8	1.1	6	0.5
Shar Pei	2	0.3	8	0.7
Shetland Sheepdog	3	0.4	33	2.8
Shih Tzu	3	0.4	20	1.7
Siberian Husky	6	0.8	10	0.8
Spitz (American Eskimo)	1	0.1	11	0.9
Springer Spaniel	24	3.4	16	1.4
West Highland White Terrier	31	4.3	9	0.8
Yorkshire Terrier	2	0.3	23	1.9

* Breeds are included only if there were at least five cases or five controls of the breed reported in the survey.

Table 5.8. Breed-Specific Odds Ratios (OR) for Dogs with Hypoadrenocorticism from 1994 Survey in the United States of Veterinarians Enrolled in Clinical Trial*

Breed**	Number of cases n=714	Number of controls n=1,184	OR	95% confidence interval for OR[49]	χ^2 statistic (p value) Uncorrected[40]	Fisher exact (2-tailed p value)***[162]
Airedale Terrier	14	9	2.61	1.06 - 6.56	5.36 (0.0206)	
Akita	5	4	2.08	0.45 - 10.52****	1.24 (0.2655)	0.3098
Alaskan Malamute	7	6	1.94	0.56 - 7.03****	1.47 (0.2255)	0.2567
Australian Shepherd	7	20	0.58	0.20 - 1.43****	1.60 (0.2065)	
Basset Hound	20	10	3.38	1.50 - 7.79	10.96 (0.0009)	
Beagle	11	30	0.60	0.28 - 1.26	2.08 (0.1494)	
Bearded Collie	10	4	4.19	1.20 - 18.36****	6.87 (0.0088)	
Bichon Frise	3	9	0.55	0.10 - 2.22****	0.82 (0.3654)	0.5520
Border Collie	7	6	1.94	0.56 - 7.03****	1.47 (0.2255)	0.2567
Boston Terrier	0	7	0.00	0.00 - 1.15****	4.24 (0.0396)	0.0498
Boxer	1	14	0.12	0.00 - 0.77****	6.17 (0.0130)	
Brittany	4	7	0.95	0.20 - 3.74****	0.01 (0.9313)	1.0000
Chihuahua	5	10	0.83	0.22 - 2.67****	0.12 (0.7309)	
Chow Chow	7	22	0.52	0.19 - 1.28****	2.28 (0.1310)	
Cocker Spaniel	21	67	0.51	0.30 - 0.85	7.44 (0.0064)	
Collie	10	19	0.87	0.38 - 1.98	0.12 (0.7254)	
Dachshund	11	23	0.79	0.36 - 1.71	0.41 (0.5225)	
Dalmatian	0	14	0.00	0.00 - 0.50****	8.51 (0.0035)	

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Table 5.8 (continued)

Breed[**]	Number of cases n=714	Number of controls n=1,184	OR	95% confidence interval for OR[49]	χ^2 statistic (p value) Uncorrected[40]	Fisher exact (2-tailed p value)[***][162]
Doberman Pinscher	8	25	0.53	0.22 - 1.23	2.56 (0.1096)	
English Bulldog	0	6	0.00	0.00 - 1.41[****]	3.63 (0.0568)	0.0895
German Shepherd	40	86	0.76	0.50 - 1.13	1.98 (0.1590)	
German Shorthaired Pointer	15	10	2.52	1.06 - 6.06	5.41 (0.0200)	
Golden Retriever	32	68	0.77	0.49 - 1.21	1.42 (0.2334)	
Great Dane	18	4	7.63	2.50 - 31.09[****]	18.53 (< 0.0001)	
Irish Setter	4	7	0.95	0.20 - 3.74[****]	0.01 (0.9313)	1.0000
Jack Russell Terrier	0	5	0.00	0.00 - 1.81[****]	3.02 (0.0821)	0.1639
Labrador Retriever	71	118	1.00	0.72 - 1.38	0.00 (0.9875)	
Lhasa Apso	3	22	0.22	0.04 - 0.75[****]	7.09 (0.0078)	
Maltese	5	19	0.43	0.13 - 1.20[****]	2.92 (0.0876)	
Mixed	72	152	0.76	0.56 - 1.04	3.24 (0.0716)	
Pekingese	3	7	0.71	0.12 - 3.12[****]	0.25 (0.6180)	0.7515
Pit Bull Terrier	0	9	0.00	0.00 - 0.84[****]	5.45 (0.0195)	0.0165
Pomeranian	1	14	0.12	0.00 - 0.77[****]	6.17 (0.0130)	
Poodle	122	65	3.55	2.55 - 4.93	67.44 (< 0.0001)	
Pug	0	6	0.00	0.00 - 1.41[****]	3.63 (0.0568)	0.0895
Rottweiler	24	32	1.25	0.71 - 2.21	0.67 (0.4114)	

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Table 5.8 (continued)

Breed**	Number of cases n=714	Number of controls n=1,184	OR	95% confidence interval for OR[49]	χ² statistic (p value)	
					Uncorrected[40]	Fisher exact (2-tailed p value)***[162]
Saint Bernard	5	0	*****	*****	8.31 (0.0039)	0.0075
Schnauzer	11	25	0.73	0.33 - 1.55	0.78 (0.3771)	
Scottish Terrier	8	6	2.22	0.67 - 7.81****	2.29 (0.1301)	
Shar Pei	2	8	0.41	0.04 - 2.08****	1.33 (0.2488)	0.3367
Shetland Sheepdog	3	33	0.15	0.03 - 0.47****	13.41 (0.0003)	
Shih Tzu	3	20	0.25	0.05 - 0.83****	5.99 (0.0144)	
Siberian Husky	6	10	0.99	0.30 - 3.04****	0.00 (0.9922)	
Spitz (American Eskimo)	1	11	0.15	0.00 - 1.03****	4.41 (0.0357)	0.0377
Springer Spaniel	24	16	2.54	1.29 - 5.04	8.72 (0.0031)	
West Highland White Terrier	31	9	5.93	2.69 - 13.46	27.69 (< 0.0001)	
Yorkshire Terrier	2	23	0.14	0.02 - 0.58****	9.47 (0.0021)	

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* Breeds are included only if there were at least five cases or five controls of the breed reported in the survey.

** The comparison group is all other dogs.

*** Calculated only if an expected cell value is < 5; the preferred p value for this OR.

**** Exact confidence limits.[128]

***** Undefined.

Body Weights

Body weights were reported for 657 (91.4%) of the 719 cases (Figure 5.5).[w] The average body weight (kg) for cases was 24.5 (SD 14.5) (SEM 0.6) (Range 2.3 - 81.8). Body weights were reported for 1,111 (93.2%) of the 1,192 controls (Figure 5.6). The average body weight (kg) for controls was 19.7 (SD 12.7) (SEM 0.4) (Range 1.4 - 68.2). Body weight-specific OR were calculated for 5 kg body weight increments (Table 5.9).

Selected Clinical Findings Hypothetically Associated with Canine Hypoadrenocorticism

Odds ratios were calculated for clinical findings which were either anecdotally linked to hypoadrenocorticism or had a putative autoimmune etiology. Table 5.10 tabulates these results and relevant statistics. Since aging may affect the occurrence of many of these clinical findings, OR for clinical findings were calculated after stratifying the ages into five-year intervals (Tables 5.11-5.13).

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[w]The questionnaire simply asked the veterinarian to report "body weight," so the weight reported was, presumably, the most recently recorded body weight in the patient's medical record.
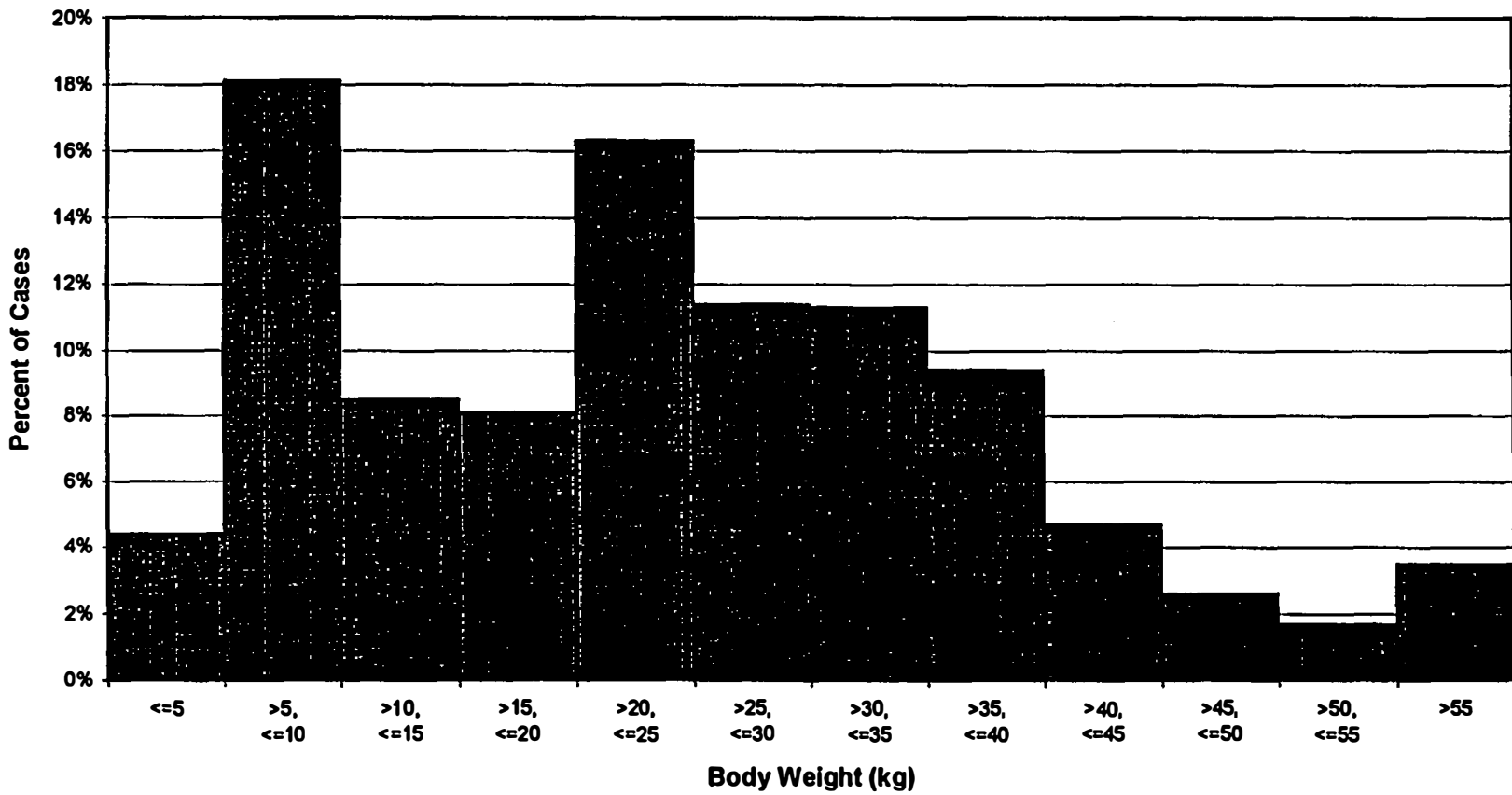
Figure 5.5. Body Weights of 657 Dogs with Hypoadrenocorticism from 1994 Survey in the United States of Veterinarians Enrolled in Clinical Trial
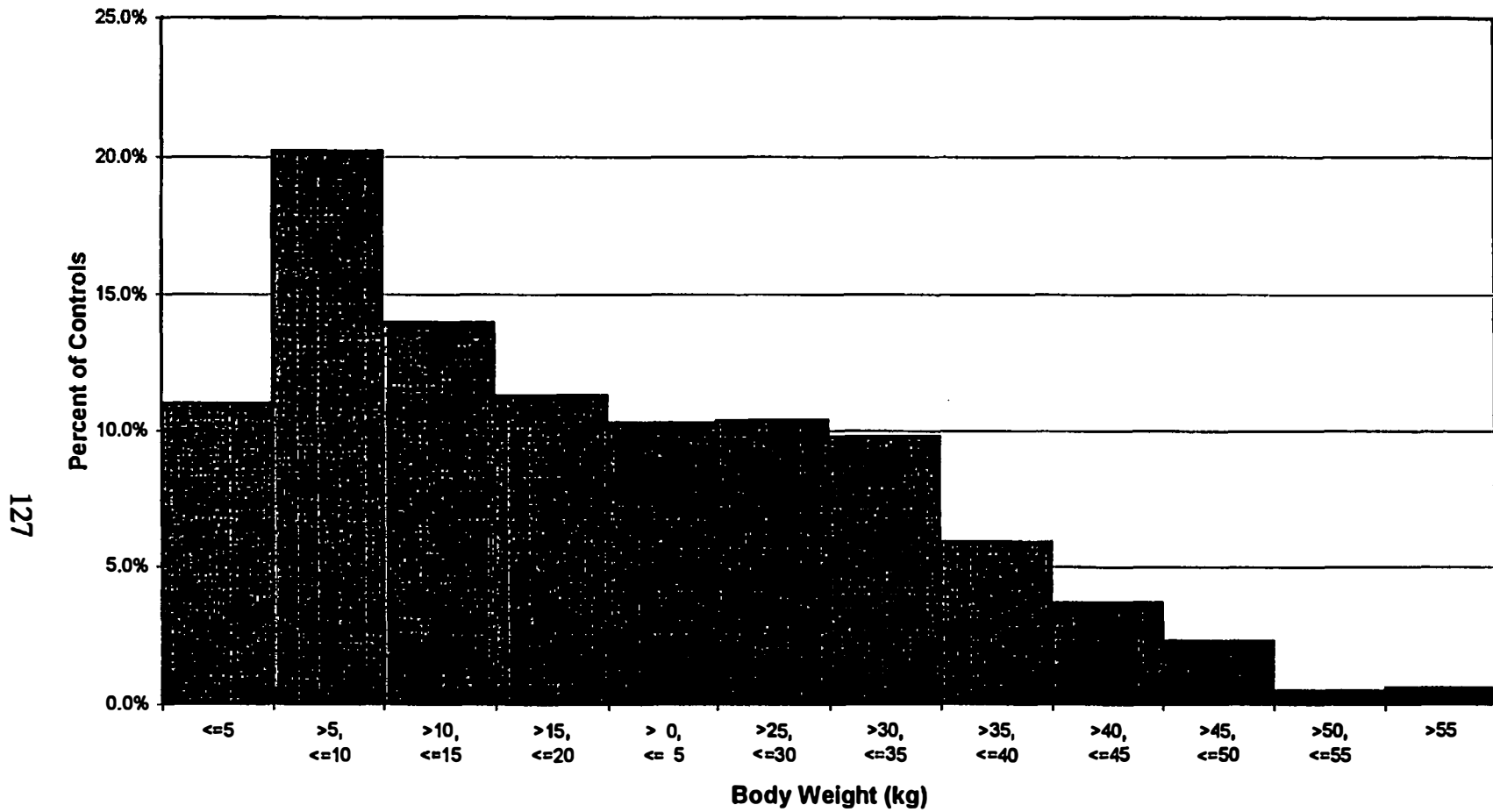
Figure 5.6. Body Weights of 1,111 Control Dogs from 1994 Survey in the United States of Veterinarians Enrolled in Clinical Trial

Table 5.9. Body Weight-Specific Odds Ratios (OR) for Dogs with Hypoadrenocorticism from 1994 Survey in the United States of Veterinarians Enrolled in Clinical Trial

Body weight interval (kg)*	Number of cases n=657	Number of controls n=1,111	OR	95% confidence interval for OR[49]	χ^2 statistic (p value) Uncorrected[40]
0 < weight ≤ 5	29	122	0.37	0.24 - 0.58	22.79 (< 0.0001)
5 < weight ≤ 10	119	224	0.88	0.68 - 1.13	1.11 (0.2923)
10 < weight ≤ 15	56	155	0.57	0.41 - 0.80	11.57 (0.0007)
15 < weight ≤ 20	53	125	0.69	0.49 - 0.98	4.62 (0.0315)
20 < weight ≤ 25	107	114	1.70	1.27 - 2.28	13.70 (0.0002)
25 < weight ≤ 30	75	116	1.11	0.80 - 1.52	0.41 (0.5236)
30 < weight ≤ 35	74	109	1.17	0.84 - 1.61	0.94 (0.3327)
35 < weight ≤ 40	62	66	1.65	1.13 - 2.40	7.51 (0.0061)
40 < weight ≤ 45	31	41	1.29	0.78 - 2.13	1.12 (0.2906)
45 < weight ≤ 50	17	26	1.11	0.57 - 2.14	0.11 (0.7443)
50 < weight ≤ 55	11	6	3.14	1.06 - 10.37**	5.58 (0.0182)
weight > 55	23	7	5.72	2.36 - 15.86**	20.40 (< 0.0001)

* The comparison group is all other dogs.

** Exact confidence limits.[128]

Table 5.10. Odds Ratios (OR) for Clinical Findings Associated with Hypoadrenocorticism in Dogs from 1994 Survey in the United States of Veterinarians Enrolled in Clinical Trial

Clinical finding*	Number of cases n=666	Number of controls n= 1,147	OR	95% confidence interval for OR[49]	χ^2 statistic (p value) Uncorrected[40]	Fisher exact (2-tailed p value)**[162]
Anemia	68	7	18.52	8.43 - 48.03***	97.92 (< 0.0001)	
Arthritis	105	80	2.50	1.81 - 3.44	35.54 (< 0.0001)	
Cruciate ligament rupture	17	13	2.28	1.05 - 5.02	5.21 (0.0224)	
Diabetes mellitus	5	4	2.16	0.46 - 10.93***	1.38 (0.2403)	0.3023
Hepatitis	29	7	7.41	3.15 - 20.14	30.35 (< 0.0001)	
Hypothyroidism	85	35	4.65	3.04 - 7.12	64.29 (< 0.0001)	
Keratoconjunctivitis sicca	18	9	3.51	1.49 - 8.49	10.57 (0.0012)	
Megaesophagus	3	1	5.19	0.41 - 272.46***	2.53 (0.1120)	0.1434
Myasthenia gravis	3	0	****	****	5.18 (0.0229)	0.0494
Nephritis	41	11	6.77	3.33 - 14.08	40.85 (< 0.0001)	
Thrombocytopenia	9	3	5.22	1.30 - 30.07***	7.61 (0.0058)	0.0119

* Clinical findings either anecdotally linked to hypoadrenocorticism or with a putative autoimmune etiology; comparison group is all other dogs.

** Calculated only if an expected cell value is < 5; the preferred p value for this OR.

*** Exact confidence limits.[128]

**** Undefined.

Table 5.11. Odds Ratios (OR) for Clinical Findings Associated with Hypoadrenocorticism in Dogs (0 yr < Age < 5 yr) from 1994 Survey in the United States of Veterinarians Enrolled in Clinical Trial

Clinical finding*	Number of cases n=79	Number of controls n=477	OR	95% confidence interval for OR[49]	χ^2 statistic (p value) Uncorrected[40]	Fisher exact (2-tailed p value)**[162]
Anemia	6	2	19.52	3.38 - 199.41***	24.61 (< 0.0001)	0.0002
Arthritis	5	8	3.96	0.99 - 14.12***	6.42 (0.0113)	0.0260
Cruciate ligament rupture	0	1	0.00	0.00 - 235.48***	0.17 (0.6838)	1.0000
Hepatitis	0	1	0.00	0.00 - 235.48***	0.17 (0.6838)	1.0000
Hypothyroidism	6	6	6.45	1.67 - 24.71***	12.89 (0.0003)	0.0031
Keratoconjunctivitis sicca	1	0	****	****	6.05 (0.0139)	0.1421
Megaesophagus	1	1	6.10	0.08 - 479.99***	2.11 (0.1464)	0.2642
Myasthenia gravis	1	0	****	****	6.05 (0.0139)	0.1421
Nephritis	2	1	12.36	0.63 - 730.86***	6.81 (0.0091)	0.0544
Thrombocytopenia	0	1	0.00	0.00 - 235.48***	0.17 (0.6838)	1.0000

* Clinical findings either anecdotally linked to hypoadrenocorticism or with a putative autoimmune etiology; comparison group is all other dogs; there were no cases or controls for diabetes mellitus.

** Calculated only if an expected cell value is < 5; the preferred p value for this OR.

*** Exact confidence limits.[128]

**** Undefined.

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Table 5.12. Odds Ratios (OR) for Clinical Findings Associated with Hypoadrenocorticism in Dogs (5 yr ≤ Age < 10 yr) from 1994 Survey in the United States of Veterinarians Enrolled in Clinical Trial

Clinical finding*	Number of cases n=307	Number of controls n=389	OR	95% confidence interval for OR[49]	χ^2 statistic (p value) Uncorrected[40]	Fisher exact (2-tailed p value)**[162]
Anemia	29	2	20.19	5.02 - 175.44***	32.17 (< 0.0001)	
Arthritis	27	15	2.40	1.20 - 4.84	7.38 (0.0066)	
Cruciate ligament rupture	5	5	1.27	0.29 - 5.58***	0.14 (0.7055)	0.7561
Diabetes mellitus	1	2	0.63	0.01 - 12.21***	0.14 (0.7064)	1.0000
Hepatitis	16	1	21.33	3.27 - 896.86***	17.68 (< 0.0001)	
Hypothyroidism	43	14	4.36	2.26 - 8.55	24.72 (< 0.0001)	
Keratoconjunctivitis sicca	7	1	9.05	1.15 - 409.05***	6.18 (0.0129)	
Megaesophagus	2	0	****	****	2.54 (0.1109)	0.1942
Myasthenia gravis	2	0	****	****	2.54 (0.1109)	0.1942
Nephritis	17	2	11.34	2.65 - 101.72***	16.31 (0.0001)	
Thrombocytopenia	5	1	6.42	0.71 - 304.60***	3.78 (0.0520)	0.0925

* Clinical findings either anecdotally linked to hypoadrenocorticism or with a putative autoimmune etiology; comparison group is all other dogs.

** Calculated only if an expected cell value is < 5; the preferred p value for this OR.

*** Exact confidence limits.[128]

**** Undefined.

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Table 5.13. Odds Ratios (OR) for Clinical Findings Associated with Hypoadrenocorticism in Dogs (Age ≥ 10 yr) from 1994 Survey in the United States of Veterinarians Enrolled in Clinical Trial

Clinical finding*	Number of cases n=249	Number of controls n=254	OR	95% confidence interval for OR[49]	χ^2 statistic (p value) Uncorrected[40]	Fisher exact (2-tailed p value)**[162]
Anemia	30	3	11.46	3.48 - 59.27***	24.22 (< 0.0001)	
Arthritis	67	53	1.40	0.91 - 2.15	2.53 (0.1120)	
Cruciate ligament rupture	12	6	2.09	0.71 - 6.90***	2.20 (0.1380)	
Diabetes mellitus	4	2	2.06	0.29 - 22.90***	0.72 (0.3976)	0.4462
Hepatitis	12	4	3.16	0.94 - 13.62***	4.30 (0.0382)	
Hypothyroidism	33	15	2.43	1.24 - 4.84	7.86 (0.0050)	
Keratoconjunctivitis sicca	9	8	1.15	0.40 - 3.34	0.08 (0.7730)	
Nephritis	19	6	3.41	1.28 - 10.61***	7.39 (0.0066)	
Thrombocytopenia	4	1	4.13	0.40 - 204.21***	1.88 (0.1704)	0.2123

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* Clinical findings either anecdotally linked to hypoadrenocorticism or with a putative autoimmune etiology; comparison group is all other dogs; there were no cases or controls for megaesophagus and myasthenia gravis.

** Calculated only if an expected cell value is < 5; the preferred p value for this OR.

*** Exact confidence limits.[128]

Logistic Regression

<u>General</u>

There were two objectives for the logistic regression: evaluating the relationship of age, breed, sex, and body weight with the occurrence of hypoadrenocorticism in the dog, and developing models which would predict the *relative* probability of hypoadrenocorticism in dogs. The response variable was dichotomous: the dog either had hypoadrenocorticism or did not. Next, unless otherwise noted, the word "significant" means that the factor, interaction, test, or model being evaluated had a p value less than 0.05. Finally, R^2 is "the proportion of the total uncertainty that is attributed to the model fit."[178] More specifically, it is the negative loglikelihood of the model divided by the negative loglikelihood of a model in which no effects were specified.[178]

<u>Factor Evaluation</u>

<u>Single factor models</u>. A model was fit for each of the individual independent variables--age, breed, sex, and body weight--and the response variable. In each of these models, the factor and the model itself (the words "factor" and "independent variable" are used interchangeably) were significant. The R^2 values were very low, ranging from 0.02 to 0.10.

The models for age and body weight each had significant lack of fit. Therefore, the following higher order models were fit: case = age age∗age, case

= age age★age age★age★age, case = body weight body weight★body weight, and case = body weight body weight★body weight body weight★body weight★body weight. The model case = age age★age still had a lack of fit problem, although only a borderline one (p=0.0423). The lack of fit problem disappeared in the case = age age★age age★age★age model (p=0.1605). (However, for the sake of parsimony, the cubic term involving age was not used in model development.) The lack of fit problem continued for both the higher order models using body weight as the independent variable. Detailed results are included in Appendix C1.

<u>Two factor models with no interactions</u>. A model was fit for each pair of the individual independent variables and the response variable. In each model, both factors considered singly and the model were significant. The R^2 values ranged from 0.07 to 0.17. Detailed results are included in Appendix C2.

<u>Two factor models with interactions</u>. A model was fit for each pair of the individual independent variables, plus the interaction involving those variables, and the response variable. In these models, the factors considered singly may or may not have been significant, but in no case was the interaction significant. The models were all significant. The R^2 values ranged from 0.07 to 0.18. Detailed results are included in Appendix C3.

<u>Three factor models with no interactions</u>. A model was fit for each combination of three of the independent variables and the response variable. In each of these models, all three factors considered singly and the model itself were

significant. The R^2 values ranged from 0.12 to 0.19. Detailed results are included in Appendix C4.

Three factor models with two-way interactions. A model was fit for each combination of three of the independent variables, plus all two-way interactions involving those variables, and the response variable. In these models, the factors considered singly may or may not have been significant, but no two-way interactions except two were significant. The exceptions were the age★sex interaction (p=0.0470) in the model case = age breed sex age★breed age★sex breed★sex, and the sex★body weight interaction (p=0.0327) in the model case = age sex body weight age★sex age★body weight sex★body weight. The age★sex interaction in the first model disappeared if dogs 1.5 yr old and younger were removed from the data set. It also disappeared if sex was categorized as just female and male, rather than female-intact, female-spayed, male-intact, and male-castrated. The models were all significant. The R^2 values ranged from 0.13 to 0.23. Detailed results are included in Appendix C5.

Three factor models with two- and three-way interactions. A model was fit for each combination of three of the independent variables, plus all two-way interactions and the one three-way interaction involving those variables, and the response variable. In these models, the factors considered singly were, with two exceptions, not significant. The two-way interactions were, with three exceptions, similarly not significant. Two of the four three-way interactions were significant;

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two were not. The models were all significant. The R^2 values ranged from 0.13 to 0.24. Detailed results are included in Appendix C6.

Model fitting. The results from more than 100 models were evaluated in choosing the two models which are presented below.[x] The final models were chosen to meet four criteria: the model itself had to be significant, each term in the model had to be significant, the model lack of fit had to be insignificant, and the model had to be reasonably parsimonious.

The factor evaluation described above provided a starting point for designing the two recommended models. First, the single factor models and the two factor models (with and without interactions) established that all factors were related to the response variable. Adding the quadratic term for age improved the model's fit, and, though the cubic term improved the fit more, the cubic term was not included because of respect for parsimony. Therefore, the following basic model was evaluated: case = age age$\star$age breed sex body weight. This model met all the selection criteria listed above. The model was significant ($p < 0.0001$). Each term in the model was significant (each at $p < 0.0001$). The model lack of fit was not significant ($p = 0.2692$). And, excepting the quadratic term for age, the model was as parsimonious as a model could be and still include all four factors. The R^2

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[x]It should be noted here that four factor--age, breed, sex, and body weight--models with all two- and three-way interactions included were beyond the computer's capability. Thus, they were not considered.

value for this model was 0.2418; but large R^2 values are rare in categorical models.[179] Appendix C7 includes more details about this model.

This model was then evaluated after the addition, *one at a time*, of all the two-way interactions: age⋆breed, age⋆sex, age⋆body weight, breed⋆sex, breed⋆body weight, and sex⋆body weight. Four of these six interactions were not significant, but two of them were: age⋆body weight (p = 0.0003) and sex⋆body weight (p = 0.0368). Based on these results, both of these interactions were added to the model above to yield a second useful model: case = age age⋆age breed sex body weight age⋆body weight sex⋆body weight. This model also met all the selection criteria. The model was significant (p < 0.0001). Each term in the model was significant (each at p < 0.0001, except sex at p = 0.0046, age⋆body weight at p = 0.0003, and sex⋆body weight at p = 0.0370). The model lack of fit was not significant (p = 0.3833). The R^2 value for this model was 0.2516. Appendix C7 includes more details about this model.

Discussion

Questionnaire Responses and Description of Veterinary Clinics

This was a large case control study involving questionnaires returned from 519 veterinarians, 494 separate veterinary clinics, 720 cases, and 1,192 controls. The response rate was 90.9%. The cases sampled probably do not represent the average veterinarian in clinical practice, nor veterinarians from veterinary referral

hospitals (Chapter 4). They probably represent veterinarians who are more diligent than the randomly selected veterinarians surveyed (Chapter 6) since they were submitted by private practitioners who went to the trouble of seeking DOCP and doing the administrative work associated with enrolling in the clinical trial.

Figure 5.1 reveals that 91.8% of the responses received were received within 60 da of the initial mailing. This is useful for planning similar future studies. A cutoff of responses at 60 da would seem reasonable.

The average veterinary clinic had 2.60 full-time veterinarians (Figure 5.2), and reported an average estimated number of dogs first diagnosed in 1993 of 1.23. If 2.60 full-time veterinarians see 1.23 newly diagnosed hypoadrenal dogs per yr, this suggested that the average small animal practitioner might see one-half case per yr. This probably underestimated the number of cases since one individual in each clinic filled out the questionnaire. This veterinarian, being asked for summary data about the entire practice, may not have been aware of all cases seen in the practice. Nevertheless, this one-half case per yr per veterinarian probably can serve as a useful benchmark. The average number of dogs seen per veterinarian per yr (individual dogs, not dog visits) of 1,504.7 could serve as a similar benchmark.

Incidence and Prevalence Estimates

The incidence estimate of 0.34 case/1000 dogs/yr and the prevalence estimate of 1.7 cases/1000 dogs suggested an approximate rate at which new cases may be acquired, and a rough indicator of how many cases a veterinarian might expect to be treating at any one time among all the dogs seen in the practice.

Ages

The mean age for hypoadrenal dogs was higher (8.7 yr) than the mean for control dogs (6.2 yr). Similarly, the average age for live hypoadrenal dogs (8.1 yr) exceeded that for live control dogs (6.1 yr).

Table 5.1 shows the ages of hypoadrenal patients which might be expected among a veterinarian's patient files. Compared to controls, dogs up to approximately 4 yr were less likely to have adrenal insufficiency than other dogs, those approximately 4 to 7 yr were about equally likely to be hypoadrenal, and those approximately 7 to 14 yr were more likely to have adrenal insufficiency. Dogs older than approximately 14 yr were about equally likely to be hypoadrenal compared to controls. This might be explained by the earlier death of hypoadrenal dogs when compared to controls.

The estimated average disease duration of 4.9 yr, coupled with the average age at death of 9.8 yr, suggested that hypoadrenal dogs can live long lives.

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Sexes

The assertion that canine hypoadrenocorticism is more frequent in female dogs[41,43,93,148,189] was confirmed. Females comprised 54.8% of controls, but 69.1% of cases (Table 5.2). The OR for female dogs compared to males was 1.84 with a 95% confidence interval of 1.51 to 2.25 (Table 5.3).

These data suggested that neutered animals were much more likely to be hypoadrenal. The OR for female-spayed dogs compared to female-intact dogs was 4.06 (95% confidence interval 2.74 - 6.06), and the OR for male-castrated dogs compared to male-intact dogs was 2.20 (95% confidence interval 1.56 - 3.10) (Table 5.3). The OR for female-intact dogs compared to all other dogs was 0.35 (95% confidence interval 0.24 - 0.51). These results suggested that female-intact dogs were less likely to have adrenal insufficiency than other dogs, and, specifically, female-spayed dogs. This contradicted another study.[148] The OR for female-spayed compared to all other dogs was 2.53 (95% confidence interval 2.07 - 3.08), and the OR for male-castrated dogs compared to other dogs was 0.95 (95% confidence interval 0.75 - 1.20). The OR for neutered dogs of either sex compared to intact dogs of either sex was 3.24 (95% confidence interval 2.54 - 4.13) (Table 5.3). Except for the comparison of male-castrated dogs with all other dogs, and this was mitigated by the comparison of male-castrated dogs with male-intact dogs, the comparisons above led to the conclusion that neutered dogs were at greater risk of disease. The possibility existed that other variables, such as age,

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may have perturbed these data and reduced (or enhanced) the predispositions of females and neutered dogs for the disease. To explore the possibility that age was affecting these associations, age-stratified analyses were conducted. The results generally confirmed the above conclusions.

That canine hypoadrenocorticism was more frequent in female dogs was supported by the data for female dogs 5 yr and older (Tables 5.5-5.6), but not for females less than 5 yr (Table 5.4). Age-stratified data suggested that neutered dogs of either sex were more likely than intact dogs to have adrenal insufficiency (Tables 5.4-5.6).

Overall, there was little evidence from age stratification that age perturbed the conclusions about the associations between sex and hypoadrenocorticism in the dog. Female or neutered dogs were more likely to be hypoadrenal than their male or intact kin.

Breeds

Tables 5.7 and 5.8 provide references for veterinarians and dog owners interested in whether or not a particular breed was represented among the cases or controls or both. Information about less common breeds has until now been difficult to come by. Table 5.8 indicated that, using an OR greater than one and a 95% confidence interval which did not include one as criteria, the following breeds were predisposed to hypoadrenocorticism: Airedale Terrier, Basset Hound,

Bearded Collie, German Shorthaired Pointer, Great Dane, Poodle, Springer Spaniel, and West Highland White Terrier. It indicated that, using the criteria of an OR less than one and a confidence interval which did not include one, the following breeds were less likely to be hypoadrenal than other breeds: Boxer, Cocker Spaniel, Dalmatian, Lhasa Apso, Pit Bull Terrier, Pomeranian, Shetland Sheepdog, Shih Tzu, and Yorkshire Terrier. Another study, using the statistical criterion of significance at the 0.05 level, found that Great Danes, Standard Poodles, and West Highland White Terriers were predisposed to hypoadrenocorticism, while Lhasa Apsos and Yorkshire Terriers were less likely to be hypoadrenal.[148] Using the more exacting significance level of less than 0.01 (p value of uncorrected chi-square statistic), the Basset Hound, Bearded Collie, Great Dane, Poodle, Springer Spaniel, and West Highland White Terrier were predisposed to the disease, while the Cocker Spaniel, Dalmatian, Lhasa Apso, Shetland Sheepdog, and Yorkshire Terrier were less likely to be afflicted. Table 5.7 suggested that, since there were five Saint Bernards in 714 cases and none in 1,184 controls, Saint Bernards were predisposed to the disease. Though the OR for Saint Bernards was undefined, the uncorrected chi-square statistic was significant at $p < 0.01$ (Table 5.8).

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Body Weights

The evaluation of body weights must be done with the understanding that reported body weights were likely an admixture of exact body weights determined by weighing the dogs, and less exact body weights estimated by veterinarians and their personnel. The latter should, nevertheless, be reasonably accurate. The statistical comparison of average body weight of cases (24.5 kg) with that of controls (19.7 kg) showed a difference ($p < 0.0005$) between these weights.

The body weight-specific OR (Table 5.9) suggested that canine hypoadrenocorticism was more likely in larger dogs. They suggested that small dogs (lighter than about 20 kg) were less likely to be hypoadrenal, that middle-sized dogs (from about 20 kg to about 50 kg) were neither more nor less likely to be hypoadrenal, and that large dogs (heavier than about 50 kg) were more likely to be hypoadrenal. The conclusions about small dogs and large dogs were supported by the data, while the conclusion about middle-sized dogs was not as compelling. Recognizing that this body weight effect might be confounded with other variables such as breed, body weight-specific OR were calculated in 10 kg increments for Mixed dogs. These OR did not demonstrate a body weight effect suggesting that body weight may be confounded with breed. Regarding one specific breed, though the Poodle was clearly predisposed to hypoadrenocorticism, it was the large Standard Poodle in which the predisposition has previously been reported.[11,44,192]

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Though not specifically related to canine hypoadrenocorticism, Figure 5.6 provided a profile of the body weights of dogs seen in clinical veterinary practice. About one dog in five (20.2%) weighed between 5 and 10 kg, and almost half (45.2%) weighed 15 kg or less. Only 1.1% were heavier than 50 kg.

Selected Clinical Findings Associated with Canine Hypoadrenocorticism

Before age stratification and based on OR and their 95% confidence intervals (Table 5.10), all the clinical findings except diabetes mellitus and megaesophagus were associated with hypoadrenocorticism; i.e., the OR were greater than one, and the 95% confidence interval did not include one.[y] After age (yr) stratification, the results were for the most part either confirmed or became equivocal, in most of the latter cases because the sample sizes dropped to a point that made demonstrating statistically significant associations difficult or impossible.

Anemia was associated with hypoadrenocorticism after age stratification: $0 < age < 5$, OR 19.52, Table 5.11; $5 \leq age < 10$, OR 20.19, Table 5.12); and $age \geq 10$, OR 11.46, Table 5.13. The uncorrected chi-square statistics were significant at less than 0.0001 for all these OR.

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[y]The OR for myasthenia gravis was undefined, but its uncorrected chi-square statistic and its two-tailed Fisher exact computation were each significant at $p < 0.05$.

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Arthritis was associated with hypoadrenocorticism before age stratification. Its OR was 2.50, significant at less than 0.0001 (Table 5.10) (here, and subsequently in this section, the significance levels will, unless otherwise stated, be for the uncorrected chi-square statistics). After age stratification, the association between hypoadrenocorticism and arthritis became equivocal. The OR were all greater than one, but for the age group $0 < age < 5$, the 95% confidence interval for the OR of 3.96 included one even though the uncorrected chi-square statistic was significant at less than 0.05 (Table 5.11) (this resulted here, and in a few other places later in this section, from different statistical techniques used to calculate the 95% confidence interval and the uncorrected chi-square statistic). For the age group $5 \leq age < 10$, the OR was 2.40, the 95% confidence interval did not include one, and the OR was significant at less than 0.01 (Table 5.12). For the age group $age \geq 10$, the OR was 1.40, the 95% confidence interval did include one, and the significance level was greater than 0.05 (Table 5.13). Therefore, the arthritis results suggested an association between hypoadrenocorticism and arthritis, but the association may or may not be perturbed by age.

Cruciate ligament rupture was not associated with hypoadrenocorticism after age stratification (Tables 5.11-5.13). Therefore, it was impossible to say whether or not the association between hypoadrenocorticism and cruciate ligament rupture was affected by age.

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Although the OR before age stratification for diabetes mellitus was 2.16, its 95% confidence interval included one, and its significance level was greater than 0.05 (Table 5.10). Thus, there was no evidence that diabetes mellitus and canine hypoadrenocorticism were associated.

Hepatitis was associated with hypoadrenocorticism before age stratification. Its OR was 7.41, significant at less than 0.0001 (Table 5.10). For the age group $0 < age < 5$, the OR was 0.00 (Table 5.11). For the age group $5 \leq age < 10$, the OR was 21.33, the 95% confidence interval did not include one, and the OR was significant at less than 0.0001 (Table 5.12). For the age group $age \geq 10$, the OR was 3.16, the 95% confidence interval did include one, but the significance level was less than 0.05 (Table 5.13). These results suggested an association between hepatitis and hypoadrenocorticism, but whether or not the association was affected by age remained unknown.

Hypothyroidism was associated with hypoadrenocorticism before age stratification (Table 5.10). For the age group $0 < age < 5$, the OR was 6.45, the 95% confidence interval did not include one, and the 2-tailed Fisher exact p value was 0.0031 (Table 5.11). For the age group $5 \leq age < 10$, the OR was 4.36, the 95% confidence interval did not include one, and the OR was significant at less than 0.0001 (Table 5.12). For the age group $age \geq 10$, the OR was 2.43, the 95% confidence interval did not include one, and the significance level of the OR was less than 0.05 (Table 5.13). Thus, there was evidence of an association

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between hypothyroidism and hypoadrenocorticism after age stratification. However, hypothyroidism is not unique to hypoadrenocorticism.

Keratoconjunctivitis sicca was associated with hypoadrenocorticism before age stratification (Table 5.10). For the age group $0 < \text{age} < 5$, the OR was undefined because there were no control dogs with keratoconjunctivitis sicca, but the p value for the uncorrected chi-square statistic was less than 0.05 (Table 5.11). For the age group $5 \leq \text{age} < 10$, the OR was 9.05, the 95% confidence interval did not include one, and the OR was significant at less than 0.05 (Table 5.12). For the age group $\text{age} \geq 10$, the OR was 1.15, the 95% confidence interval did include one, and the p value for the uncorrected chi-square statistic exceeded 0.05 (Table 5.13). These results suggested that keratoconjunctivitis sicca and hypoadrenocorticism were associated; the association was affected by age, and the effect disappeared as the dogs aged.

The OR before age stratification for megaesophagus was 5.19, its 95% confidence interval included one, and its significance level was greater than 0.05 (Table 5.10). Age stratification yielded no additional useful results (Tables 5.11-5.13).

Although the OR for myasthenia gravis was undefined, its two-tailed Fisher exact p value was less than 0.05 (Table 5.10). This suggested an association between myasthenia gravis and hypoadrenocorticism. Age stratification yielded no useful results because of small sample sizes.

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Nephritis was associated with hypoadrenocorticism before and after age stratification (Tables 5.10-5.13).

Thrombocytopenia was associated with adrenal insufficiency before age stratification (Table 5.10). For the age group $0 < age < 5$, the OR was 0.00 because there were no cases with thrombocytopenia (Table 5.11). For the age group $5 \leq age < 10$, the OR was 6.42, its 95% confidence interval included one, and its significance level was greater than 0.05 (Table 5.12). For the age group $age \geq 10$, the OR was 4.13, the 95% confidence interval included one, and the p value for the uncorrected chi-square statistic was greater than 0.05 (Table 5.13). Therefore, thrombocytopenia was associated with hypoadrenocorticism, but whether or not age or other variables were involved was unclear.

Logistic Regression

Several things must be understood before discussion of the logistic regression begins. The most important understanding is that the specific results in Appendices C1-C8 should be examined by the reader. While the discussion below attempts to describe and summarize, based on the logistic distribution, the effects of age, breed, sex, and body weight on the probability of occurrence of hypoadrenocorticism in dogs, the reader must understand that these relationships do not lend themselves to simple characterizations. So, while easy clear relationships can be sought, they are seldom found with this kind of data. Results

are always model-dependent. Conclusions should always be viewed skeptically, and a look at the specific results in the appendices is usually appropriate.

The R^2 values in this study were low, never getting above about 0.25. While this is expected since categorical models seldom yield high R^2 values,[179] it leaves many of the factors associated with canine hypoadrenocorticism completely undiscovered.

Next, the logistic regression model, like other models, is imperfect. While it is useful in describing biologic systems, and, while a better categorical model will seldom provide a better fit,[81] it is an imperfect description of how the world works. The reader should keep this in mind.

The reader should also be aware that the probabilities predicted from the models outlined in Appendix C7 are *relative,* not absolute. Probabilities calculated from the use of the estimated coefficients represent probabilities based on the data set extant. This data set is, of necessity, *not* a random one in terms of the number of cases vs. the number of controls. At a prevalence rate of 1.7 cases/1000 dogs, a data set large enough to include 30 hypoadrenal dogs would have to contain about 18,000 randomly selected dogs. This is impractical. Nevertheless, the probabilities are still useful. They can be used to compare *relative* probabilities. For example, the estimated probability of hypoadrenocorticism for a 4 yr old, female-spayed, 11 kg West Highland White Terrier is, using the case = age age⋆age breed sex body weight model, 0.74061. The probability for a 1 yr old,

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male-intact, 30 kg Boxer is, using the same model, 0.00001. While these probabilities mean *nothing* in the absolute sense, they say that the West Highland White Terrier is *relatively much* more likely to be diseased than the Boxer.

And, finally, the reader should remember that not all breeds were included in the logistic regression. The data set included 75 breeds, and the use of that many breeds in a categorical variable was impractical because of computational difficulties.

Given the above, interpretation of the results was straightforward. The factors age, breed, sex, and body weight were each associated with hypoadrenocorticism.[z] The single factor models (Appendix C1), the two factor models with no interactions (Appendix C2), and the three factor models with no interactions (Appendix C4) were evidence of this. The evidence for whether or not two-way interactions existed was muddier.

The two factor models with interactions (Appendix C3) suggested no significant two-way interactions. However, when a third factor was added, a significant age★sex interaction appeared in one model, and a significant sex★body weight interaction in another (Appendix C5). The three factor models with two- and three-way interactions included significant age★sex, breed★body weight, and sex★body weight interactions, again depending on the model specified. There were

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[z]Whether or not this association constituted causation is discussed in Appendix D.

significant *model-dependent* age★breed★sex and breed★sex★body weight interactions. Among the dozens of other models considered, there were also many which included significant two- and three-way interactions. So were there significant two- and three-way interactions? This question was not definitively answered. However, the second model selected included age★body weight and sex★body·weight interactions because they provided the best fit based on the model selection criteria.

Conclusions

1.   <u>Questionnaire Responses and Description of Veterinary Clinics</u>. The size (720 cases and 1,192 controls) of this study suggested that its results should be viewed as reasonably reliable. Over 90% of the questionnaire responses received were received within 60 da, indicating that a 60 da cutoff of responses would be reasonable for similar studies. In 1993, the veterinary clinics had an average 2.60 full-time veterinarians, and initially diagnosed 1.23 dogs with hypoadrenocorticism. A veterinarian in predominantly small animal practice might expect to initially diagnose about one-half case of canine hypoadrenocorticism per yr. The full-time small animal practitioners in this study saw about 1,500 dogs (individual dogs, not dog visits) per yr in 1993.

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2.   Incidence and Prevalence Estimates. The incidence (0.34 case/1000 dogs/yr) and prevalence (1.7 cases/1000 dogs) estimates for canine hypoadrenocorticism were lower than for veterinary referral hospitals (Chapter 4).

3.   Ages. On average, hypoadrenal dogs were older than control dogs, but the age at death was similar. This suggested that with proper medical management, hypoadrenal dogs may live a normal life span. The estimated average disease duration was 4.9 yr. Age-specific OR suggested that the risk of adrenal insufficiency increased with age.

4.   Sexes. Females, as previously reported,[41,43,93,148,189] were more likely to be hypoadrenal. Female-spayed dogs were more likely to be hypoadrenal than their intact counterparts, and male-castrated dogs were more likely to be hypoadrenal than intact ones. Thus, neutered dogs of either sex were more likely to have adrenal insufficiency than intact dogs. Other variables such as age may have perturbed these results. However, results after stratification by age generally supported the above conclusions.

5.   Breeds. Using an OR of greater than one and the absence of one in the 95% confidence interval as criteria, these breeds were predisposed to adrenal insufficiency: Airedale Terrier, Basset Hound, Bearded Collie, German Shorthaired Pointer, Great Dane, Poodle, Springer Spaniel, and West Highland White Terrier. Using the same criteria, except an OR less than one, these breeds were less likely to be hypoadrenal: Boxer, Cocker Spaniel, Dalmatian, Lhasa

Apso, Pit Bull Terrier, Pomeranian, Shetland Sheepdog, Shih Tzu, and Yorkshire Terrier. Using the more exacting criterion of a significance level of less than 0.01 (p value of uncorrected chi-square statistic), the Basset Hound, Bearded Collie, Great Dane, Poodle, Springer Spaniel, and West Highland White Terrier were more likely to have disease, while the Cocker Spaniel, Dalmatian, Lhasa Apso, Shetland Sheepdog, and Yorkshire Terrier were less likely. The results suggested that Saint Bernards were predisposed to the disease, and that Boston Terriers were less likely to be affected.

6. <u>Body Weights</u>. Small dogs were less likely to be hypoadrenal. Middle-sized dogs were neither more nor less likely to have adrenal insufficiency. Large dogs were more likely to be hypoadrenal.

7. <u>Selected Clinical Findings Associated with Canine Hypoadrenocorticism</u>. Anemia, hypothyroidism, and nephritis were associated with hypoadrenocorticism, and the association remained after age stratification.

Arthritis, cruciate ligament rupture, hepatitis, keratoconjunctivitis sicca, myasthenia gravis, and thrombocytopenia were all associated with hypoadrenocorticism, but the associations became equivocal after age stratification.

8. <u>Logistic Regression</u>. Age, breed, sex, and body weight were significantly associated with hypoadrenocorticism in the dog. The probability of occurrence of canine hypoadrenocorticism increased with age and body weight, was greater in females than males, was greater in neutered than intact dogs, and

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varied with breed. There was model-dependent evidence of higher order interactions; the exact nature of these interactions could not be determined. Models were selected which could predict the *relative* probability of this disease in different dogs.

CHAPTER 6

CASE CONTROL STUDY USING PATIENTS OF RANDOMLY SELECTED VETERINARIANS FROM THE AMERICAN VETERINARY MEDICAL ASSOCIATION'S LIST OF SMALL ANIMAL PRACTITIONERS

Introduction

While the case control study using the patients of veterinarians enrolled in the clinical trial (Chapter 5) introduced randomly selected control animals to the overall study, this group of veterinarians and their patients might be a biased sample. Veterinarians enrolled in the clinical trial had to enroll the dog with its attendant signatures, paperwork, restrictions on use of the drug, and other inconveniences. Consequently, a case control study of randomly selected veterinarians was developed.

Methods

The American Veterinary Medical Association (AVMA) maintains a list of veterinarians in the United States which includes AVMA members and nonmembers. Veterinarians on the list self-classify themselves as to principal

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occupation within the profession such as small animal practitioners, large animal practitioners, practitioners in mixed practice, academics, and military veterinarians. From the AVMA list, 1,000 veterinarians were randomly selected who had classified themselves as either exclusively small animal practitioners or as practitioners in mixed practice whose patients were predominantly small animals.

A questionnaire with instructions (Appendices A8 and A9) was designed to query these veterinarians about cases of hypoadrenocorticism and controls. The cases were hypoadrenal dogs diagnosed by the veterinarians. The control was the next dog in the veterinarian's patient record file owned by a different client. Whether the control dogs were sick or well was not considered. The method of Dillman,[35] slightly abbreviated, was used to distribute the questionnaires. A reminder letter was sent to the veterinarians approximately one week after the first mailing, and another mailing with two more questionnaires and a cover letter was made to those not known to have responded approximately four weeks after the first mailing.

The questionnaire requested the number of dogs (not dog visits) seen in the veterinary practice in 1993, and the age, breed, sex, body weight, and selected clinical findings for cases and controls. These data were used to calculate odds ratios (OR).

Confidence intervals for OR were calculated using Cornfield's approximation.[49] If Cornfield confidence limits were inexact, exact confidence

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limits were calculated.[128] Uncorrected chi-square statistics were reported.[40] Fisher exact probability calculations for 2x2 contingency tables were calculated when the expected value of a cell was less than five.[162] Appendix B contains further details regarding these calculations. Body weights for cases and controls were compared using a technique for comparing means of unequal variances.[130]

Dogs were frequently reported as simply "Poodle" or "Schnauzer" without size specification. Therefore, all Poodles have been combined as one breed, and all Schnauzers have been combined as one breed.

The selected clinical findings were chosen because of their anecdotal association with canine hypoadrenocorticism, or their putative autoimmune etiology. The list of selected clinical findings is not exhaustive.

Results

Questionnaire Responses and Description of Veterinary Clinics

Five hundred fifty-five (55.5%) of the 1,000 veterinarians returned questionnaires which included a total of 151 cases and 141 controls. The first response was received 3 da after the first mailing, and the last response was received 116 da after. Figure 6.1 graphs the number of responses received vs. time after the initial mailing. Forty-eight (8.6%) of the responses were excluded because no useful data were received, usually because the veterinarian saw no dogs during 1993. The reasons for excluding responses are catalogued in Table 6.1.

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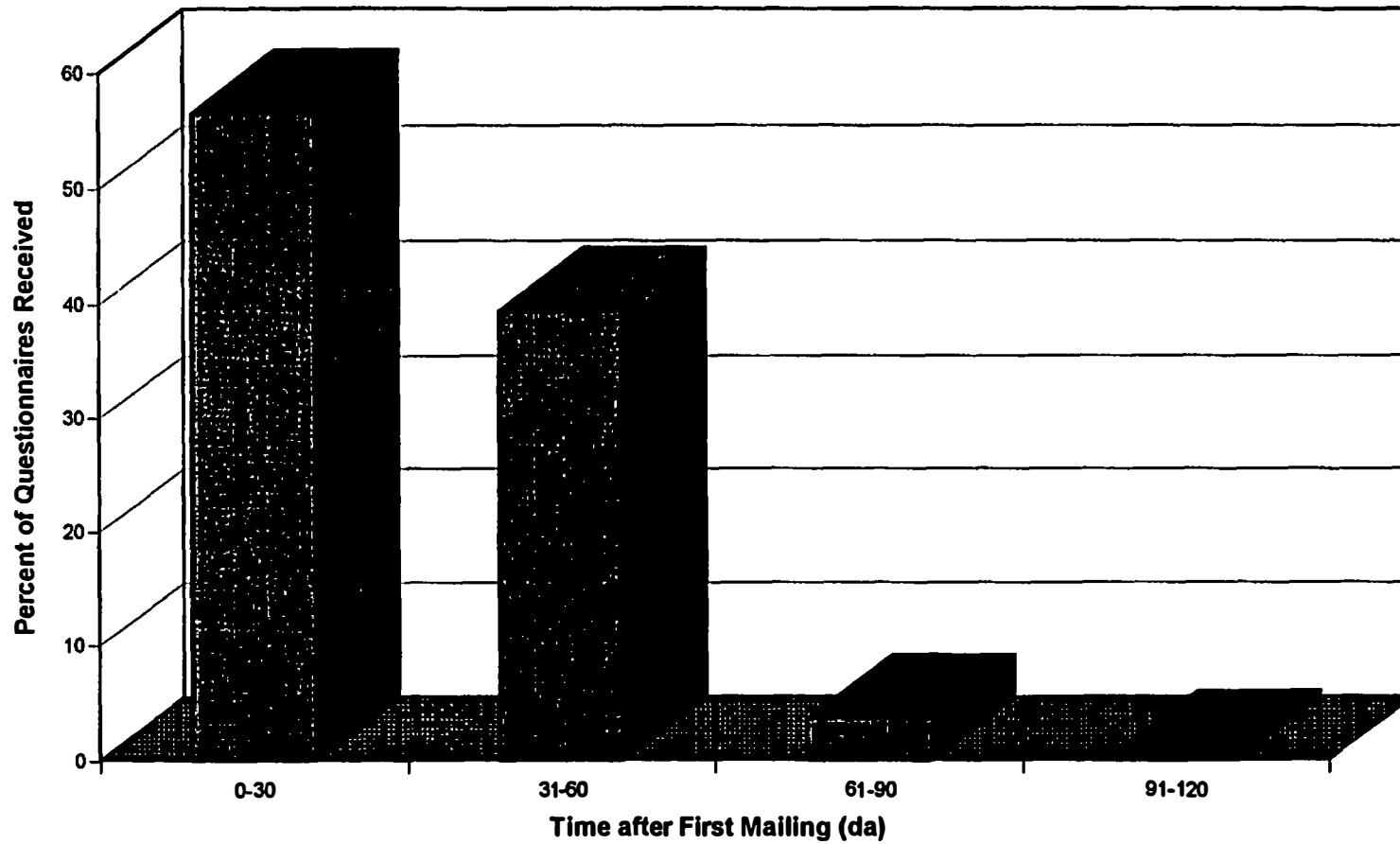
Figure 6.1. Time Questionnaires Received After First Mailing from 1994 Survey of Randomly Selected Veterinarians in the United States

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Table 6.1. Reasons for Excluding 48 Questionnaires from 1994 Survey of Randomly Selected Veterinarians in the United States

Reason	Number	Percent
1994 graduate	3	6.3
Cats-only practice	6	12.5
Consultant	3	6.3
Miscellaneous	6	12.5
No access to records	7	14.6
Not in practice	17	35.4
Referral practice	2	4.2
Retired	1	2.1
University employee	3	6.3
Total	48	100.2

Four hundred ninety-five veterinarians reported 1,050 full-time veterinarians in 495 clinics for an average number of full-time veterinarians per clinic of 2.1 (SD 1.3) (SEM[aa] 0.1) (Range 1.0 - 9.0). Figure 6.2 plots the number of full-time veterinarians in the clinics vs. the percent of individual clinics employing that number of full-time veterinarians.

Four hundred fifty-six of the veterinarians reported the number of dogs diagnosed in 1993 and the estimated number of active dog patients[bb] seen. The estimate of hypoadrenal dogs diagnosed for 1993 was 159 divided by the 456 veterinary clinics for a mean of 0.35 dogs diagnosed per clinic (SD 0.8) (SEM 0.04) (Range 0.0 - 10.0). These 456 clinics estimated 1,246,229 active dog patients during 1993. Four hundred ninety-one veterinarians reported the number of dogs diagnosed in 1993 and the number of full-time veterinarians employed in their practices. The average number of dogs diagnosed per full-time veterinarian was 0.17 (SD 0.41) (SEM 0.02) (Range 0.00 - 3.33). Four hundred fifty-one veterinarians reported the number of active dog patients in 1993 and the number of full-time veterinarians employed. The average number of active dog patients seen per full-time veterinarian was 1455.6[cc] (SD 1,156.3) (SEM 54.4) (Range 25.0 - 11,000.0).

[aa]Standard error of the mean (SEM) equals the standard deviation (SD) divided by the square root of the sample size.

[bb]An active dog patient was a dog seen in the practice in 1993. Dogs were counted only once, even if several visits to the hospital were made in 1993.

[cc]This was similar to the estimate of 1,600 dogs seen per veterinarian per yr obtained on July 29, 1996 from personal communication with Dr. J. Karl Wise, Center for Information Management, American Veterinary Medical Association.
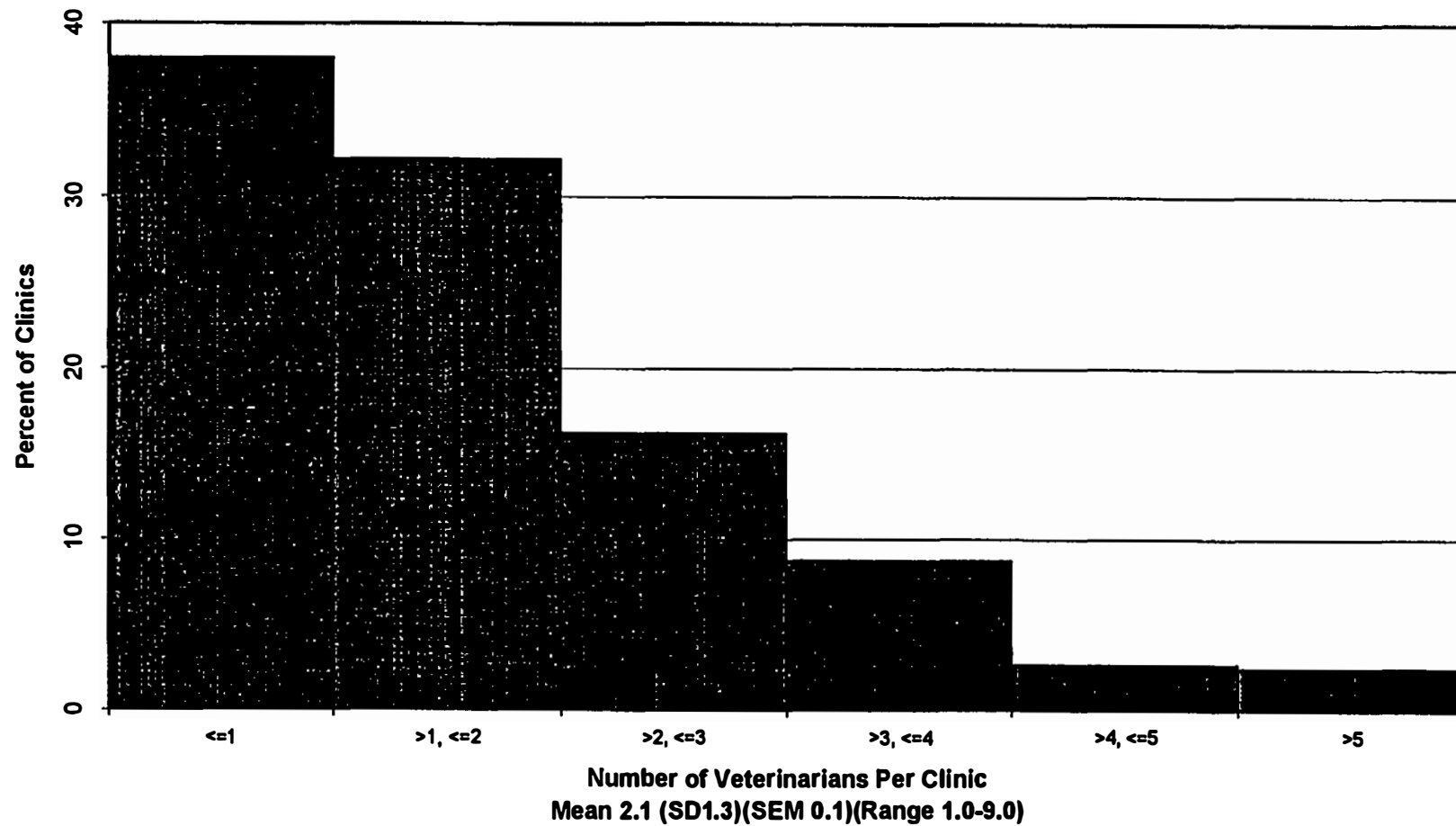
Figure 6.2. Number of Veterinarians Per Clinic from 1994 Survey of Randomly Selected Veterinarians in the United States

Incidence and Prevalence Estimates

Incidence was estimated at 0.13 case/1000 dogs/yr by dividing the estimate of 159 cases in 1993 by the estimate of the total number of active dog patients of 1,246,229.

A prevalence estimate of 0.6 case/1000 dogs was obtained by multiplying 0.13 case/1000 dogs/yr times the average disease duration estimate of 4.9 yr (see Chapter 5) using the formula:[3,98,120,123,168,200,215,239]

Prevalence = (Incidence) (Average disease duration)

Ages

Ages at diagnosis were reported for 149 (98.7%) of the 151 cases. These ages are, notably, differently defined from the current age *or* age at death *or* age when lost to follow-up used in Chapter 5. The mean age was 6.7 yr (SD 3.7) (SEM 0.3) (Range 0.5 - 16.0). These ages are displayed in Figure 6.3. Of these 149 cases, 114 (76.5%) were alive, 27 (18.1%) were dead, 6 (4.0%) were lost to follow-up, and 2 (1.3%) were of unknown status. The average age at diagnosis of the live dogs was 6.5 yr (SD 3.8) (SEM 0.4) (Range 0.5 - 16.0). The average age at diagnosis of the dead dogs was 7.9 yr (SD 3.2) (SEM 0.6) (Range 0.5 - 14.0). The average age at diagnosis of the dogs lost to follow-up was 4.3 yr (SD 2.4) (SEM 1.0) (Range 2.0 - 8.0).
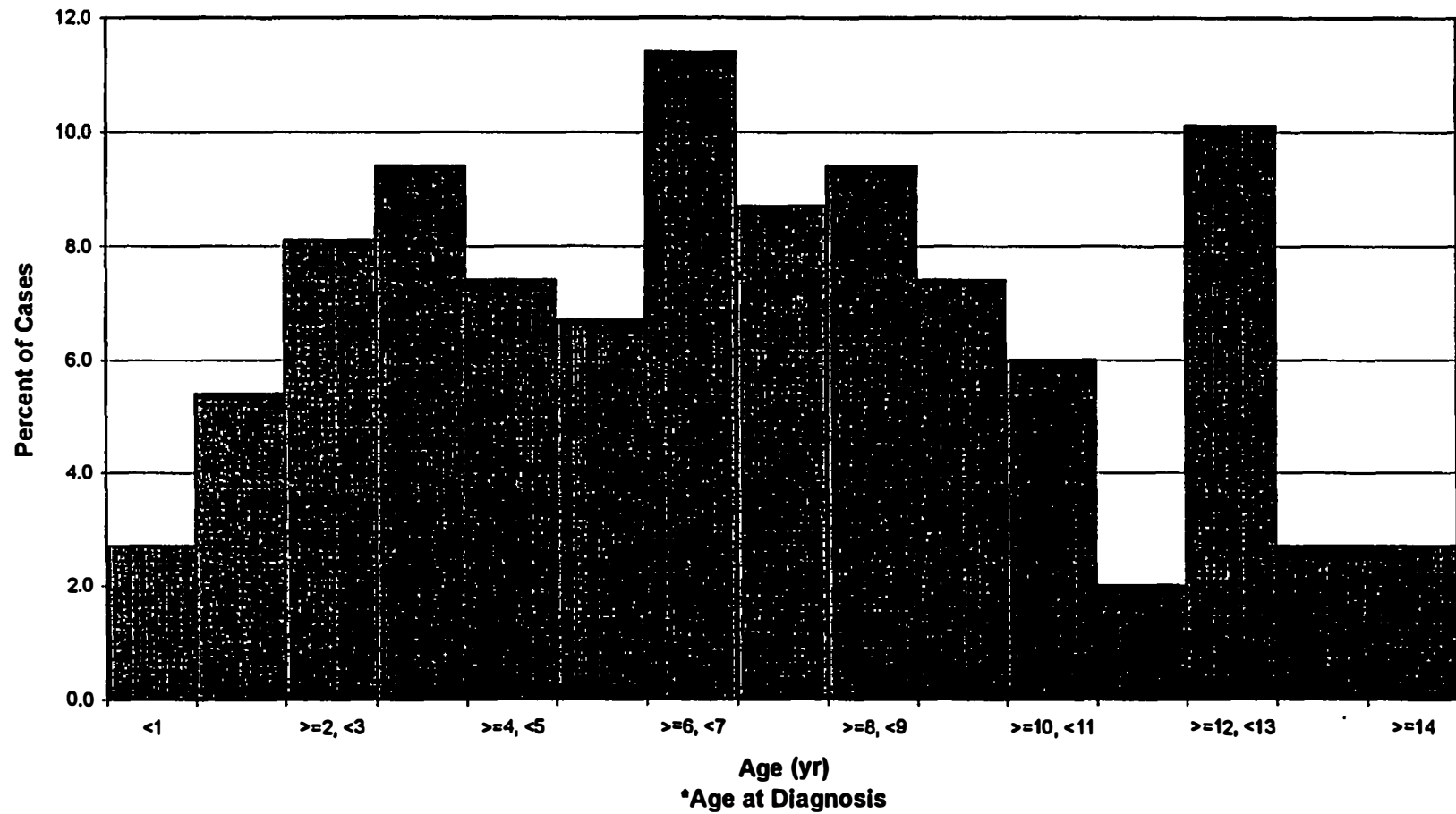
Figure 6.3. Ages* of 149 Dogs with Hypoadrenocorticism from 1994 Survey of Randomly Selected Veterinarians in the United States

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Age was reported for 138 (97.9%) of the 141 controls. The mean age was 5.6 yr (SD 3.6) (SEM 0.3) (Range 0.2 - 16.0). These ages are displayed in Figure 6.4. Of these 138 controls, 130 (94.2%) were alive, 2 (1.4%) were dead, 4 (2.9%) were lost to follow-up, and 2 (1.4%) were of unknown status. The average age of live dogs was 5.5 yr (SD 3.6) (SEM 0.3) (Range 0.2 - 15.0). The sample sizes for dead dogs (two) and dogs lost to follow-up (four) were so small that averages for these groups were not meaningful.

Age-specific OR with relevant statistics are presented in Table 6.2.

Sexes

Sex was reported for 147 (97.4%) of the 151 cases, and 139 (98.6%) of the 141 controls (Table 6.3). Sex-specific OR were calculated with 95% confidence intervals, chi-square statistics, and significance levels (p values) for the chi-square statistics (Table 6.4).

Breeds

Breeds were reported for 149 (98.7%) of the 151 cases (Table 6.5). The seven most frequently reported case breeds with number (%) were: Poodle 22 (14.8); Mixed 15 (10.1); German Shepherd 11 (7.4); Labrador Retriever 8 (5.4); Cocker Spaniel 6 (4.0); Rottweiler 6 (4.0); and Schnauzer 6 (4.0).
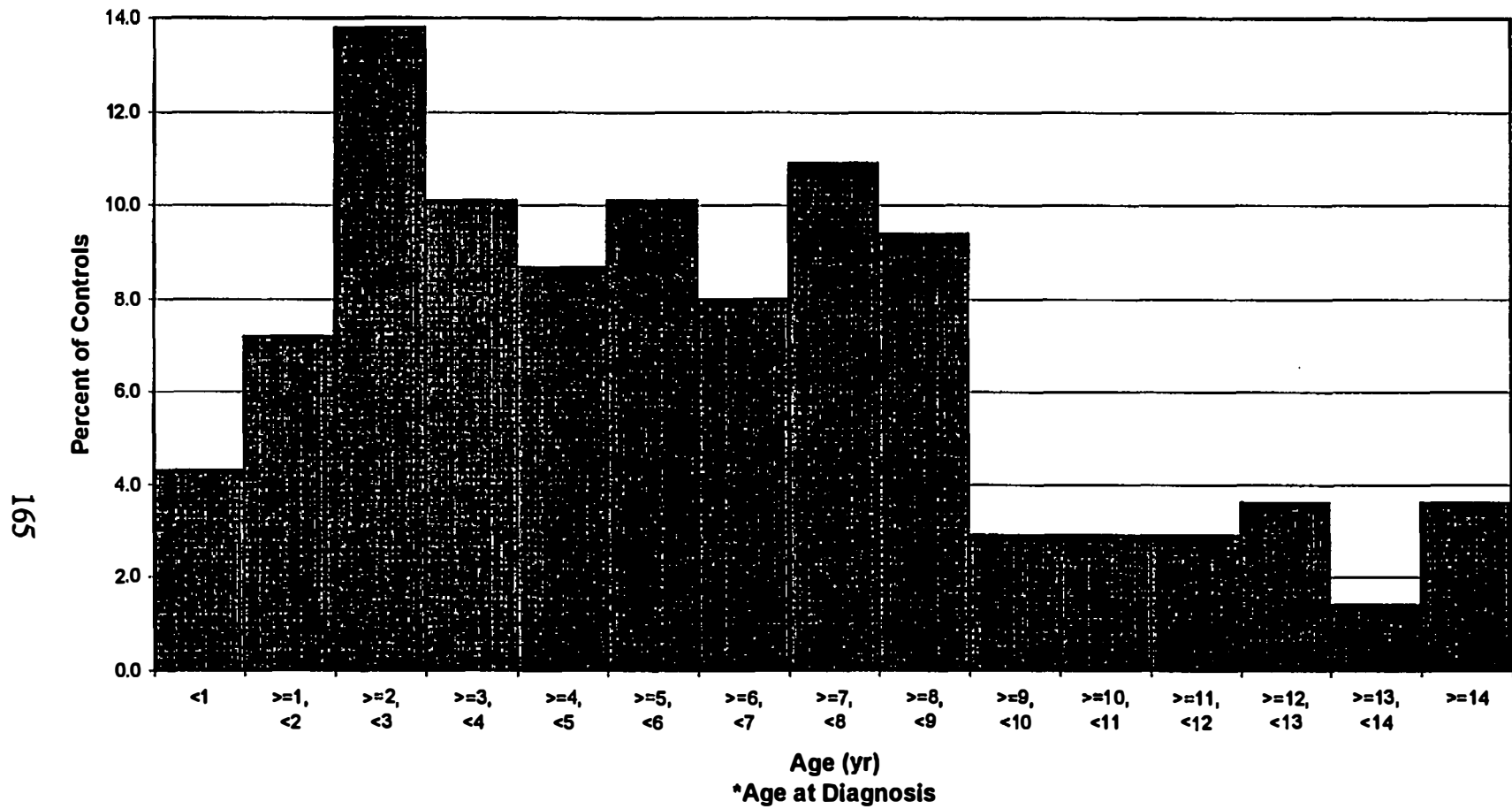
Figure 6.4. Ages* of 138 Control Dogs from 1994 Survey of Randomly Selected Veterinarians in the United States

Table 6.2. Age*-Specific Odds Ratios (OR) for Dogs with Hypoadrenocorticism from 1994 Survey of Randomly Selected Veterinarians in the United States

Age interval (yr)**	Number of cases n=149	Number of controls n=138	OR	95% confidence interval for OR[49]	χ^2 statistic (p value) Uncorrected[40]
0 < age < 5	49	61	0.62	0.37 - 1.03	3.88 (0.0488)
5 ≤ age < 10	65	57	1.10	0.67 - 1.81	0.16 (0.6912)
age ≥ 10	35	20	1.81	0.95 - 3.48	3.74 (0.0530)

* Age at diagnosis.

** The comparison group is all other dogs.

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Table 6.3. Sexes of 147 Cases of Canine Hypoadrenocorticism and 139 Controls from 1994 Survey of Randomly Selected Veterinarians in the United States

Sexes	Cases		Controls	
	Number	Percent	Number	Percent
Female-intact	4	2.7	17	12.2
Female-spayed	78	53.1	68	48.9
All females	82	55.8	85	61.2
Male-intact	22	15.0	21	15.1
Male-castrated	43	29.3	33	23.7
All males	65	44.2	54	38.8
All sexes	147	100.0	139	100.0

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Table 6.4. Sex-Specific Odds Ratios (OR) for Dogs with Hypoadrenocorticism from 1994 Survey of Randomly Selected Veterinarians in the United States

Sex*	Number of cases n=147	Number of controls n=139	OR	95% confidence interval for OR[49]	χ^2 statistic (p value) Uncorrected[40]
Female-intact	4	17	0.20	0.05 - 0.64****	9.50 (0.0021)
Female-spayed	78	68	1.18	0.72 - 1.93	0.49 (0.4839)
Female-spayed**	78	68	4.88	1.48 - 20.70****	8.68 (0.0032)
Female (intact and spayed)	82	85	0.80	0.49 - 1.32	0.85 (0.3572)
Male-intact	22	21	0.99	0.49 - 1.99	0.00 (0.9732)
Male-castrated	43	33	1.33	0.76 - 2.33	1.11 (0.2917)
Male-castrated***	43	33	1.24	0.55 - 2.82	0.33 (0.5686)
Neutered (either sex)	121	101	1.75	0.96 - 3.20	3.83 (0.0503)

* Except as noted, the comparison group is all other dogs.

** Female-spayed compared to female-intact.

*** Male-castrated compared to male-intact.

**** Exact confidence limits.[128]

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Table 6.5. Breeds of 149 Cases of Hypoadrenocorticism and 140 Controls from 1994 Survey of Randomly Selected Veterinarians in the United States*

Breed	Cases		Controls	
	Number	Percent	Number	Percent
Akita	3	2.0	0	0.0
Australian Shepherd	2	1.3	5	3.6
Basset Hound	5	3.4	0	0.0
Beagle	3	2.0	2	1.4
Bearded Collie	2	1.3	0	0.0
Boston Terrier	3	2.0	2	1.4
Brittany	2	1.3	1	0.7
Cairn Terrier	2	1.3	0	0.0
Chihuahua	1	0.7	3	2.1
Chow Chow	3	2.0	2	1.4
Cocker Spaniel	6	4.0	9	6.4
Dachshund	3	2.0	0	0.0
Doberman Pinscher	3	2.0	3	2.1
German Shepherd	11	7.4	13	9.3
Golden Retriever	4	2.7	8	5.7
Great Dane	3	2.0	0	0.0
Great Pyrennes	2	1.3	0	0.0
Labrador Retriever	8	5.4	15	10.7
Lhasa Apso	1	0.7	3	2.1
Mixed	15	10.1	28	20.0
Pomeranian	2	1.3	2	1.4
Poodle	22	14.8	13	9.3
Rottweiler	6	4.0	4	2.9
Schnauzer	6	4.0	2	1.4
Scottish Terrier	3	2.0	0	0.0
Shetland Sheepdog	1	0.7	2	1.4
Shih Tzu	2	1.3	2	1.4
Springer Spaniel	5	3.4	2	1.4
Welsh Corgi	2	1.3	0	0.0
West Highland White Terrier	3	2.0	0	0.0

* Breeds are included only if there were at least two cases or two controls of the breed reported in the survey.

Breeds were reported for 140 (99.3%) of the 141 controls (Table 6.5). The seven most frequently reported control breeds with number (%) were: Mixed 28 (20.0); Labrador Retriever 15 (10.7); German Shepherd 13 (9.3); Poodle 13 (9.3); Cocker Spaniel 9 (6.4); Golden Retriever 8 (5.7); and Australian Shepherd 5 (3.6). The number (%) of each of the most frequently reported case breeds among controls was (in the same order as listed above for cases) Poodle 13 (9.3); Mixed 28 (20.0); German Shepherd 13 (9.3); Labrador Retriever 15 (10.7); Cocker Spaniel 9 (6.4); Rottweiler 4 (2.9); and Schnauzer 2 (1.4).

Breed-specific OR were calculated for all breeds for which there were at least five cases or five controls. These OR are reported in Table 6.6.

Body Weights

Body weights were reported for 149 (98.7%) of the 151 cases (Figure 6.5). The average body weight (kg) for cases was 20.2 (SD 14.1) (SEM 1.2) (Range 1.1 - 63.6). Body weights were reported for 140 (99.3%) of the 141 controls (Figure 6.6). The average body weight (kg) for controls was 19.8 (SD 13.5) (SEM 1.1) (Range 1.4 - 74.1). Body weight-specific OR were calculated for 5 kg body weight increments (Table 6.7).

Table 6.6. Breed-Specific Odds Ratios (OR) for Dogs with Hypoadrenocorticism from 1994 Survey of Randomly Selected Veterinarians in the United States*

Breed**	Number of cases n=149	Number of controls n=140	OR	95% confidence interval for OR[49]	χ^2 statistic (p value) Uncorrected[40]	Fisher exact (2-tailed p value)***[162]
Australian Shepherd	2	5	0.37	0.03 - 2.30****	1.52 (0.2180)	0.2698
Basset Hound	5	0	*****	*****	4.78 (0.0288)	0.0609
Cocker Spaniel	6	9	0.61	0.17 - 1.98****	0.85 (0.3577)	
German Shepherd	11	13	0.78	0.31 - 1.93	0.34 (0.5579)	
Golden Retriever	4	8	0.46	0.10 - 1.75****	1.66 (0.1970)	
Labrador Retriever	8	15	0.47	0.18 - 1.24	2.82 (0.0934)	
Mixed	15	28	0.45	0.22 - 0.92	5.62 (0.0177)	
Poodle	22	13	1.69	0.77 - 3.73	2.04 (0.1536)	
Rottweiler	6	4	1.43	0.33 - 7.02****	0.30 (0.5866)	0.7508
Schnauzer	6	2	2.90	0.51 - 29.71****	1.81 (0.1785)	0.2841
Springer Spaniel	5	2	2.40	0.38 - 25.48****	1.13 (0.2869)	0.4490

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* Breeds are included only if there were at least five cases or five controls of the breed reported in the survey.

** The comparison group is all other dogs.

*** Calculated only if an expected cell value is < 5; the preferred p value for this OR.

**** Exact confidence limits.[128]

***** Undefined.
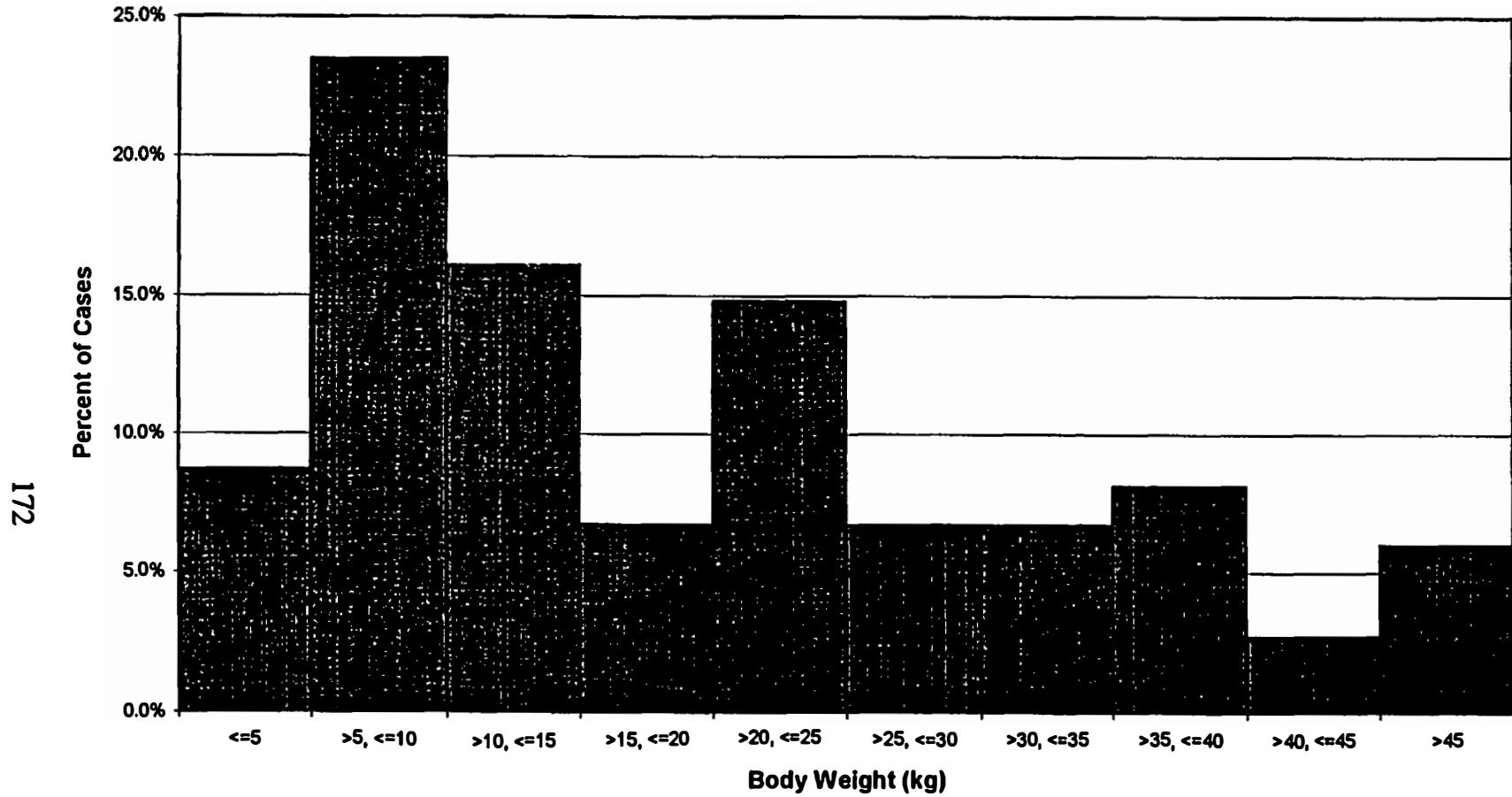
Figure 6.5. Body Weights of 149 Dogs with Hypoadrenocorticism from 1994 Survey of Randomly Selected Veterinarians in the United States
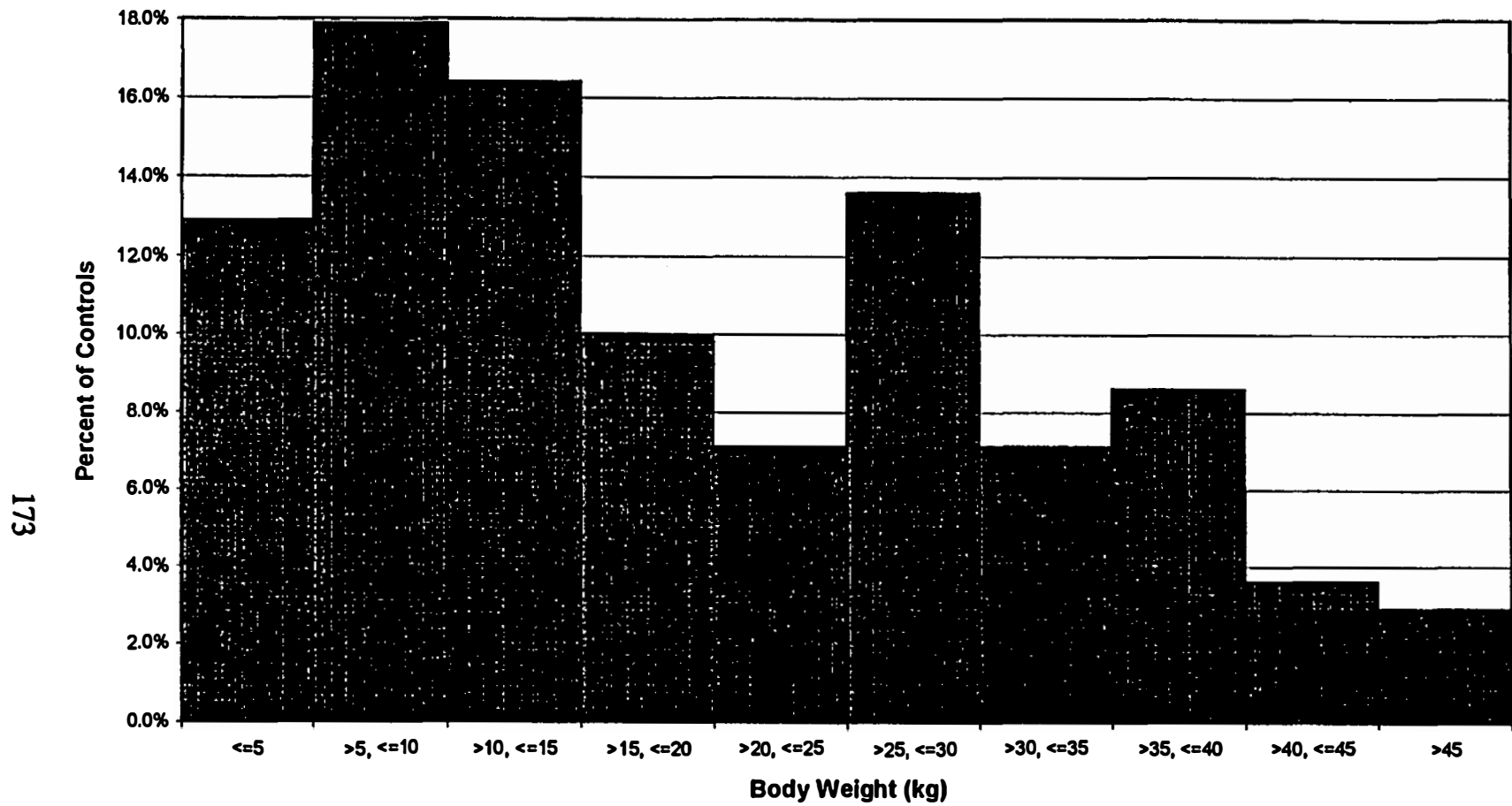
Figure 6.6. Body Weights of 140 Control Dogs from 1994 Survey of Randomly Selected Veterinarians in the United States

Table 6.7. Body Weight-Specific Odds Ratios (OR) for Dogs with Hypoadrenocorticism from 1994 Survey of Randomly Selected Veterinarians in the United States*

Body weight interval (kg)*	Number of cases n=149	Number of controls n=140	OR	95% confidence interval for OR[49]	χ^2 statistic (p value) Uncorrected[40]	Fisher exact (2-tailed p value)**[162]
0 < weight ≤ 5	13	18	0.65	0.29 - 1.46	1.29 (0.2566)	
5 < weight ≤ 10	35	25	1.41	0.77 - 2.61	1.39 (0.2380)	
10 < weight ≤ 15	24	23	0.98	0.50 - 1.91	0.01 (0.9411)	
15 < weight ≤ 20	10	14	0.65	0.26 - 1.62	1.03 (0.3113)	
20 < weight ≤ 25	22	10	2.25	0.97 - 5.33	4.26 (0.0390)	
25 < weight ≤ 30	10	19	0.46	0.19 - 1.09	3.76 (0.0524)	
30 < weight ≤ 35	10	10	0.94	0.35 - 2.52	0.02 (0.8852)	
35 < weight ≤ 40	12	12	0.93	0.38 - 2.32	0.03 (0.8734)	
40 < weight ≤ 45	4	5	0.74	0.14 - 3.54***	0.19 (0.6645)	0.7435
weight > 45	9	4	2.19	0.59 - 9.92***	1.70 (0.1920)	

* The comparison group is all other dogs.

** Calculated only if an expected cell value is < 5; the preferred p value for this OR.

*** Exact confidence limits.[128]

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Selected Clinical Findings Associated with Canine Hypoadrenocorticism

Odds ratios were calculated for the selected clinical findings, including 95% confidence intervals and uncorrected chi-square statistics with significance levels (p values) (Table 6.8).

Discussion

Questionnaire Responses and Description of Veterinary Clinics

A review of these results must recognize the limitations of sending a questionnaire to veterinarians randomly selected from the AVMA's mailing list. These include: the list must be accurate; and certain veterinarians, such as 1994 graduates and those with cats-only practice, did not see any patients in 1993.

This case control study was large, particularly for an uncommon disease, since it obtained 555 responses. The response rate of 55.5% of those initially sent questionnaires was satisfactory, though less than ideal. Figure 6.1 revealed that 95.9% of the responses were received within 60 da. This suggested that a cutoff of responses after 60 da would be reasonable in similar studies.

The average veterinary clinic had 2.10 full-time veterinarians (Figure 6.2), and reported an average estimated number of dogs first diagnosed in 1993 of 0.35 dogs. If 2.10 full-time veterinarians see 0.35 newly diagnosed hypoadrenal dogs per yr, this suggested an average small animal practitioner might expect to see 0.2 case per yr. This probably understated the number of cases since one veterinarian filled out the questionnaire for the entire practice. This veterinarian, being asked

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Table 6.8. Odds Ratios (OR) for Clinical Findings Associated with Hypoadrenocorticism in Dogs from 1994 Survey of Randomly Selected Veterinarians in the United States

Clinical finding*	Number of cases n=143	Number of controls n=140	OR	95% confidence interval for OR[49]	χ^2 statistic (p value) Uncorrected[40]	Fisher exact (2-tailed p value)**[162]
Anemia	22	1	25.27	3.94 - 1050.33***	20.39 (< 0.0001)	
Arthritis	19	11	1.80	0.77 - 4.22	2.20 (0.1380)	
Cruciate ligament rupture	3	3	0.98	0.13 - 7.43***	0.00 (0.9791)	
Diabetes mellitus	8	0	****	****	8.06 (0.0045)	0.0071
Hepatitis	17	0	****	****	17.71 (< 0.0001)	
Hypothyroidism	23	4	6.52	2.13 - 26.51***	14.34 (0.0002)	
Keratoconjunctivitis sicca	8	0	****	****	8.06 (0.0045)	0.0071
Nephritis	11	0	****	****	11.20 (0.0008)	
Thrombocytopenia	2	1	1.97	0.10 - 117.14***	0.32 (0.5741)	1.0000

* Clinical findings either anecdotally linked to hypoadrenocorticism or with a putative autoimmune etiology; comparison group is all other dogs; there were no cases or controls for either megaesophagus or myasthenia gravis.

** Calculated only if an expected cell value is < 5; the preferred p value for this OR.

*** Exact confidence limits.[128]

**** Undefined.

for summary data about the entire practice, may not have been aware of all cases diagnosed. In any event, 0.2 new case per yr might be used as a minimum benchmark for the number of cases a small animal practitioner could expect to diagnose each yr. Another useful benchmark was that the average full-time veterinarian saw 1,455.6 dogs (individual dogs, not dog visits) per yr.

Incidence and Prevalence Estimates

The incidence estimate of 0.13 case/1000 dogs/yr and the prevalence estimate of 0.6 case/1000 dogs suggested an approximate rate at which new cases may be acquired, and a rough indicator of how many cases a veterinarian might expect to be treating at any one time.

Ages

The mean age of all hypoadrenal dogs was higher (6.7 yr) than the mean age for all control dogs (5.6 yr). This suggested that hypoadrenocorticism tended to be present in older dogs. Similarly, the average age for live hypoadrenal dogs (6.5 yr) exceeded that for live control dogs (5.5 yr). Since the sample sizes for dead and lost to follow-up dogs were so small, no meaningful comparisons could be made between cases and controls.

Age at diagnosis was a poor age definition for this survey. In the survey of veterinarians whose patients were enrolled in the clinical trial (Chapter 5), the definition of age was current age *or* age at death *or* age when lost to follow-up.

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If a veterinarian or a veterinary assistant looks up the age of a dog in the dog's medical record, the age found, assuming that the age has been periodically updated, will likely be current age *or* age at death *or* age when lost to follow-up. If the veterinarian knows the dog is alive, the age will be current age; if the veterinarian knows the dog is dead, the age is likely to be the age at or near death; and if the veterinarian does not know whether the dog is alive or dead, then the recorded age is probably age when lost to follow-up. So the age reported by the veterinarian is very likely to fit the current age *or* age at death *or* age when lost to follow-up definition. Determining age at diagnosis, on the other hand, requires some computation. The age listed on the medical record is, unless the dog was very recently diagnosed with disease, irrelevant to age at diagnosis. The veterinarian would need to know specifically when the diagnosis was made in relation to the animal's birth, and some veterinarians may not have gone to the trouble of making the necessary computation. Consequently, some of the ages reported in this study were probably specious.

A second reason for making age at diagnosis a poor age definition was that age at diagnosis has no meaning in a control dog. Thus, case to control comparisons would be specious.

The age results suggested that they were not reliable. The mean age at diagnosis estimate was 6.7 yr, much older than the 4.3 yr estimate reported for the

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244 literature review cases (Chapter 2), the 4.9 yr estimate reported for the 232 cases enrolled in the clinical trial (Chapter 3), the 5.4 yr estimate reported for the 329 cases from the veterinary referral hospitals (Chapter 4), or the 4.9 yr estimate obtained by a weighted average of the previous three estimates (Chapter 5).[dd]

Therefore, age at diagnosis was a poor way to define age in this survey, and is probably a poor way to define it in most case control studies; consequently, the age results obtained from this survey, including Figures 6.3 and 6.4, and Table 6.2, should not be trusted. Future surveys should avoid this error by defining age as current age *or* age at death *or* age when lost to follow-up.

Sexes

The sex data in Table 6.4 can be characterized as equivocal. The 95% confidence intervals for the OR all include one except for female-intact (comparison group all other dogs) which had a 95% confidence interval of 0.05 - 0.64 and a p value for its uncorrected chi-square statistic of 0.0021, and female-spayed (comparison group female-intact dogs) which had a 95% confidence interval of 1.48 - 20.70 and a p value for its uncorrected chi-square statistic of

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[dd]It is notable that the literature review cases, clinical trial cases, and veterinary referral hospital cases all came from studies which focused specifically on age at diagnosis.

0.0032. This suggested that female-spayed dogs were more likely to be hypoadrenal than intact ones, and that female-intact dogs were less likely to be hypoadrenal than other dogs. None of the other results, except possibly the one discussed below, showed any predilection for or against hypoadrenocorticism.

The OR for neutered (either sex) was 1.75 with a 95% confidence interval of 0.96 - 3.20 (p=0.05 for its uncorrected chi-square statistic). A neutered dog of either sex may be more likely to have adrenal insufficiency.

Breeds

No OR (Table 6.6) except one was significant at the 0.05 level. The one exception was the Mixed dog which had an OR of 0.45, a 95% confidence interval of 0.22 - 0.92, and a p value for the uncorrected chi-square statistic of 0.0177. This suggested that a Mixed dog was less likely to be hypoadrenal. Though the OR for the Basset Hound was undefined, the p value for the uncorrected chi-square statistic was 0.0288, indicating a predisposition for the disease.

Body Weights

As with breeds, sample sizes were too small to establish clear body weight predilections for or against disease. The statistical comparison of average body

weight of cases (20.2 kg) with controls (19.8 kg) revealed no significant difference.

Body weight-specific OR (Table 6.7) revealed little to suggest association between body weights and either an increase or decrease in the probability of hypoadrenocorticism. There were two possible exceptions.

First, the 20 kg < weight ≤ 25 kg weight range had an OR of 2.25 with a 95% confidence interval of 0.97 - 5.33 and a p value for the uncorrected chi-square statistic of 0.0390, suggesting a predilection for hypoadrenocorticism. Second, the 25 kg < weight ≤ 30 kg weight range had an OR of 0.46 with a 95% confidence interval of 0.19 - 1.09 and a p value for the uncorrected chi-square statistic of 0.0524, suggesting they may be less likely to be hypoadrenal. These results seemed inconsistent, since it is counterintuitive to conclude dogs in the 20 kg < weight ≤ 25 kg weight range were predisposed to disease, and dogs in the 25 kg < weight ≤ 30 kg weight range were less likely to be diseased. This remains unexplained.

Selected Clinical Findings Associated with Canine Hypoadrenocorticism

Of the five clinical findings with defined OR displayed in Table 6.8, anemia, arthritis, hypothyroidism, and thrombocytopenia had OR which exceeded one. The OR for cruciate ligament rupture was less than one. The OR for anemia of 25.27 and the OR for hypothyroidism of 6.52 were both highly significant (p < 0.001

for uncorrected chi-square statistics). The OR for arthritis, cruciate ligament rupture, and thrombocytopenia were not significant at the 0.05 level. Though the OR for diabetes mellitus, hepatitis, keratoconjunctivitis sicca, and nephritis were undefined, there was evidence that these conditions were associated with hypoadrenocorticism ($p < 0.01$ for their uncorrected chi-square statistics). Sample sizes were too small to permit meaningful stratification by age.

Conclusions

1. <u>Questionnaire Responses and Description of Veterinary Clinics</u>. With a response rate of slightly over half (55.5%), all results of this study should be considered carefully. Over 90% of the questionnaire responses received were received within 60 da, suggesting a 60 da cutoff would be reasonable in similar studies. In 1993 the average veterinary clinic had an estimated 2.10 full-time veterinarians, and initially diagnosed 0.35 dogs. A veterinarian in small animal practice might expect to initially diagnose about 0.2 case per yr. This is probably an underestimate. The average full-time small animal practitioner saw about 1,500 dogs (individual dogs, not dog visits) in 1993.

2. <u>Incidence and Prevalence Estimates</u>. Incidence and prevalence estimates for canine hypoadrenocorticism were, respectively, 0.13 case/1000 dogs/yr and 0.6 case/1000 dogs, which were lower than the estimates obtained from the survey of veterinarians enrolled in the clinical trial (Chapter 5).

3. <u>Ages</u>. The age results should be disregarded since they were unreliable.

4. <u>Sexes</u>. Female-intact dogs were less likely to have adrenal insufficiency. Female-spayed dogs were more likely.

5. <u>Breeds</u>. The Mixed breed dog was less likely than other breeds to be hypoadrenal. The Basset Hound may be predisposed to hypoadrenocorticism. There were no statistically significant predilections for or against hypoadrenocorticism in other breeds; this likely resulted from the relatively small sample sizes rather than from a real absence of them.

6. <u>Body Weights</u>. Body weight data led to no meaningful conclusions.

7. <u>Selected Clinical Findings Associated with Canine Hypoadrenocorticism</u>. Anemia, diabetes mellitus, hepatitis, hypothyroidism, keratoconjunctivitis sicca, and nephritis were each associated with hypoadrenocorticism at a significance level of less than 0.01. No significant associations were found between the other clinical findings and hypoadrenocorticism; this was likely the result of small sample sizes rather than the real absence of them.

8. <u>General</u>. While this survey augmented the other studies comprising this overall study of canine hypoadrenocorticism, it did not in itself provide much useful information. It was limited by: the small number of cases reported; the uncertainty about the diagnostic method used by responding veterinarians; the method of estimation of active dog patients; the definition of age; and the fact that

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veterinarians have different procedures for removing medical records from their files after a dog's death. Thus, a survey of randomly selected veterinarians would generally, because of the time and expense required, be a poor vehicle for the primary study of an uncommon animal disease. If the disease being studied were more common or if larger samples could be obtained at minimal expense, a survey of randomly selected veterinarians might nevertheless be appropriate.

CHAPTER 7 .

CONCLUSIONS

Introduction and Comments Regarding Methodology

These conclusions are an amalgam of those from the preceding six chapters. However, before the conclusions can be presented, a few issues must be discussed as background. These include the general strengths and weaknesses of case series, case control studies, and mail surveys, particularly as they apply to this work.

A case series is a "cross-sectional study with no defined population and no comparison group."[203.] The data from the canine literature review (Chapter 2), from the microcrystalline desoxycorticosterone pivalate (DOCP) clinical trial (Chapter 3), and from the Veterinary Medical Data Base (VMDB) (Chapter 4) were case series. Case series are useful since information is available quickly, and they lend themselves to stimulating more definitive research. They are, however, prone to overinterpretation, and often provoke "authoritarian (rather than authoritative) clinical advice about etiology, prevention, and therapy."[174] Case series do not prospectively follow patient cohorts, "do not have a time dimension," and "suffer from the absence of a comparison group."[52] The use of case series is particularly appropriate for rare diseases.[51] Data in Chapters 2, 3, and 4

represented the first logical step in epidemiology: observe and study those cases already available and documented, then develop other studies. Specifically, the case series in Chapters 2, 3, and 4 were used as forerunners of the case-control studies based on surveys of veterinarians enrolled in the clinical trial of DOCP (Chapter 5) and randomly selected veterinarians (Chapter 6).

A case-control study is one in which "individuals with a particular condition or disease (the *cases*) are selected for comparison with a series of individuals in whom the condition or disease is absent (the *controls*). Cases and controls are compared with respect to existing or past attributes or exposures thought to be relevant to the development of the condition or disease under study [Italics in original]."[186] Case control studies are an important way to learn about uncommon diseases; they generally are inexpensive and the researcher can obtain results fairly quickly.[53] They make use of readily available cases which are often cataloged in places like hospitals, disease registries,[187] and veterinary practices.[201] This has become particularly appealing and useful as these records and registries become computerized.[173] Case-control studies are favored for uncommon diseases and those with long latency periods, and they enable the researcher to explore large numbers of potential risk or causal factors.[202] While case-control studies are useful and popular, they suffer from selection bias and measurement bias.[55] The studies using cases and controls from the clinical trial of DOCP (Chapter 5), and cases and

controls from the randomly selected veterinarians (Chapter 6) were case-control studies in which mail survey methodology was used to gather data. These studies did no matching of cases and controls since little information already existed about factors associated with hypoadrenocorticism. They were inexpensive, assembled information from several sources on hundreds of cases of an uncommon disease, and explored many factors and their possible association with the disease.

Selection bias was at work in the printed literature. Many things have to come together before a case finds its way into print: an owner willing to seek treatment for a sick dog; an observant veterinarian willing to carefully diagnose and document the case; a veterinarian willing and able to write the article; a compliant editor; and so on. Similarly, specific sets of circumstances are required before cases find their way into the files of the VMDB or Ciba Animal Health, and still others have to be present before practitioners respond to mail surveys.

Measurement bias was probably also at work. There are three kinds of measurement bias:[54]

1. The presence of the outcome directly affects the exposure. (For example, if a dog repeatedly has fleas, the dog's owner will try to keep the dog from being infested with fleas.)

2. The presence of the outcome affects the subject's recollection of the exposure. (For example, a dog's owner is more likely to remember when the dog was hit by a car than when the dog had a mild diarrhea.)

3. The presence of the outcome affects the measurement or recording of the exposure. (For example, a dog who has suffered a serious illness is more likely to have a thoroughly documented medical history than a dog who has received only routine wormings and vaccinations.)

It is unlikely that this study suffered from the first bias listed, but it almost certainly did from the second two. It likely occurred with regard to clinical findings. A veterinarian or dog owner with a hypoadrenal dog is more likely to recall clinical findings in the dog's history than the owner of a control dog. Along the same lines, the veterinarian is more likely to inquire about clinical findings in a hypoadrenal dog compared to a dog presented for a routine visit or minor illness. The veterinarian is also more likely to do more diagnostic testing and, perhaps, to record the diagnostic results more carefully when the patient is viewed as "serious" (cases) rather than "routine" (controls).

The advantages and disadvantages of mail survey methodology were also at work in these studies. The survey of veterinarians enrolled in the clinical trial of DOCP (Chapter 5) and the survey of randomly selected veterinarians (Chapter 6) were both mail surveys. Low response rate is an important problem with mail

surveys. A prominent text in the field states, "Surveys by mail typically elicited extremely low response rates, even with short questionnaires, and high response to relatively long questionnaires was very rare indeed . . . ."[30] Another problem is nonresponse to particular items on questionnaires among those questionnaires actually received.[33] Another shortcoming of mail questionnaires is that they are often far shorter than needed to elicit the necessary research data.[32] The survey of randomly selected veterinarians may have suffered from all these problems, though particularly from the last.

The need for a high response rate stems from the idea that selection bias is introduced when some people respond and some do not. If responders and nonresponders have different characteristics, then the study is biased by these differences. This problem becomes less important as the response rate increases. This "unknown bias from refusals"[34] is difficult or impossible to quantify, since it is by definition "unknown." The mail survey of veterinarians enrolled by Ciba Animal Health in the clinical trial of DOCP (Chapter 5) was probably not greatly affected by a response rate problem since the rate was 90.9% compared to the survey of randomly selected veterinarians with a rate of 55.5%. Though no definitive minimum response rate can be established, one source suggests by implication that a 50% response rate may be a useful working minimum.[31] By that standard, the response rate for both surveys was satisfactory.

Specific item nonresponse may have been a small problem. The DOCP clinical trial veterinarians (Chapter 5) were asked for two controls for each of their cases. They provided 1.66 controls per case, ages for 92.6% of cases and 97.6% of controls, and sexes for 98.9% of cases and 96.6% of controls. The randomly selected veterinarians (Chapter 6) were asked for one control per case. They provided 0.93 controls per case, ages for 98.7% of cases and 97.9% of controls, and sexes for 97.4% of cases and 98.6% of controls. There were some nonresponses for other variables as well, which leads to the question of whether or not these nonresponses perturbed the results. The answer is no, for two reasons. First, the samples for these variables were quite large. Given these large samples, a responder/nonresponder bias, even if present, would have to be overwhelming before it could materially change the results. Second, it is almost impossible to postulate how a responder/nonresponder bias could occur which would have affected the results. Responding veterinarians might have less busy practices than nonresponders who, having busier practices, have less time to fill out questionnaires. However, no plausible scenario could systematically change the characteristics of the case of canine hypoadrenocorticism in a veterinarian's medical records or the characteristics of the control dog which followed. Therefore, nonresponses were not viewed as a problem.

The most significant problem with mail surveys is the compromise between response rate and length of questionnaire. If the questionnaire is long and

complicated, the response rate will go down. Conversely, if the questionnaire is short and simple, the response rate will go up, and responder/nonresponder bias will be less troublesome. These questionnaires were deliberately written to be brief. The result was good response rates, but lots of unanswered questions. For example, lots of dogs had anemia, but what kind of anemia? A more detailed questionnaire might have inquired about the specific nature of each anemia. But then it might not have been returned. Consequently, shortening the questionnaire was an undesirable, though unavoidable, part of the mail surveys.

Finally, the estimates of active dog patients reported by the DOCP clinical trial veterinarians (Chapter 5) and the randomly selected veterinarians (Chapter 6) may have introduced error in the incidence and prevalence estimates. How this error may have affected the results is unknown. Some veterinarians probably guessed at the number of active dog patients; others likely obtained it from computerized medical records. The method used for these studies did not determine how the veterinarians arrived at the number of active dog patients. Future studies should address this issue. In this regard, the numbers of active dog patients seen per full-time veterinarian were virtually identical for the DOCP clinical trial veterinarians (1504.7) and the randomly selected veterinarians (1455.6).^{cc} This suggested that this study flaw was, if present, minimal.

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ccThese were similar to the estimate of 1600 dogs seen per veterinarian per yr obtained on July 29, 1996 from personal communication with Dr. J. Karl Wise,

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Overall, the mail survey served a purpose. Assembling a credible group of several hundred cases with controls of a disease as uncommon as canine hypoadrenocorticism was useful and the mail survey methodology was the only practical way to obtain this information.

Recognizing the advantages and disadvantages of case series, case-control studies, and mail survey questionnaires, the following conclusions are presented. They are a composite and comparison of the conclusions drawn in Chapters 2 through 6.

Incidence and Prevalence Estimates

The incidence and prevalence estimates appear in Table 7.1. The incidence was highest for the veterinary referral hospitals; next for the Ciba Animal Health veterinarians, who might be considered more motivated than the randomly selected veterinarians since they went to the trouble of enrolling in the clinical trial; and last for the randomly selected veterinarians. These results suggested that 0.36 case/1000 dogs/yr (a simple mean of the three incidences) can be used as a point estimate of incidence. Similarly, 1.8 cases/1000 dogs can be used as a point estimate for prevalence. These point estimates can be used by veterinary clinicians.

Center for Information Management, American Veterinary Medical Association.

Table 7.1. Incidence and Prevalence Estimates Determined in Three Epidemiologic Studies of Naturally Occurring and Iatrogenically Produced Canine Hypoadrenocorticism

Study	Incidence estimate (cases/1000 dogs/yr)*	Prevalence estimate (cases/1000 dogs)
Case series: veterinary referral hospitals	0.6	3.2
Case control: survey of veterinarians enrolled in clinical trial	0.34	1.7
Case control: survey of randomly selected veterinarians	0.13	0.6

*Each estimate differs significantly from each other estimate ($p < 0.0001$).

Ages

The average age at diagnosis (SD) (SEM[ff]) (Range) in yr for dogs with adrenal insufficiency was 4.3 ([gg]) ([hh]) (0.2-12.0) for dogs included in the literature review (Chapter 2),[ii] 4.9 (3.0) (0.2) (0.3-13.0) for dogs in the Ciba Animal Health clinical trial of DOCP (Chapter 3), and 5.4 (3.2) (0.2) (0.1-15.0) for the dogs diagnosed in veterinary referral hospitals (Chapter 4). A simple mean of these three results was 4.9 yr, a result consistent with estimates provided in two well-known veterinary references.[41,43] The results demonstrated that the disease can be diagnosed in very young and very old dogs.

The ages reported in the survey of veterinarians enrolled by Ciba Animal Health in the clinical trial of DOCP (Chapter 5) were current age *or* age at death *or* age when lost to follow-up. The mean age (SD) (SEM) (Range) for cases in yr was for live dogs 8.1 (3.0) (0.1) (1.5-18.0), for dead dogs 9.8 (3.4) (0.2) (1.0-17.2), and for dogs lost to follow-up 8.6 (3.1) (0.7) (4.0-13.0). It was for controls 6.1 (3.9) (0.1) (0.1-19.0) for live dogs, 10.2 (5.2) (0.8) (0.3-17.0) for dead dogs, and 5.7 (4.3) (0.4) (0.2-16.0) for dogs lost to follow-up. Average disease duration

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[ff]Standard error of the mean (SEM) equals the standard deviation (SD) divided by the square root of the sample size.

[gg]Not reported for all cases.

[hh]Not reported for all cases.

[ii]This assumes that the articles reviewed actually reported "age at diagnosis"; in fact, they reported "age."

was estimated at 4.9 yr (Chapter 5). This suggested that hypoadrenal dogs tended to be older than control dogs. Age-specific odds ratios (OR) suggested that the risk of hypoadrenocorticism increased with age. The ages reported in the survey of randomly selected veterinarians (Chapter 6) should be disregarded because they were unreliable.

Sexes

The sexes for hypoadrenal dogs were 16.8% female-intact, 47.8% female-spayed, 22.3% male-intact, and 13.0% male-castrated in the literature review (Chapter 2); 6.1, 61.8, 13.0, and 19.1 (percentages ordered female-intact, female-spayed, male-intact, and male-castrated) for the clinical trial of DOCP (Chapter 3); 14.0, 53.8, 13.1, and 19.1 for veterinary referral hospitals (Chapter 4); 5.2, 63.9, 10.3, and 20.7 for the mail survey of Ciba Animal Health veterinarians (Chapter 5); and 2.7, 53.1, 15.0, and 29.3 for the mail survey of randomly selected veterinarians (Chapter 6). These were remarkably similar, and taken together using simple averages, suggested that hypoadrenal dogs were 9% female-intact, 56% female-spayed, 15% male-intact, and 20% male-castrated. This was consistent with previous assertions that canine hypoadrenocorticism is primarily a disease of the female dog.[41,43,93,148,189]

Sex-specific OR and sex-specific incidence estimates calculated from veterinary referral hospitals (Chapter 4), from the mail survey of Ciba Animal

Health veterinarians (Chapter 5), and from the mail survey of randomly selected veterinarians (Chapter 6) supported the conclusion that females were more likely to be hypoadrenal, but also suggested that female-spayeds were more likely than female-intacts, that male-castrateds were more likely than male-intacts, and that neutered dogs were more likely than intact ones. This contradicted one study which reported that female-intacts had an increased probability of disease compared to female-spayeds.[148] These associations between neutering and hypoadrenocorticism could be influenced by the age at which dogs were neutered. Though these studies did not address this possibility, future studies might do so. Table 7.2 summarizes the sex-specific OR. These data can be used by veterinary clinicians when evaluating potential cases of hypoadrenocorticism.

Breeds

The data demonstrated that canine hypoadrenocorticism was widespread among breeds. Several breeds were at increased risk of disease and several at decreased risk. The results from veterinary referral hospitals (Chapter 4), the survey of veterinarians enrolled by Ciba Animal Health in the clinical trial of DOCP (Chapter 5), and the survey of randomly selected veterinarians (Chapter 6) were consistent (Table 7.3).

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Table 7.2. Sex-Specific Risks of Canine Hypoadrenocorticism Based on Three Epidemiologic Studies

Study	Sexes*	Sex-specific odds ratio (OR)	95% confidence interval for OR[49]	Uncorrected χ^2 statistic (p value)[40]
Case series: veterinary referral hospitals				
	Female-intact	0.56	0.40 - 0.78	13.05 (0.0003)
	Female-spayed	2.88	2.28 - 3.64	90.60 (< 0.0001)
	Female-spayed**	3.02	2.13 - 4.30	45.75 (< 0.0001)
	Female (intact and spayed)	1.97	1.53 - 2.53	30.81 (< 0.0001)
	Male-intact	0.32	0.23 - 0.45	49.81 (< 0.0001)
	Male-castrated	1.25	0.92 - 1.69	2.21 (0.1371)
	Male-castrated***	2.92	1.91 - 4.47	29.16 (< 0.0001)
	Neutered (either sex)	3.29	2.53 - 4.27	94.99 (< 0.0001)
Case control: survey of veterinarians enrolled in clinical trial				
	Female-intact	0.62	0.23 - 1.68	1.05 (0.3061)
	Female-spayed	2.40	1.54 - 3.74	16.94 (< 0.0001)
	Female-spayed**	2.16	0.79 - 6.03	2.75 (0.0974)
	Female (intact and spayed)	2.31	1.46 - 3.66	14.31 (0.0002)
	Male-intact	0.35	0.18 - 0.69	11.08 (0.0009)
	Male-castrated	0.65	0.38 - 1.12	2.70 (0.1002)
	Male-castrated***	1.77	0.78 - 4.07	2.19 (0.1387)
	Neutered (either sex)	2.58	1.45 - 4.61	12.19 (0.0005)

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Table 7.2 continued

Study	Sexes*	Sex-specific odds ratio (OR)	95% confidence interval for OR[49]	Uncorrected χ^2 statistic (p value)[40]
Case control: survey of randomly selected veterinarians				
	Female-intact	0.20	0.05 - 0.64****	9.50 (0.0021)
	Female-spayed	1.18	0.72 - 1.93	0.49 (0.4839)
	Female-spayed**	4.88	1.48 - 20.70****	8.68 (0.0032)
	Female (intact and spayed)	0.80	0.49 - 1.32	0.85 (0.3572)
	Male-intact	0.99	0.49 - 1.99	0.00 (0.9732)
	Male-castrated	1.33	0.76 - 2.33	1.11 (0.2917)
	Male-castrated***	1.24	0.55 - 2.82	0.33 (0.5686)
	Neutered (either sex)	1.75	0.96 - 3.20	3.83 (0.0503)

* Except as noted, the comparison group is all other dogs.

** Female-spayed compared to female-intact.

*** Male-castrated compared to male-intact.

**** Exact confidence limits.[128]

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Table 7.3. Breeds at Increased or Decreased Risk of Canine Hypoadrenocorticism Based on Three Epidemiologic Studies*

Study	Breed	Breed-specific odds ratio (OR)	95% confidence interval for OR[49]	Uncorrected χ^2 statistic (p value)[40]	Fisher exact (2-tailed p value)**[162]
Case series: veterinary referral hospitals					
	Poodle	3.17	2.18 - 4.58	44.65 (< 0.0001)	
	Labrador Retriever	0.49	0.24 - 0.98	4.61 (0.0317)	
	Great Dane	4.56	2.28 - 8.83	26.48 (< 0.0001)	0.0001
	West Highland White Terrier	7.33	3.90 - 13.46	61.83 (< 0.0001)	< 0.0001
Case control: survey of veterinarians enrolled in clinical trial					
	Airedale Terrier	2.61	1.06 - 6.56	5.36 (0.0206)	
	Basset Hound	3.38	1.50 - 7.79	10.96 (0.0009)	
	Bearded Collie	4.19	1.20 - 18.36***	6.87 (0.0088)	
	Boxer	0.12	0.00 - 0.77***	6.17 (0.0130)	
	Cocker Spaniel	0.51	0.30 - 0.85	7.44 (0.0064)	
	Dalmatian	0.00	0.00 - 0.50***	8.51 (0.0035)	
	German Shorthaired Pointer	2.52	1.06 - 6.06	5.41 (0.0200)	
	Great Dane	7.63	2.50 - 31.09***	18.53 (< 0.0001)	
	Lhasa Apso	0.22	0.04 - 0.75***	7.09 (0.0078)	
	Pit Bull Terrier	0.00	0.00 - 0.84***	5.45 (0.0195)	0.0165
	Pomeranian	0.12	0.00 - 0.77***	6.17 (0.0130)	
	Poodle	3.55	2.55 - 4.93	67.44 (< 0.0001)	

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Table 7.3 continued

Study	Breed	Breed-specific odds ratio (OR)	95% confidence interval for OR[49]	Uncorrected χ^2 statistic (p value)[40]	Fisher exact (2-tailed p value)**[162]
	Shetland Sheepdog	0.15	0.03 - 0.47***	13.41 (0.0003)	
	Shih Tzu	0.25	0.05 - 0.83***	5.99 (0.0144)	
	Springer Spaniel	2.54	1.29 - 5.04	8.72 (0.0031)	
	West Highland White Terrier	5.93	2.69 - 13.46	27.69 (< 0.0001)	
	Yorkshire Terrier	0.14	0.02 - 0.58***	9.47 (0.0021)	
Case control: survey of randomly selected veterinarians					
	Mixed	0.45	0.22 - 0.92	5.62 (0.0177)	

* Breeds are included if the 95% confidence interval did not contain one.

** Calculated only if an expected cell value is < 5; the preferred p value for this OR.

*** Exact confidence limits.[128]

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These results were remarkably consistent in that in no case was a breed found to be at increased risk in one study and at decreased risk in another. Three of the breeds reported at increased risk were also reported by another study[148] as being predisposed to hypoadrenocorticism. These were Great Danes, Poodles (the previously published study reported only Standard Poodles), and West Highland White Terriers. Portuguese Water Dogs, Rottweilers, and Wheaten Terriers have been reported to be predisposed to hypoadrenocorticism.[148] This was not confirmed by this study. A decreased risk among Golden Retrievers, Lhasa Apsos, and Yorkshire Terriers has been reported.[148] This study did not find a decreased risk among Golden Retrievers, but it did among the other two breeds. One textbook reported that Labrador Retrievers might be predisposed to adrenal insufficiency.[69] This is in conflict with the results of this study, which showed Labrador Retrievers at decreased risk. This is viewed as a minor discrepancy since the textbook stated that the predisposition was a possibility, not a certainty. These data can be used by veterinary clinicians when evaluating potential cases of hypoadrenocorticism.

Body Weights

The average body weight (SD) (SEM) (Range) in kg for dogs enrolled in the clinical trial of DOCP (Chapter 3) was 23.4 (13.6) (0.8) (2.7-72.7). For cases and controls, respectively, the results based on the survey of veterinarians enrolled by Ciba Animal Health in the clinical trial of DOCP (Chapter 5) were 24.5 (14.5) (0.6) (2.3-81.8) and 19.7 (12.7) (0.4) (1.4-68.2). For cases and controls, respectively, the results based on the survey of randomly selected veterinarians (Chapter 6) were 20.2 (14.1) (1.2) (1.1-63.6) and 19.8 (13.5) (1.1) (1.4-74.1). Body weight specific OR were calculated in both surveys, Chapters 5 and 6, and are tabulated in Tables 5.9 and 6.7, respectively.

A simple average of the averages from the three studies above was 22.5 kg; a weighted average of the averages was 23.6 kg. These were comparable to the median weight of 20.0 kg reported for 225 hypoadrenal dogs in another study,[148] and suggested that the average dog with hypoadrenocorticism weighs over 20 kg.

Data from the survey of veterinarians enrolled in the clinical trial of DOCP (Chapter 5) provided evidence that the probability of hypoadrenocorticism increased with body weight. The average body weight of 24.5 kg for cases differed significantly ($p < 0.0005$) from the 19.7 kg for controls. Body weight-specific OR

(Table 5.9) suggested that the probability of hypoadrenocorticism increased with body weight. Data from the survey of randomly selected veterinarians (Chapter 6) did not support this conclusion. The average body weight of 20.2 kg for cases was not significantly greater than the 19.8 kg for controls. Body weight-specific OR (Table 6.7) failed to demonstrate a relationship between body weight and disease. Table 7.4 summarizes the body weight-specific risks of hypoadrenocorticism. A few comments are appropriate here.

First, though the survey of randomly selected veterinarians did not confirm the proposition that the probability of canine hypoadrenocorticism varied directly with body weight, neither did it refute it. Second, the survey of randomly selected veterinarians was much smaller than the survey of veterinarians enrolled in the clinical trial, and thus should not be given as much weight. The counter-argument is that, though the survey of randomly selected veterinarians was much smaller, it was still much too large (149 cases and 140 controls for body weight) to ignore. Third, the possibility existed that the ostensible body weight effect is really an effect from some confounding variable such as breed.

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Table 7.4. Body Weight-Specific Risks of Canine Hypoadrenocorticism Based on Two Epidemiologic Studies

Study	Body weight (kg)*	Body weight-specific odds ratio (OR)	95% confidence interval for OR[49]	Uncorrected χ^2 statistic (p value)[40]	Fisher exact (2-tailed p value)**[162]
Case control: survey of veterinarians enrolled in clinical trial					
	0 < weight ≤ 5	0.37	0.24 - 0.58	22.79 (< 0.0001)	
	5 < weight ≤ 10	0.88	0.68 - 1.13	1.11 (0.2923)	
	10 < weight ≤ 15	0.57	0.41 - 0.80	11.57 (0.0007)	
	15 < weight ≤ 20	0.69	0.49 - 0.98	4.62 (0.0315)	
	20 < weight ≤ 25	1.70	1.27 - 2.28	13.70 (0.0002)	
	25 < weight ≤ 30	1.11	0.80 - 1.52	0.41 (0.5236)	
	30 < weight ≤ 35	1.17	0.84 - 1.61	0.94 (0.3327)	
	35 < weight ≤ 40	1.65	1.13 - 2.40	7.51 (0.0061)	
	40 < weight ≤ 45	1.29	0.78 - 2.13	1.12 (0.2906)	
	45 < weight ≤ 50	1.11	0.57 - 2.14	0.11 (0.7443)	
	50 < weight ≤ 55	3.14	1.06 - 10.37***	5.58 (0.0182)	
	weight > 55	5.72	2.36 - 15.86***	20.40 (< 0.0001)	

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Table 7.4 continued

Study	Body weight (kg)*	Body weight-specific odds ratio (OR)	95% confidence interval for OR[49]	Uncorrected χ^2 statistic (p value)[40]	Fisher exact (2-tailed p value)**[162]
Case control: survey of randomly selected veterinarians					
	0 < weight ≤ 5	0.65	0.29 - 1.46	1.29 (0.2566)	
	5 < weight ≤ 10	1.41	0.77 - 2.61	1.39 (0.2380)	
	10 < weight ≤ 15	0.98	0.50 - 1.91	0.01 (0.9411)	
	15 < weight ≤ 20	0.65	0.26 - 1.62	1.03 (0.3113)	
	20 < weight ≤ 25	2.25	0.97 - 5.33	4.26 (0.0390)	
	25 < weight ≤ 30	0.46	0.19 - 1.09	3.76 (0.0524)	
	30 < weight ≤ 35	0.94	0.35 - 2.52	0.02 (0.8852)	
	35 < weight ≤ 40	0.93	0.38 - 2.32	0.03 (0.8734)	
	40 < weight ≤ 45	0.74	0.14 - 3.54***	0.19 (0.6645)	0.7435
	weight > 45	2.19	0.59 - 9.92***	1.70 (0.1920)	

* The comparison group is all other dogs.

** Calculated only if an expected cell value is < 5; the preferred p value for this OR.

*** Exact confidence limits.[128]

Serum Sodium and Potassium Concentrations

The average serum sodium and potassium concentration (SD) (SEM) (Range) in meq/L for hypoadrenal dogs in the literature review (Chapter 2) were, respectively, 129.4 ([ii]) ([kk]) (114.0-150.0) and 7.2 ([ll]) ([mm]) (4.6-10.8). The ratio of serum sodium to potassium concentrations was 18.0. The corresponding values, in the same order, for the DOCP clinical trial (Chapter 4) and veterinary referral hospitals (Chapter 5), respectively, were: 131.8 (9.4) (0.6) (104.0-174.0), 6.8 (1.3) (0.1) (3.2-12.8), 20.2 (4.8) (0.3) (10.5-38.8); and 135.2 (10.6) (0.7) (97.0-160.0), 5.9 (1.7) (0.1) (2.9-11.7), 25.2 (8.3) (0.5) (11.1-46.6). Simple means of these results yielded 132.1 for sodium, 6.6 for potassium, and 21.1 for the sodium to potassium ratio. These values supported the propositions that dogs with adrenal insufficiency are hyponatremic and hyperkalemic,[41,43] and that their sodium to potassium ratios are under 25.0[129] or 27.0.[41,43,189]

Electrolyte results from the clinical trial of DOCP (Chapter 3) established that hypoadrenocorticism *did occur* in dogs with normal values for serum sodium, potassium, and sodium to potassium ratio--specifically, about one case in 20 had

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[ii]Not reported for all cases.

[kk]Not reported for all cases.

[ll]Not reported for all cases.

[mm]Not reported for all cases.

normal values for all three diagnostic indicators. The results from the veterinary referral hospitals (Chapter 4) were that *no* case was normal for all three diagnostic indicators. This suggested that a veterinarian with a patient normal for these three diagnostic indicators should, in most cases, provisionally remove adrenal insufficiency from the list of differential diagnoses, thereby avoiding the time and cost of the adrenocorticotropic hormone (ACTH) stimulation test.

Clinical Findings

Clinical findings included: anorexia; vomiting; depression; weakness; weight loss; azotemia; diarrhea; cardiac anomalies such as microcardia, bradycardia, and arrhythmias; skin and hair problems; gastroenteric difficulties such as gastroenteritis and abdominal pain; polyuria or polydipsia; limb stiffness; muscle atrophy; shock or collapse; and shaking or trembling. This comprehensive list mirrors the clinical findings reported elsewhere.[44]

The following results should be viewed skeptically. The clinical findings were selected because of their anecdotal association with canine hypoadrenocorticism or their putative autoimmune etiology. These included anemia, arthritis, cruciate ligament rupture, diabetes mellitus, hepatitis, hypothyroidism, keratoconjunctivitis sicca, megaesophagus, myasthenia gravis, nephritis, and thrombocytopenia. Ostensible associations between some of these clinical findings, notably anemia and nephritis, and hypoadrenocorticism may have resulted from the fact that the

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clinical finding can be associated with any chronic disease, not specifically with hypoadrenocorticism. For example, dogs with normal kidneys presented with hypoadrenocorticism often appear to have nephritis because of shock and renal failure produced by poor renal perfusion. This is a normal part of the pathophysiology of hypoadrenocorticism and should not be confused with true nephritis, a separate disease. Also, comparisons between cases and controls probably included measurement bias. The health of cases was probably explored more thoroughly because of their illness than the health of controls. Thus, it was more likely that clinical findings were discovered for cases than controls. It is impossible to determine the extent of this measurement bias.

Anemia, arthritis, cruciate ligament rupture, diabetes mellitus, hepatitis, hypothyroidism, keratoconjunctivitis sicca, myasthenia gravis, nephritis, and thrombocytopenia were all associated with hypoadrenocorticism in at least one study. This is all the selected clinical findings except megaesophagus. This may be testament to the wisdom of the selection process for clinical findings, or could be due to measurement bias. Which, if either, of these interpretations has merit will remain a mystery. These ostensible associations should be explored with further studies, particularly studies which control measurement bias. Table 7.5 summarizes the clinical finding-specific risks of hypoadrenocorticism.

Table 7.5. Clinical Finding-Specific Risks of Canine Hypoadrenocorticism Based on Two Epidemiologic Studies

Study	Clinical finding*	Clinical finding-specific odds ratio (OR)	95% confidence interval for OR[49]	Uncorrected χ^2 statistic (p value)[40]	Fisher exact (2-tailed p value)**[162]
Case control: survey of veterinarians enrolled in clinical trial					
	Anemia	18.52	8.43 - 48.03***	97.92 (< 0.0001)	
	Arthritis	2.50	1.81 - 3.44	35.54 (< 0.0001)	
	Cruciate ligament rupture	2.28	1.05 - 5.02	5.21 (0.0224)	
	Diabetes mellitus	2.16	0.46 - 10.93***	1.38 (0.2403)	0.3023
	Hepatitis	7.41	3.15 - 20.14	30.35 (< 0.0001)	
	Hypothyroidism	4.65	3.04 - 7.12	64.29 (< 0.0001)	
	Keratoconjunctivitis sicca	3.51	1.49 - 8.49	10.57 (0.0012)	
	Megaesophagus	5.19	0.41 - 272.46***	2.53 (0.1120)	0.1434
	Myasthenia gravis	****	****	5.18 (0.0229)	0.0494
	Nephritis	6.77	3.33 - 14.08	40.85 (<0.0001)	
	Thrombocytopenia	5.22	1.30 - 30.07***	7.61 (0.0058)	0.0119

Table 7.5 continued

Study	Clinical finding*	Clinical finding-specific odds ratio (OR)	95% confidence interval for OR[49]	Uncorrected χ^2 statistic (p value)[40]	Fisher exact (2-tailed p value)**[162]
Case control: survey of randomly selected veterinarians*****					
	Anemia	25.27	3.94 - 1050.33***	20.39 (< 0.0001)	
	Arthritis	1.80	0.77 - 4.22	2.20 (0.1380)	
	Cruciate ligament rupture	0.98	0.13 - 7.43***	0.00 (0.9791)	
	Diabetes mellitus	****	****	8.06 (0.0045)	0.0071
	Hepatitis	****	****	17.71 (< 0.0001)	
	Hypothyroidism	6.52	2.13 - 26.51***	14.34 (0.0002)	
	Keratoconjunctivitis sicca	****	****	8.06 (0.0045)	0.0071
	Nephritis	****	****	11.20 (0.0008)	
	Thrombocytopenia	1.97	0.10 - 117.14***	0.32 (0.5741)	1.0000

* Clinical findings either anecdotally linked to hypoadrenocorticism or with a putative autoimmune etiology; comparison group is all other dogs.

** Calculated only if an expected cell value is < 5; the preferred p value for this OR.

*** Exact confidence limits.[128]

**** Undefined.

***** There were no cases or controls for either megaesophagus or myasthenia gravis.

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Case Definition in Epidemiologic

Studies of Canine Hypoadrenocorticism

Detailed analyses of the data from the clinical trail of DOCP (Chapter 3) demonstrated that epidemiologic studies of canine hypoadrenocorticism may be conducted using a case definition less restrictive than one requiring an ACTH stimulation test. Data indicated that the population diagnosed using the ACTH stimulation test was virtually identical to the population diagnosed without it. Thus, while the ACTH stimulation test is desirable in establishing the diagnosis for an individual patient, requiring it in epidemiologic studies is unnecessarily restrictive. Consequently, epidemiologic studies can benefit from the salutary effects of greater case numbers, less complexity, more convenience, and less cost afforded by the less restrictive case definition that, if the veterinarian says the dog has hypoadrenocorticism, then, by definition, it does.

Logistic Regression

Age, breed, sex, and body weight were significantly associated with the occurrence of hypoadrenocorticism in the dog. Specifically, the probability of occurrence of canine hypoadrenocorticism increased with age and body weight, was greater in females than males, was greater in neutered than intact dogs, and varied with breed. There was model-dependent evidence of higher order interactions, but the exact nature of these interactions could not be determined.

Models were prepared which could, recognizing that many factors other than age, breed, sex, and body weight are involved in the occurrence of adrenal insufficiency, predict the *relative* probability of this disease in different dogs.

Methodology

Data from the veterinary literature, VMDB, clinical trial of DOCP, and mail survey of veterinarians enrolled in the clinical trial were all useful. The survey of veterinarians selected from the American Veterinary Medical Association's list of veterinarians suggested that mail survey methodology was a poor vehicle for obtaining data about an uncommon disease from randomly selected veterinarians; this limitation could be mitigated by substantially increasing the sample size and questionnaire response rate. Mail survey methodology can be useful for studying other diseases and obtaining basic descriptive data about veterinarians and their patients. Survey responses may be cut off 60 da after mailing.

Future Studies

The incidence and prevalence estimates presented in Table 7.1, while different statistically, were the same order of magnitude, and, thus, can be considered useful overall estimates. Future studies could focus on incidence and prevalence estimates for particular ages, breeds, sexes, or body weights.

Mail surveys which request data on clinical findings should, if possible, precisely define the clinical findings. For example, what exactly constitutes "anemia" or "nephritis"? This must be done without making the survey so onerous or complicated that veterinarians do not respond at all.

Matched case-control studies of hypoadrenal dogs would be a logical next step for those sexes and breeds already identified as associated with the disease. Matching on sex or breed or both would effectively remove these variables from the analyses, and permit focus on other variables such as age and body weight, the influence of which have been less well defined. This would require large data bases, perhaps the entire 1964-to-date VMDB.

REFERENCES

REFERENCES

1.   Addison, Thomas, English physician, 1793-1860, biography. *Med Classics* 1937;2(3):233.

2.   Addison T. On the constitutional and local effects of disease of the supra-renal capsules. *Med Classics* 1937;2(3):244-291.

3.   Ahlbom A, Norell S. *Introduction to modern epidemiology*. Chestnut Hill, MA: Epidemiology Resources Inc, 1984;7.

4.   Ahlbom A, Norell S. *Introduction to modern epidemiology*. Chestnut Hill, MA: Epidemiology Resources Inc, 1984;34.

5.   American Diabetes Association. Studies on the effects of adrenal cortical hormones on carbohydrate metabolism in human subjects. In: American Diabetes Association. *Proceedings of the American Diabetes Association*. Cincinnati: American Diabetes Association, 1949;9:149-169.

6.   American Veterinary Medical Association. *U.S. pet ownership & demographics handbook*. Schaumburg, IL: American Veterinary Medical Association, 1993;7.

7.   Anderson E, Haymaker W, Henderson E. Successful sublingual therapy in Addison's disease. *J Am Med Assoc* 1940;115:2167-2168.

8.   Anderson E, Kinsell LW, Daniels TC, et al. The treatment of Addison's disease by the intraoral administration of desoxycorticosterone acetate tablets. *J Clin Endocrinol* 1949;9:1324-1332.

9.   Annis JR. Adrenal cortical failure in the dog. *Vet Med* 1960;55:35-38.

10.   Atwell RB, Filippich LJ, O'Grady A. Hypoadrenocorticism in a dog. *Aust Vet Pract* 1979;9(3):167-168.

11.   Auge P. Addison's disease in littermates. *Vet Med* 1985;80:43-45.

12.   Bartges JW, Nielson DL. Reversible megaesophagus associated with atypical primary hypoadrenocorticism in a dog. *J Am Vet Med Assoc* 1992;201:889-891.

13.   Bath ML, Hill FWG. Adrenocortical insufficiency in the dog. *Aust Vet J* 1978;54:128-132.

14.   Bonneau N, Reed JH. Adrenocortical insufficiency in a dog. *Can Vet J* 1971;12:100-101.

15.   Boyd W. Acute adrenal insufficiency. *J Lab Clin Med* 1918;4:133-137.

16.   Britton SW, Silvette H. Some effects of cortico-adrenal extract and other substances on adrenalectomized animals. *Am J Physiol* 1931;99:15-32.

17.   Buell MV, Turner E. Cation distribution in the muscles of adrenalectomized rats. *Am J Physiol* 1941;134:225-239.

18.   Bunge M. *Causality, the place of the causal principle in modern science.* Cleveland: World Publishing Co, 1959;31-32.

19.   Bunge M. *Causality, the place of the causal principle in modern science.* Cleveland: World Publishing Co, 1963;34.

20.   Burrows CF. Reversible mega-oesophagus in a dog with hypoadrenocorticism. *J Small Anim Pract* 1987;28:1073-1078.

21.   Chauveau A. *The comparative anatomy of the domesticated animals.* 2nd ed. New York: D Appleton and Co, 1905;578-579.

22.   Cleghorn RA, Fowler JLA, Wenzel JS. The treatment of Addison's disease by a synthetic adrenal cortical hormone (desoxycorticosterone acetate). *Can Med Assoc J* 1939;41:226-231.

23.   Clinton, Jr M, Thorn GW, Eisenberg H, et al. Effect of synthetic desoxycorticosterone acetate therapy on plasma volume and electrolyte balance in normal dogs. *Endocrinol* 1942;31:578-581.

24.   Cornelius LM. Canine distemper presenting as acute adrenocortical insufficiency: a case report. *J Am Animal Hosp Assoc* 1974;10:153-157.

25. Cowie DM, Beaven PW. On the clinical evidence of involvement of the suprarenal glands in influenza and influenzal pneumonia. *Arch Int Med* 1919;24:78-88.

26. Crenshaw WE. A case of adrenocortical hypofunction in a dog. *Southwestern Vet* 1979;32:125-131.

27. de Lahunta A, Ross G, Whitlock R, et al. Clinical pathological conference. *Cornell Vet* 1972;62:145-164.

28. DiBartola SP. Canine hypoadrenocorticism: a brief review. *Calif Vet* 1980;34(4):15-20.

29. DiBartola SP, Johnson SE, Davenport DJ, et al. Clinicopathologic findings resembling hypoadrenocorticism in dogs with primary gastrointestinal disease. *J Am Vet Med Assoc* 1985;187:60-63.

30. Dillman DA. *Mail and telephone surveys, the total design method*. New York: John Wiley & Sons, 1978;1.

31. Dillman DA. *Mail and telephone surveys, the total design method*. New York: John Wiley & Sons, 1978;2.

32. Dillman DA. *Mail and telephone surveys, the total design method*. New York: John Wiley & Sons, 1978;9.

33. Dillman DA. *Mail and telephone surveys, the total design method*. New York: John Wiley & Sons, 1978;27.

34. Dillman DA. *Mail and telephone surveys, the total design method*. New York: John Wiley & Sons, 1978;52.

35. Dillman DA. *Mail and telephone surveys, the total design method*. New York: John Wiley & Sons, 1978; 160-199.

36. Ditchfield J, Archibald J, Cawley AJ. Adrenal cortical failure in dogs. *Can Vet J* 1961;2:175-177.

37. Drazner FH. The adrenal cortex. In: Drazner FH, ed. *Small animal endocrinology*. New York: Churchill Livingstone, 1986:201-277.

38. Einstein A. Letter to Max Born, 1924. Cited in French AP, ed. *Einstein, a centenary volume.* Cambridge, MA: Harvard University Press, 1979 from Rothman KJ. *Modern epidemiology.* Boston: Little, Brown and Co, 1986;10.

39. Elliott TR. Some results of excision of the adrenal glands. *J Physiol* 1914;49:38-53.

40. Everitt BS. *The analysis of contingency tables.* London: Chapman and Hall, 1977; 13-14.

41. Feldman EC. Adrenal gland disease. In: Ettinger SJ, ed. *Textbook of veterinary internal medicine.* 3rd ed. Philadelphia:WB Saunders Co, 1989;1756-1774.

42. Feldman EC, Ettinger SJ, Peters G. Hypoadrenocorticism in a dog. *Mod Vet Pract* 1977;58:433-438.

43. Feldman EC, Nelson RW. *Canine and feline endocrinology and reproduction.* Philadelphia:WB Saunders Co, 1987;195-217.

44. Feldman EC, Nelson RW, Lynn RC. Desoxycorticosterone pivalate (DOCP) treatment of canine and feline hypoadrenocorticism. In: Kirk RW, Bonagura JD, ed. *Current veterinary therapy XI, small animal practice.* 11th ed. Philadelphia: WB Saunders Co, 1992;353-355.

45. Feldman EC, Tyrrell JB. Hypoadrenocorticism. *Vet Clin North Am* 1977;7:555-581.

46. Feldman EC, Tyrrell JB, Bohannon NV. The synthetic ACTH stimulation test and measurement of endogenous plasma ACTH levels: useful diagnostic indicators for adrenal disease in dogs. *J Am Anim Hosp Assoc* 1978;14:524-531.

47. Ferrebee JW, Parker D, Carnes WH, et al. Certain effects of desoxycorticosterone. *Am J Physiol* 1941;135:230-237.

48. Ferrebee JW, Ragan C, Atchley DW, et al. Desoxycorticosterone esters, certain effects in the treatment of Addison's disease. *J Am Med Assoc* 1939;113:1725-1731.

49. Fleiss JL. *Statistical methods for rates and proportions*. New York: John Wiley and Sons, 1981; 172-173.

50. Fletcher RH, Fletcher SW, Wagner EH. *Clinical epidemiology, the essentials*. 2nd ed. Baltimore: Williams & Wilkins, 1988;78.

51. Fletcher RH, Fletcher SW, Wagner EH. *Clinical epidemiology, the essentials*. 2nd ed. Baltimore: Williams & Wilkins, 1988;191.

52. Fletcher RH, Fletcher SW, Wagner EH. *Clinical epidemiology, the essentials*. 2nd ed. Baltimore: Williams & Wilkins, 1988;191-192.

53. Fletcher RH, Fletcher SW, Wagner EH. *Clinical epidemiology, the essentials*. 2nd ed. Baltimore: Williams & Wilkins, 1988;198.

54. Fletcher RH, Fletcher SW, Wagner EH. *Clinical epidemiology, the essentials*. 2nd ed. Baltimore: Williams & Wilkins, 1988;202.

55. Fletcher RH, Fletcher SW, Wagner EH. *Clinical epidemiology, the essentials*. 2nd ed. Baltimore: Williams & Wilkins, 1988;205.

56. Ford J. Chaos: solving the unsolvable, predicting the unpredictable! In: Barnsley M, Demko, S, eds. *Chaotic dynamics and fractals*. Orlando, FL: Academic Press, 1986;1-52 from Kellert SH. *In the wake of chaos, unpredictable order in dynamical systems*. Chicago: The University of Chicago Press, 1993;141.

57. Forsham PH, Thorn GW, Bergner GE, et al. Metabolic changes induced by synthetic 11-dehydrocorticosterone acetate. *Am J Med* 1946;1:105-134.

58. Forsham PH, Thorn GW, Prunty FTG, et al. Clinical studies with pituitary adrenocorticotropin. *J Clin Endocrinol* 1948;8:15-66.

59. Fox JG, Beatty JO. Adrenal insufficiency in the dog: two case reports. *J Small Anim Pract* 1973;14:167-175.

60. Gassner FX, Nelson DH, Reich H, et al. Isolation of an androgenic compound from the adrenal venous blood of cows. *Proc Soc Exp Biol Med* 1951;77:829-831.

61. Gates FL. Antibody production after partial adrenalectomy in guinea pigs. *J Exp Med* 1918;27:725-738.

62. Gaunt R, Hays HW. The life-maintaining effect of crystalline progesterone in adrenalectomized ferrets. *Science* 1938;88:576-577.

63. Gleick J. *Chaos, making a new science*. New York: Viking Penguin Inc, 1987;1-4.

64. Gleick J. *Chaos, making a new science*. New York: Viking Penguin Inc, 1987;5-6.

65. Gleick J. *Chaos, making a new science*. New York: Viking Penguin Inc, 1987;8.

66. Greep RO, Deane HW. The cytology and cytochemistry of the adrenal cortex. *Ann New York Acad Sci* 1949;50:596-615.

67. Grünbaum A. Philosophical significance of relativity theory. In: Edwards P, ed. *The encyclopedia of philosophy*. Vol 7. New York: Macmillan Publishing Co Inc & The Free Press, 1967;133.

68. Hadlow WJ. Adrenal cortical atrophy in the dog. *Am J Path* 1953;29:353-361.

69. Hardy RM. Hypoadrenal gland disease. In: Ettinger SJ, Feldman EC, ed. *Textbook of veterinary internal medicine*. 4th ed. Philadelphia: WB Saunders Co, 1995;1579-1593.

70. Harlton BW. Addison's disease in a dog. *Vet Med/Small Anim Clin* 1976;71:285-288.

71. Harrop GA, Weinstein A. Studies on the suprarenal cortex. I. Cortical suprarenal insufficiency and the action of the cortical hormone upon the normal and suprarenalectomized dog. *J Exp Med* 1931;58:305-333.

72. Hartman FA, Blatz WE. Death produced by tying the adrenal veins. *Endocrinol* 1919;3:137-144.

73. Hartman FA, MacArthur CG, Hartman WE. A substance which prolongs the life of adrenalectomized cats. *Proc Soc Exp Biol Med* 1927;25:69-70.

74. Hawking SW. *A brief history of time, from the big bang to black holes*. Toronto: Bantam Books, 1988; 175.

75.   Hill FWG. Adrenocortical insufficiency in the dog. In: Grunsell CSG, Hill FWG, ed. *The veterinary annual*. Bristol: Scientechnica, 1979;223-228.

76.   Hills AG, Forsham PH, Finch CA. Changes in circulating leukocytes induced by the administration of pituitary adrenocorticotrophic hormone (ACTH) in man. *Blood* 1948;3:755-768.

77.   Honderich T. *The Oxford companion to philosophy*. Oxford: Oxford University Press, 1995;126.

78.   Hosmer, Jr DW, Lemeshow S. *Applied logistic regression*. New York: John Wiley & Sons, 1989;1.

79.   Hosmer, Jr DW, Lemeshow S. *Applied logistic regression*. New York: John Wiley & Sons, 1989;16-17.

80.   Hosmer, Jr DW, Lemeshow S. *Applied logistic regression*. New York: John Wiley & Sons, 1989;82-91.

81.   Hosmer, Jr DW, Lemeshow S. *Applied logistic regression*. New York: John Wiley & Sons, 1989;168.

82.   Houssay BA, Lewis JT. The relative importance to life of cortex and medulla of the adrenal glands. *Am J Physiol* 1923;64:512-521.

83.   Howell JM, Ormrod AN. Calcification of the adrenal glands in a dog. *Vet Rec* 1962;74:469-472.

84.   Hurlbutt III RH. *Hume, Newton, and the design argument*. Revised ed. Lincoln, NE: University of Nebraska Press, 1985;4-5.

85.   Ingle DJ. The biologic properties of cortisone: a review. *J Clin Endocrinol* 1950;10:1312-1354.

86.   Joseph DB. Canine hypoadrenocorticism. *Vet Tech* 1989;10:348-353.

87.   Keeton KS, Schechter RD, Schalm OW. Adrenocortical insufficiency in the dog. *Calif Vet* 1972;26:12-18.

88.   Kellert SH. *In the wake of chaos, unpredictable order in dynamical systems*. Chicago: The University of Chicago Press, 1993;xi.

89. Kellert SH. *In the wake of chaos, unpredictable order in dynamical systems*. Chicago: The University of Chicago Press, 1993;xii.

90. Kellert SH. *In the wake of chaos, unpredictable order in dynamical systems*. Chicago: The University of Chicago Press, 1993;2.

91. Kellert SH. *In the wake of chaos, unpredictable order in dynamical systems*. Chicago: The University of Chicago Press, 1993;134-135.

92. Kelly DF. Necrosis of the adrenal cortex and adrenal capsular myoarteritis in a dog. *Vet Rec* 1965;77:998-1001.

93. Kintzer PP, Peterson ME. Hypoadrenocorticism in dogs. In: Bonagura JD, ed. *Kirk's current veterinary therapy XII, small animal practice*. 12th ed. Philadelphia: WB Saunders Co, 1995;425-429.

94. Kuhlmann D, Ragan C, Ferrebee JW, et al. Toxic effects of desoxycorticosterone esters in dogs. *Science* 1939;90:496-497.

95. Levy JK, Schaer M, Bruyette D. Hypoglycemic seizures attributable to hypoadrenocorticism in a dog. *J Am Vet Med Assoc* 1994;204:526-530.

96. Lewis RA, Kuhlman D, Delbue C, et al. The effect of the adrenal cortex on carbohydrate metabolism. *Endocrinol* 1940;27:971-982.

97. Li CH, Evans HM, Simpson ME. Adrenocorticotropic hormone. *J Biol Chem* 1943;149:413-424.

98. Lilienfeld AM, Lilienfeld DE. *Foundations of epidemiology*. 2nd ed. New York: Oxford University Press, 1980;35.

99. Lilienfeld AM, Lilienfeld DE. *Foundations of epidemiology*. 2nd ed. New York: Oxford University Press, 1980;294-295.

100. Lilienfeld AM, Lilienfeld DE. *Foundations of epidemiology*. 2nd ed. New York: Oxford University Press, 1980;295.

101. Loeb RF. Effect of sodium chloride in treatment of a patient with Addison's disease. *Proc Soc Exp Biol Med* 1933;30:808-812.

102. Lucas GHW. Blood and urine findings in desuprarenalized dogs. *Am J Physiol* 1926;77:114-125.

103. Lusk G, Riche JA. Animal calorimetry: paper VIII. The alleged influence of the adrenals on diabetic metabolism. *Arch Int Med* 1914;13:673-681.

104. Lynn RC, Feldman EC. Treatment of canine hypoadrenocorticism with microcrystalline desoxycorticosterone pivalate. *Br Vet J* 1991;147:478-483.

105. Lynn RC, Feldman EC, Nelson RW. Efficacy of microcrystalline desoxycorticosterone pivalate for treatment of hypoadrenocorticism in dogs. *J Am Vet Med Assoc* 1993;202:392-396.

106. Lyons MC, Towers B, ed. *Galen on anatomical procedures, the later books*. London: Cambridge at the University Press, 1962;148.

107. Mandeville J. Registration statistics. *Pure-Bred Dogs American Kennel Gazette* 1983;100(4):35-43.

108. Mandeville J. 1981 registration statistics. *Pure-Bred Dogs American Kennel Gazette* 1982;99(4):56-61.

109. Mandeville J. 1983 registration statistics. *Pure-Bred Dogs American Kennel Gazette* 1984;101(4):34-41.

110. Mandeville J. 1984 registration statistics. *Pure-Bred Dogs/American Kennel Gazette* 1985;102(4):48-55.

111. Mandeville J. 1985 registration statistics. *Pure-Bred Dogs/American Kennel Gazette* 1986;103(4):40-47.

112. Mandeville J. 1986 registration statistics. *Pure-Bred Dogs/American Kennel Gazette* 1987;104(4):24-31.

113. Mandeville J. 1987 registration statistics. *Pure-Bred Dogs/American Kennel Gazette* 1988;105(4):33-39.

114. Mandeville J. 1988 registration statistics. *Pure-Bred Dogs/American Kennel Gazette* 1989;106(5):44-52.

115. Mandeville J. 1989 registration statistics. *Pure-Bred Dogs/American Kennel Gazette* 1990;107(4):48-55.

116. Mandeville J. 1990 registration statistics. *Pure-Bred Dogs/American Kennel Gazette* 1991;108(4):60-67.

117. Mandeville J. 1991 registration statistics. *Pure-Bred Dogs/American Kennel Gazette* 1992;109(4):40-48.

118. Marañón G. Adrenal insufficiency in the infections. *Endocrinol* 1920;4:437-438.

119. Marshak RR, Webster GD Jr, Skelley JF. Observations on a case of primary adrenocortical insufficiency in a dog. *J Am Vet Med Assoc* 1960;136:274-280.

120. Martin SW, Meek AH, Willeberg P. *Veterinary epidemiology, principles and methods*. Ames: Iowa State University Press, 1987;55.

121. Martin SW, Meek AH, Willeberg P. *Veterinary epidemiology, principles and methods*. Ames, IA: Iowa State University Press, 1987;146-147.

122. Mason HL, Myers CS, Kendall EC. The chemistry of crystalline substances isolated from the suprarenal gland. *J Biol Chem* 1936;114:613-631.

123. Mausner JS, Kramer S. *Mausner & Bahn epidemiology--an introductory text*. Philadelphia: WB Saunders Co, 1985; 44.

124. Mausner JS, Kramer S. *Mausner & Bahn epidemiology--an introductory text*. Philadelphia: WB Saunders Co, 1985;184.

125. McCullagh EP. Sodium and chloride retention in Addison's disease treated with desoxycorticosterone acetate. *Cleveland Clin Quarterly* 1939;6:105-108.

126. McCullagh EP, Ryan EJ. The use of desoxycorticosterone acetate in Addison's disease. *J Am Med Assoc* 1940;114:2530-2537.

127. Medinger TL, Williams DA, Bruyette DS. Severe gastrointestinal tract hemorrhage in three dogs with hypoadrenocorticism. *J Am Vet Med Assoc* 1993;202:1869-1872.

128. Mehta CR, Patel NR, Gray R. Computing an exact confidence interval for the common odds ratio in several 2x2 contingency tables. *J Am Stat Assoc* 1985; 80:969-973.

129. Merck & Co, Inc. Hypoadrenocorticism (Addison's disease). In: Fraser CM, ed. *The Merck veterinary manual*. 7th ed. Rahway, NJ:Merck & Co Inc, 1991;264-266.

130. Milton JS, Arnold JC. *Introduction to probability and statistics: principles and applications for engineering and the computing sciences*. New York: McGraw-Hill, 1990; 320-322.

131. Montagu MFA. *Edward Tyson, M.D., F.R.S., 1650-1708, and the rise of human and comparative anatomy in England, a study in the history of science.* Philadelphia: The American Philosophical Society, 1943;xxv,67,&393.

132. Moore B, Purinton CO. On the effects of complete removal of the suprarenal glands. *Am J Physiol* 1901;5:182-190.

133. Morales GA, Nielsen SW. Canine adrenocortical atrophy: review of literature and a report of two cases. *J Small Anim Pract* 1970;11:257-263.

134. Mulnix JA. Hypoadrenocorticism in the dog. *J Am Anim Hosp Assoc* 1971;7:220-241.

135. Murrell KA. Hypoadrenocorticism in a dog. *Mod Vet Pract* 1980;61:625-626.

136. Musselman EE. Electrocardiographic signs of adrenocortical insufficiency with hypercalcemia in the dog. *Vet Med/Small Anim Clin* 1975;70:1433-1437.

137. Nadler S. Introduction. In: Nadler S, ed. *Causation in early modern philosophy, Cartesianism, occasionalism, and preestablished harmony*. University Park, PA: The Pennsylvania University Press, 1993;6-7.

138. Nelson DH. *The adrenal cortex: physiological function and disease*. Philadelphia: WB Saunders Co, 1980;113-133.

139. Nelson DH, Reich H, Samuels LT. Isolation of a steroid hormone from the adrenal-vein blood of dogs. *Science* 1950;111:578-579.

225

140. Nelson DH, Samuels LT. A method for the determination of 17-hydroxycorticosteroids in blood: 17-hydroxycorticosterone in the peripheral circulation. *J Clin Endocrinol Metab* 1952;12:519-526.

141. Nelson RW, Couto CG. *Essentials of small animal internal medicine.* St. Louis: Mosby-Year Book Inc, 1992;600-604.

142. Nimmons GB, McManus JL. Adreno-cortical insufficiency in a dog. *Can Vet J* 1968;9:252-253.

143. O'Rourke MD. A medical approach to adrenal gland problems: a report of three cases. *J Am Anim Hosp Assoc* 1975;11:762-764.

144. Osler W. On six cases of Addison's disease, with the report of a case greatly benefited by the use of the suprarenal extract. *Internat Med Mag* 1896;5:3-11.

145. Owens D. *Causes and coincidences.* Cambridge: Cambridge University Press, 1992;1.

146. Owens D. *Causes and coincidences.* Cambridge: Cambridge University Press, 1992;5.

147. Peterson ME, Feinman JM. Hypercalcemia associated with hypoadrenocorticism in sixteen dogs. *J Am Vet Med Assoc* 1982;181:802-804.

148. Peterson ME, Kintzer PP, Kass PH. Pretreatment clinical and laboratory findings in dogs with hypoadrenocorticism: 225 cases (1979-1993). *J Am Vet Med Assoc* 1996;208:85-91.

149. Pfiffner JJ. The preparation of an active extract of the suprarenal cortex. *Anatomical Rec* 1929;44:225.

150. Podell M. Canine hypoadrenocorticism, diagnostic dilemmas associated with the "great pretender." *Prob Vet Med* 1990;2:717-737.

151. Ragan C, Ferrebee JW, Phyfe P, et al. A syndrome of polydipsia and polyuria induced in normal animals by desoxycorticosterone acetate. *Am J Physiol* 1940;131:73-78.

152. Rakich PM, Lorenz MD. Clinical signs and laboratory abnormalities in 23 dogs with spontaneous hypoadrenocorticism. *J Am Anim Hosp Assoc* 1984;20:647-649.

153. Reimers MW, Dodd RR. Hypoadrenocorticism in the dog. *Canine Pract* 1978;5:61-65.

154. Roche M, Forsham PH, Forsham CC, et al. A study of adrenal cortical response in health and disease. The 48-hour ACTH test. *J Clin Endocrinol* 1950;10:834.

155. Rogers W, Straus J, Chew D. Atypical hypoadrenocorticism in three dogs. *J Am Vet Med Assoc* 1981;179:155-158.

156. Rogoff JM, Stewart GN. Further studies on adrenal insufficiency in dogs. *Science* 1926;64:141-142.

157. Rogoff JM, Stewart GN. Studies on adrenal insufficiency in dogs. I. Control animals not subjected to any treatment. *Am J Physiol* 1926;78:683-710.

158. Rogoff JM, Stewart GN. Studies on adrenal insufficiency in dogs. II. Blood studies in control animals not subjected to treatment. *Am J Physiol* 1926;78:711-729.

159. Rogoff JM, Stewart GN. The influence of adrenal extracts on the survival period of adrenalectomized dogs. *Science* 1927;66:327-328.

160. Rogoff JM, Stewart GN. Studies on adrenal insufficiency. VI. The influence of "heat" on the survival period of dogs after adrenalectomy. *Am J Physiol* 1928;86:20-24.

161. Rogoff JM, Stewart GN. Studies on adrenal insufficiency in dogs. V. The influence of adrenal extracts on the survival period of adrenalectomized dogs. *Am J Physiol* 1928;84:660-674.

162. Rosner BA. *Fundamentals of biostatistics*. Boston: Duxbury Press, 1982; 308-317.

163. Rothenbacher H, Shigley RF. Adrenocortical apoplexy in a dog. *J Am Vet Med Assoc* 1966;149:406-411.

164. Rothman KJ. *Modern epidemiology*. Boston: Little, Brown and Co, 1986;7.

165. Rothman KJ. *Modern epidemiology*. Boston: Little, Brown and Co, 1986;7-21.

166. Rothman KJ. *Modern epidemiology*. Boston: Little, Brown and Co, 1986;9-10.

167. Rothman KJ. *Modern epidemiology*. Boston: Little, Brown and Co, 1986;11.

168. Rothman KJ. *Modern epidemiology*. Boston: Little, Brown and Co, 1986; 33.

169. Rothman KJ, ed. *Causal inference*. Chestnut Hill, MA: Epidemiology Resources Inc, 1988.

170. Rothman KJ, ed. *Causal inference*. Chestnut Hill, MA: Epidemiology Resources Inc, 1988;20.

171. Ruben JM, Walker MJ, Longstaffe JA. Addison's disease in a puppy. *Vet Rec* 1985;116:91-93.

172. Ryan EJ, McCullagh EP. Desoxy-corticosterone acetate in Addison's disease with presentation of a typical case. *Cleveland Clin Quarterly* 1940;7:19-23.

173. Sackett DL, Haynes RB, Guyatt GH, et al. *Clinical epidemiology, a basic science for clinical medicine*. 2nd ed. Boston: Little, Brown and Co, 1991;290.

174. Sackett DL, Haynes RB, Guyatt GH, et al. *Clinical epidemiology, a basic science for clinical medicine*. 2nd ed. Boston: Little, Brown and Co, 1991;290-291.

175. Sagan C. Introduction. In: Hawking SW. *A brief history of time, from the big bang to black holes*. Toronto: Bantam Books, 1988;x.

176. Sanger VL, Noble WE, Gehrman RS. Adrenal cortical failure in a dog. *Vet Med/Small Anim Clin* 1974;59:579-581.

177. SAS Institute Inc. *JMP® statistics and graphics guide, version 3 of JMP*. Cary, NC: SAS Institute Inc, 1994.

178. SAS Institute Inc. *JMP® statistics and graphics guide, version 3 of JMP*. Cary, NC: SAS Institute Inc, 1994;117-118.

179. SAS Institute Inc. *JMP® statistics and graphics guide, version 3 of JMP*. Cary, NC: SAS Institute Inc, 1994;117 and 216.

180. SAS Institute Inc. *JMP® statistics and graphics guide, version 3 of JMP*. Cary, NC: SAS Institute Inc, 1994;216-217.

181. Sayers G. The adrenal cortex and homeostasis. *Physiol Rev* 1950;30:241-320.

182. Sayers G, White A, Long CNH. Preparation and properties of pituitary adrenotropic hormone. *J Biol Chem* 1943;149:425-436.

183. Schaer M, Chen CL. A clinical survey of 48 dogs with adrenocortical hypofunction. *J Am Anim Hosp Assoc* 1983;19:443-452.

184. Schaer M, Riley WJ, Buergelt CD et al. Autoimmunity and Addison's disease in the dog. *J Am Anim Hosp Assoc* 1986;22:789-794.

185. Schlesinger GN. Scientists and philosophy. In: Rothman KJ, ed. *Causal inference*. Chestnut Hill, MA: Epidemiology Resources Inc, 1988;86.

186. Schlesselman JJ. *Case-control studies, design, conduct, analysis*. New York: Oxford University Press, 1982;14.

187. Schlesselman JJ. *Case-control studies, design, conduct, analysis*. New York: Oxford University Press, 1982;15.

188. Schlesselman JJ. *Case-control studies, design, conduct, analysis*. New York: Oxford University Press, 1982;28.

189. Schrader LA. Hypoadrenocorticism. In: Kirk RW, ed. *Current veterinary therapy IX, small animal practice*. 9th ed. Philadelphia:WB Saunders Co, 1986;972-977.

190. Selvin S. *Statistical analysis of epidemiologic data*. New York: Oxford University Press, 1991;7.

191. Sergent E. The white adrenal line: its production and diagnostic significance. *Endocrinol* 1917;1:18-23.

192. Shaker E, Hurvitz AI, Peterson ME. Hypoadrenocorticism in a family of Standard Poodles. *J Am Vet Med Assoc* 1988;192:1091-1092.

193. Siegel ET. Assessment of pituitary-adrenal gland function in the dog. *Am J Vet Res* 1968;29:173-180.

194. Siegel ET, Schryver HF, Fidler I. Clinico-pathologic conference. *J Am Vet Med Assoc* 1967;150:423-433.

195. Simpson SA, Tait JF, Bush IE. Secretion of a salt-retaining hormone by the mammalian adrenal cortex. *Lancet* 1952;2:226-228.

196. Simpson SL. The use of synthetic desoxycorticosterone acetate in Addison's disease. *Lancet* 1938;235:557-558.

197. Simpson SL, Wilkinson JF, Himsworth HP, et al. Discussion on recent developments in the treatment of Addison's disease. *Proc Royal Soc Med* 1939;32:685-706.

198. Sisson S. *The anatomy of the domestic animals*. Philadelphia: WB Saunders Co, 1910;563-564.

199. Smith F. *A manual of veterinary physiology*. New York: William R. Jenkins, 1899;77.

200. Smith RD. *Veterinary clinical epidemiology, a problem-oriented approach*. Boston: Butterworth-Heinemann, 1991;66-67.

201. Smith RD. *Veterinary clinical epidemiology, a problem-oriented approach*. Boston: Butterworth-Heinemann, 1991;83.

202. Smith RD. *Veterinary clinical epidemiology, a problem-oriented approach*. Boston: Butterworth-Heinemann, 1991;84.

203. Smith RD. *Veterinary clinical epidemiology, a problem-oriented approach*. Boston: Butterworth-Heinemann, 1991;209.

204. Solomon RC. *The big questions, a short introduction to philosophy*. 4th ed. Fort Worth: Harcourt Brace College Publishers, 1944;107.

205. Solomon RC. *The big questions, a short introduction to philosophy*. 4th ed. Fort Worth: Harcourt Brace College Publishers, 1944;145.

206. Sorkin SZ. Addison's disease. In: Talbott JH, ed. *Medicine, analytical reviews of general medicine, neurology and pediatrics*. Baltimore: Williams and Wilkins, 1949;28:371-425.

207. Steiger M, Reichstein T. Partial synthesis of a crystallized compound with the biological activity of the adrenal-cortical hormone. *Nature* 1937;139:925-926.

208. Steinbeck AW, Theile HM. The adrenal cortex (excluding aldosteronism). In: Bayliss RIS, ed. *Clinics in endocrinology and metabolism*. London: WB Saunders Co, 1974;3:557-591.

209. Stewart GN. Adrenal insufficiency. *Endocrinol* 1921;5:283-306.

210. Stewart GN. Blood studies in dogs after adrenalectomy. *J Pharmacol Exp Therap* 1926;29:373-380.

211. Stewart GN, Rogoff JM. The alleged relation of the epinephrin secretion of the adrenals to certain experimental hyperglycemias. *Am J Physiol* 1917;44:543-580.

212. Stewart GN, Rogoff JM. Further observations on the relation of the adrenals to certain experimental hyperglycemias (ether and asphyxia). *Am J Physiol* 1920;51:366-377.

213. Stewart GN, Rogoff JM. Studies on adrenal insufficiency. *Proc Soc Exp Biol Med* 1925;22:394-397.

214. Strehl H, Weiss O. Beiträge zur Physiologie der Nebenniere. *Archiv fuer die gesamte Physiologie* 1901;86:107-121.

215. Streiner DL, Norman GR, Blum HM. *PDQ epidemiology*. Toronto: BC Decker Inc, 1989; 68.

216. Swingle WW, Parkins WM, Taylor AR, et al. Effect of oestrus (pseudopregnancy) and certain pituitary hormones on the life-span of adrenalectomized animals. *Am J Physiol* 1937;119:675-683.

217. Swingle WW, Pfiffner JJ. Experiments with an active extract of the suprarenal cortex. *Anatomical Rec* 1929;44:225-226.

218. Swingle WW, Pfiffner JJ. Studies on the adrenal cortex. I. The effect of a lipid fraction upon the life-span of adrenalectomized cats. *Am J Physiol* 1931;96:153-163.

219. Swingle WW, Pfiffner JJ. Studies on the adrenal cortex. II. An aqueous extract of the adrenal cortex which maintains the life of bilaterally adrenalectomized cats. *Am J Physiol* 1931;96:164-179.

220. Taylor R. Causation. In: Edwards P, ed. *The encyclopedia of philosophy*. Vol 2. New York: Macmillan Publishing Co Inc & The Free Press, 1967;59.

221. Taylor R. Causation. In: Edwards P, ed. *The encyclopedia of philosophy*. Vol 2. New York: Macmillan Publishing Co Inc & The Free Press, 1967;66.

222. Theran P. Case records of the Angell Memorial Animal Hospital. *J Am Vet Med Assoc* 1968;153:1195-1202.

223. Thorn GW. The adrenal cortex. *Johns Hopkins Med J* 1968;123:49-77.

224. Thorn GW. Adrenal insufficiency and the use of synthetic adrenal cortical hormone. *1940 Proc, Inter-State Post Grad Med Assembly North Am* 1940;16-24.

225. Thorn GW, Clinton, Jr M. Metabolic changes in a patient with Addison's disease following the onset of diabetes mellitus. *J Clin Endocrinol* 1943;3:335-344.

226. Thorn GW, Dorrance SS, Day E. Addison's disease: evaluation of synthetic desoxycorticosterone acetate therapy in 158 patients. *Ann Int Med* 1942;16:1053-1095.

227. Thorn GW, Eisenberg H. Studies on desoxy-corticosterone, a synthetic adrenal cortical hormone. *Endocrinol* 1939;25:39-46.

228. Thorn GW, Engel LL, Eisenberg H. The effect of corticosterone and related compounds on the renal excretion of electrolytes. *J Exp Med* 1938;68:161-171.

229. Thorn GW, Engel LL, Lewis RA. The effect of 17-hydroxycorticosterone and related adrenal cortical steroids on sodium and chloride excretion. *Science* 1941;94:348-349.

230. Thorn GW, Firor WM. Desoxycorticosterone acetate therapy in Addison's disease, clinical considerations. *J Am Med Assoc* 1940;114:2517-2525.

231. Thorn GW, Forsham PH. Metabolic changes in man following adrenal and pituitary hormone administration. *Recent Prog Hormone Res* 1949;4:229-288.

232. Thorn GW, Forsham PH, Bennett LL, et al. Clinical and metabolic changes in Addison's disease following the administration of compound E acetate (11-dehydro, 17-hydroxycorticosterone acetate). In: Association of American Physicians. *Transactions of the Association of American Physicians*. Philadelphia: WJ Dornan Inc, 1949:233-244.

233. Thorn GW, Forsham PH, Frawley TF. Advances in the diagnosis and treatment of adrenal insufficiency. *Am J Med* 1951;10:595-611.

234. Thorn GW, Forsham PH, Prunty FTG, et al. Clinical studies in Addison's disease. *Ann New York Acad Sci* 1949;50:646-656.

235. Thorn GW, Greif RL, Coutinho MD, et al. Relative effectiveness of several methods of administering desoxycorticosterone acetate. *J Clin Endocrinol* 1941;1:967-976.

236. Thorn GW, Howard RP, Emerson, Jr K. Treatment of Addison's disease with desoxy-corticosterone acetate, a synthetic adrenal cortical hormone (preliminary report). *J Clin Invest* 1939;18:449-467.

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237. Thorn GW, Howard RP, Emerson, Jr K, et al. Treatment of Addison's disease with pellets of crystalline adrenal cortical hormone (synthetic desoxycorticosterone acetate) implanted subcutaneously. *Johns Hopkins Med J* 1939;64:339-365.

238. Thorn GW, Koepf GF, Lewis RA, et al. Carbohydrate metabolism in Addison's disease. *J Clin Invest* 1940;19:813-832.

239. Thrusfield M. *Veterinary epidemiology*. London: Butterworth & Co, 1986; 34.

240. Tooley M. *Causation, a realistic approach*. Oxford: Oxford University Press, 1987;289-296.

241. Vaughan I, ed. *Strangeways' Veterinary Anatomy*. Chicago: WT Keener & Co, 1907;343.

242. Vincent S. The chromaphil tissues and the adrenal medulla. *Proc Royal Soc London, Series B* 1910;82:502-515.

243. Vincent S. Recent views as to the function of the adrenal bodies. *Endocrinol* 1917;1:140-152.

244. Willard MD. An unusual case of hypoadrenocorticism in a dog. *Mod Vet Pract* 1980;61:830-833.

245. Willard MD, Fossum TW, Torrance A, et al. Hyponatremia and hyperkalemia associated with idiopathic or experimentally induced chylothorax in four dogs. *J Am Vet Med Assoc* 1991;199:353-358.

246. Willard MD, Schall WD, McCaw DE, et al. Canine hypoadrenocorticism: report of 37 cases and review of 39 previously reported cases. *J Am Vet Med Assoc* 1982;180:59-62.

247. Willson DM, Rynearson EH, Dry TJ. Cardiac failure following treatment of Addison's disease with desoxycorticosterone acetate. *Proc Staff Meetings Mayo Clin* 1941;16:168-173.

248. Zukav G. *The dancing wu li masters, an overview of the new physics*. New York: William Morrow and Co Inc, 1979;25.

249. Zukav G. *The dancing wu li masters, an overview of the new physics.* New York: William Morrow and Co Inc, 1979;52-53.

250. Zukav G. *The dancing wu li masters, an overview of the new physics.* New York: William Morrow and Co Inc, 1979;85-88.

251. Zukav G. *The dancing wu li masters, an overview of the new physics.* New York: William Morrow and Co Inc, 1979;88.

252. Zukav G. *The dancing wu li masters, an overview of the new physics.* New York: William Morrow and Co Inc, 1979;162.

253. Zukav G. *The dancing wu li masters, an overview of the new physics.* New York: William Morrow and Co Inc, 1979;163.

254. Zwemer RL. An experimental study of the adrenal cortex. I. The survival value of the adrenal cortex. *Am J Physiol* 1926;79:641-657.

APPENDICES

APPENDIX A

DATA COLLECTION FORMS

CONTENTS–APPENDIX A

A1. Case Data Abstract Form (VMDB Participants) (front)

**UNIVERSITY OF TENNESSEE
COLLEGE OF VETERINARY MEDICINE**

CANINE HYPOADRENOCORTICISM STUDY

CASE DATA ABSTRACT FORM

PLEASE COMPLETE A SEPARATE FORM FOR EACH CASE.

1. INSTITUTION CODE:_____   2. PATIENT ID NUMBER:_____

3. DATE OF DISCHARGE: _____/_____/_____
                        month   day   year

4. OWNER ZIP CODE: _____

5. LABORATORY TEST RESULTS <u>USED TO MAKE THE DIAGNOSIS</u>:
   (These results should come from laboratory reports dated during
   this episode of care. Copies of laboratory reports may be sent
   in lieu of completing the information below.)

   A. ACTH STIMULATION TEST (See attached sample for possible
      documentation type):

      DATE OF TEST _____/_____/_____
                     month   day   year

     PRE-STIMULATION (BASELINE OR RESTING) CORTISOL_____

     POST-STIMULATION CORTISOL_____

   B. PLASMA OR SERUM ELECTROLYTE CONCENTRATIONS:

     DATE OF <u>FIRST</u> SODIUM TEST DURING THIS EPISODE OF CARE

          _____/_____/_____
            month   day   year

     SODIUM (Na+) LEVEL _____

     DATE OF <u>FIRST</u> POTASSIUM TEST DURING THIS EPISODE OF CARE

          _____/_____/_____
            month   day   year

     POTASSIUM (K+) LEVEL _____

     PLEASE COMPLETE THE BACK OF THE FORM ALSO.

www.manaraa.com

A2. Case Data Abstract Form (VMDB Participants) (back)

6. TREATMENT:

    A. HAS THIS DOG BEEN TREATED WITH FLORINEF
       (FLUDROCORTISONE)?   YES   NO

    B. HAS THIS DOG BEEN TREATED WITH PERCORTEN
       (DESOXYCORTICOSTERONE PIVALATE)?   YES   NO

7. OTHER DIAGNOSES (Please list all diagnoses from the initial
   visit to the present):

   DIAGNOSIS   DATE OF DIAGNOSIS

   _____   _____

   _____   _____

   _____   _____

   _____   _____

   _____   _____

   _____   _____

   _____   _____

   _____   _____

   _____   _____

   _____   _____

   _____   _____

   _____   _____

   _____   _____

   _____   _____

   _____   _____

   _____   _____

   _____   _____

THANK YOU.

PLEASE RETURN THE FORMS TO DR. WILLIAM J. KELCH, DEPARTMENT OF
ENVIRONMENTAL PRACTICE, BOX 1071, KNOXVILLE, TN 37901-1071.

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A3. Population Data Abstract Form (front)

CANINE HYPOADRENOCORTICISM STUDY

POPULATION DATA ABSTRACT FORM

PLEASE COMPLETE ONE OF THESE FORMS PER INSTITUTION/FACILITY.

1. (CRITICALLY IMPORTANT!) NUMBER OF DOGS SEEN* DURING
   1989: _____
   1990: _____
   1991: _____

THE FOLLOWING INFORMATION IS OPTIONAL BUT WOULD BE VERY HELPFUL IF IT IS AVAILABLE.

2. NUMBER OF DOGS SEEN* DURING

		1989:	1990:	1991:
A.	INTACT FEMALES	_____	_____	_____
	SPAYED FEMALES	_____	_____	_____
	FEMALE, UNKNOWN	_____	_____	_____
	INTACT MALES	_____	_____	_____
	NEUTERED MALES	_____	_____	_____
	MALES, UNKNOWN	_____	_____	_____
	SEX UNKNOWN	_____	_____	_____
B.	0 TO 2 WEEKS OLD	_____	_____	_____
	2 WKS TO 2 MOS OLD	_____	_____	_____
	2 TO 6 MOS OLD	_____	_____	_____
	6 TO 12 MOS OLD	_____	_____	_____
	1 TO 2 YEARS OLD	_____	_____	_____
	2 TO 4 YEARS OLD	_____	_____	_____
	4 TO 7 YEARS OLD	_____	_____	_____
	7 TO 10 YEARS OLD	_____	_____	_____
	10 TO 15 YEARS OLD	_____	_____	_____
	15 YEARS AND OLDER	_____	_____	_____

   C. IF THE FREQUENCY OF DIFFERENT BREEDS CAN BE DETERMINED FOR THE DOGS SEEN DURING 1989 THROUGH 1991, PLEASE ATTACH A LIST OF BREED FREQUENCY.

*NOT THE NUMBER OF DOG VISITS; A DOG CAN BE COUNTED ONLY ONCE DURING THE THREE YEARS. FOR EXAMPLE, A DOG SEEN FIRST IN 1989 WOULD BE COUNTED ONCE IN 1989 AND WOULD NOT BE COUNTED AGAIN EVEN IF IT WAS SEEN AGAIN IN 1990 AND/OR 1991.

PLEASE COMPLETE THE BACK OF THE FORM ALSO.

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A4. Population Data Abstract Form (back)

PLEASE INDICATE A PERSON (USUALLY THE PERSON ABSTRACTING THE INFORMATION) WHO COULD BE CONTACTED IF THERE ARE QUESTIONS ABOUT THE INFORMATION ON THE FORMS.

NAME: _____ **PHONE:** _____

BEST TIMES TO CALL:_____

NAME OF INSTITUTION OR FACILITY:_____

PLEASE RETURN THE INFORMATION IN THE ENVELOPE PROVIDED.
THANK YOU VERY MUCH FOR YOUR ASSISTANCE.

A5. Case Data Abstract Form (VMDB Non-Participants) (front)

CANINE HYPOADRENOCORTICISM STUDY

CASE DATA ABSTRACT FORM

PLEASE COMPLETE A SEPARATE FORM FOR EACH CASE. KEY WORDS *OTHER*
THAN CANINE HYPOADRENOCORTICISM THAT MAY BE HELPFUL IN LOCATING
CASES ARE ADRENAL CORTICAL HYPOFUNCTION, ADDISON'S DISEASE, AND
ADRENAL INSUFFICIENCY.

1. INSTITUTION CODE:_____   2. PATIENT ID NUMBER:_____

3. OWNER ZIP CODE: _____

4. DATE OF FIRST DIAGNOSIS: _____ _____ _____
                                 month   day   year

5. AGE *WHEN* FIRST DIAGNOSED: BIRTH DATE:
                                 OR
   _____ _____   _____ _____
     years   months   year   month

6. SEX: (Please mark one category only)
        Intact female __
        Spayed female __
        Female, unknown __
        Intact male __
        Neutered male __
        Male, unknown __

7. BREED: _____

8. TEST RESULTS USED TO MAKE THE DIAGNOSIS:
        (These results should come from laboratory reports dated very
        near the same date as the DATE OF FIRST DIAGNOSIS. Copies
        of laboratory reports are desired and can be attached to
        this abstract form. If copies of lab reports are attached,
        the blanks below do not need to be filled in.)

   ACTH STIMULATION TEST:

        DATE OF TEST _____ _____ _____
                       month   day   year

        RESTING CORTISOL_____

        POST-STIMULATION CORTISOL_____

PLEASE COMPLETE THE BACK OF THE FORM ALSO.

243

A6. Case Data Abstract Form (VMDB Non-Participants) (back)

9. TREATMENT:

   A. HAS THIS DOG BEEN TREATED WITH FLORINEF
      (FLUDROCORTISONE)?   YES   NO

   B. HAS THIS DOG BEEN TREATED WITH PERCORTEN
      (DESOXYCORTICOSTERONE PIVALATE)?   YES   NO

10. OTHER DIAGNOSES:
    (If a summary of other diagnoses is included in the record,
     please attach a copy. If only a few other diagnoses are
     listed, please record the information below.)

   DIAGNOSIS   DATE OF DIAGNOSIS

   _____   _____

   _____   _____

   _____   _____

THANK YOU.

PLEASE RETURN THE FORMS ALONG WITH THE POPULATION DATA ABSTRACT
FORM IN THE ENVELOPE PROVIDED OR MAIL TO DR. JOHN C. NEW, JR.,
DEPARTMENT OF ENVIRONMENTAL PRACTICE, BOX 1071, KNOXVILLE, TN,
37901-1071.

A7. Case Control Study of Canine Hypoadrenocorticism (Survey Form for Veterinarians Enrolled in Clinical Trial) (front)

CASE CONTROL STUDY OF CANINE HYPOADRENOCORTICISM

Investigator Name:_____ Date:_____

Clinic Name: _____

Dog's Name:_____ Owner's Name:_____

Age' (yr):_____ Wt. (lb):____ Breed:_____ Sex: M MC F FS
(Circle one)

Health Status: (Circle one) Alive Dead Lost to follow-up

Cause of Hypoadrenocorticism: (Circle one) Lysodren Adrenalectomy Unknown

Other Diseases: (Check all that apply)

Anemia'	_____	Keratoconjunctivitis sicca	_____
Arthritis'	_____	Megaesophagus	_____
Cruciate ligament rupture	_____	Myasthenia gravis	_____
Diabetes mellitus	_____	Nephritis'	_____
Hepatitis'	_____	Thrombocytopenia	_____
Hypothyroidism	_____	None of the above	_____

Dog's Name:_____ Owner's Name:_____

Age' (yr): _____ Wt. (lb):____ Breed:_____ Sex: M MC F FS
(Circle one)

Health Status: (Circle one) Alive Dead Lost to follow-up

Other Diseases: (Check all that apply)

Anemia'	_____	Hypothyroidism	
Arthritis'	_____	Keratoconjunctivitis sicca	_____
Cruciate ligament rupture	_____	Megaesophagus	_____
Diabetes mellitus	_____	Myasthenia gravis	_____
Hepatitis'	_____	Nephritis'	_____
Hypoadrenocorticism	_____	Thrombocytopenia	_____
		None of the above _____	

Dog's Name:_____ Owner's Name:_____

Age' (yr): _____ Wt. (lb):____ Breed:_____ Sex: M MC F FS
(Circle one)

Health Status: (Circle one) Alive Dead Lost to follow-up

Other Diseases: (Check all that apply)

Anemia'	_____	Hypothyroidism	
Arthritis'	_____	Keratoconjunctivitis sicca	_____
Cruciate ligament rupture	_____	Megaesophagus	_____
Diabetes mellitus	_____	Myasthenia gravis	_____
Hepatitis'	_____	Nephritis'	_____
Hypoadrenocorticism	_____	Thrombocytopenia	_____
		None of the above _____	

In your practice how many dogs were diagnosed with hypoadrenocorticism between January 1, 1993 and December 31, 1993?' _____

Approximately how many active dog patients do you have in your practice?' _____

How many full-time veterinarians work in your practice? _____

Print the name of person filling out case report form

_____

Footnotes on Reverse

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A8. Case Control Study of Canine Hypoadrenocorticism (Survey Form for Veterinarians Enrolled in Clinical Trial) (back)

Footnotes

[1] Current age <u>or</u> age at death <u>or</u> last known age (if lost to follow-up)

[2] Anemia from any cause

[3] Any inflammatory disease of the joints

[4] Any inflammatory disease of the liver

[5] Any inflammatory disease of the kidney

[6] All cases diagnosed regardless of whether they lived or died or how they were treated.

[7] Active dog patients is the number of dogs that have visited your practice in the last year (January 1, 1993 to December 31, 1993).

Note: If you have any questions, contact Phylis Hilling, LVT, Susan Owen or Randy Lynn, DVM at 1-800-637-0281.

Return to: Ciba Animal Health
Post Office Box 18300
Greensboro, NC 27419-8300

A9. Instructions for Filling Out the Case Report Form-Case Control Study of Canine Hypoadrenocorticism (Instructions for Survey Form for Veterinarians Enrolled in Clinical Trial) (front)

INSTRUCTIONS FOR FILLING OUT THE CASE REPORT FORM

Case Control Study of Canine Hypoadrenocorticism

1. Fill in the date you are preparing the form in the upper right corner.

2. <u>For the hypoadrenal dog</u>:

   a. The investigator's name, clinic's name, dog's name, and owner's name have already been filled in.

   b. Please record the dog's current age if alive <u>or</u> age at death <u>or</u> last known age if "lost to follow-up."

   If you are not certain whether the dog is alive or dead, please contact the owner and find out. "Lost to follow-up" should include <u>only</u> dogs where it is impossible to determine whether the dog is alive or dead. In this case, record the dog's age at the time it was last known to be alive.

   c. Record the dog's health status and presumed cause of hypoadrenocorticism [lysodren therapy, adrenalectomy or unknown].

   d. Check which "Other Diseases" have been diagnosed in this dog at any time during its life. [Simply check those that apply.]

3. <u>For Control Dog No. 1</u>:

   [Your "file" of patients may be a paper file or a computer file; "next" in the file means next alphabetically.]

   a. The next record (alphabetically) in your file after the record of the hypoadrenal patient will serve as Control Dog No. 1 <u>provided</u> it has a <u>different</u> owner and is a <u>dog</u>. If the next record belongs to the same owner or is not a dog, go to the next record until a <u>dog</u> owned by a <u>different</u> owner is found. (Note: dogs which live in the same household will be considered to have the same owner.)

A10. Instructions for Filling Out the Case Report Form-Case Control Study of Canine Hypoadrenocorticism (Instructions for Survey Form for Veterinarians Enrolled in Clinical Trial) (back)

   b. Fill in the information for Control Dog No. 1. It is self-explanatory.

   c. Record age the same way as for the hypoadrenal dog.

4. <u>For Control Dog No. 2</u>:

   a. Go to the <u>fifth</u> record after the record for Control Dog No. 1 and use it as Control Dog No. 2, again <u>provided</u> it has a <u>different</u> owner and is a <u>dog</u>. If not, go to the sixth record, seventh record, etc., until you come to a <u>dog</u> with a <u>different</u> owner.

   b. Fill in the information for Control Dog No. 2. It is again self-explanatory.

   c. Record age the same way as for the hypoadrenal dog.

5. <u>For Practice Data</u>:

   a. Record the total number of cases of canine hypoadrenocorticism diagnosed in your practice between January 1, 1993 and December 31, 1993.

      This includes <u>all</u> cases diagnosed regardless of whether they were treated, how they were treated, or whether they lived or died.

   b. Record the total number of dogs seen in your practice (active dog patients) between January 1, 1993 and December 31, 1993. This <u>is</u> <u>not</u> the number of dog visits, it is the number of dogs. For example, if an individual dog was seen five times during the year, that dog is counted only <u>once</u>.

   c. Record the number of veterinarians who work full-time in your practice. If you have part-time veterinarians, estimate their total work load. For example, two veterinarians working half-time equals one full-time veterinarian.

6. <u>Print</u> the name of the person filling out the Case Report Form at the end of the form.

7. Please mail the Case Report Form(s) in the enclosed postage-paid envelope. Thanks a lot!

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A11. Case Control Study of Canine Hypoadrenocorticism (Survey Form for Randomly Selected Veterinarians)

Investigator's Name _____

CASE CONTROL STUDY OF CANINE HYPOADRENOCORTICISM
(Footnotes/Instructions on Reverse)

Approximately how many active dog patients[1] did you see in 1993? _____

How many full-time veterinarians work in your practice? _____

In your practice how many dogs were initially diagnosed with hypoadrenocorticism between January 1, 1993 and December 31, 1993?[2] _____

If your answer to the last question was greater than zero, please complete the following for all hypoadrenal dogs diagnosed in 1993 and a control dog for each (please call 1-800-447-2391 for additional forms if you need them).

HYPOADRENAL DOG

Age (yr): _____ Wt. (lb): _____ Breed: _____   Sex: M MC F FS
(at time of diagnosis)   (Circle one)

Health Status:[3] (Circle one)   Alive   Dead   Lost to follow-up

Cause of Hypoadrenocorticism: (Circle one)   Lysodren   Adrenalectomy   Unknown

Other (Please specify) _____

Other Diseases: (Check all that apply)

Anemia[4]	_____	Keratoconjunctivitis sicca	_____
Arthritis[5]	_____	Megaesophagus	_____
Cruciate ligament rupture	_____	Myasthenia gravis	
Diabetes mellitus	_____	Nephritis[7]	
Hepatitis[6]	_____	Thrombocytopenia	_____
Hypothyroidism	_____		

None of the above _____

CONTROL DOG[8]

Age (yr): _____ Wt. (lb): _____ Breed: _____   Sex: M MC F FS
(at last visit in 1993)   (Circle one)

Health Status:[3] (Circle one)   Alive   Dead   Lost to follow-up

Other Diseases: (Check all that apply)

Anemia[4]	_____	Keratoconjunctivitis sicca	_____
Arthritis[5]	_____	Megaesophagus	_____
Cruciate ligament rupture	_____	Myasthenia gravis	_____
Diabetes mellitus	_____	Nephritis[7]	
Hepatitis[6]	_____	Thrombocytopenia	_____
Hypothyroidism	_____		

None of the above _____

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A12. Instructions for Filling Out the Case Report Form-Case Control Study of Canine Hypoadrenocorticism (Instructions for Survey Form for Randomly Selected Veterinarians)

Footnotes/Instructions

[1] Record the total number of dogs seen in your practice (active dog patients) between January 1, 1993 and December 31, 1993. This is not the number of dog visits, it is the number of dogs. For example, if an individual dog was seen five times during the year, that dog is counted only once.

[2] Record the total number of cases of canine hypoadrenocorticism diagnosed in your practice between January 1, 1993 and December 31, 1993. This includes all cases diagnosed regardless of whether they were treated, how they were treated, or whether they lived or died.

[3] Lost to follow-up means it is impossible to determine whether the dog is now alive or dead.

[4] Anemia is a packed cell volume less than 30% from any cause.

[5] Any inflammatory disease of the joints.

[6] Any inflammatory disease of the liver.

[7] Any inflammatory disease of the kidney.

[8] The next record (alphabetically) in your file after the record of the hypoadrenal patient will serve as the Control Dog provided it was seen in 1993, has a different owner and is a dog which does not have hypoadrenocorticism. If the next record belongs to the same owner or is not a dog seen in 1993 or has hypoadrenocorticism, go to the next record until a dog seen in 1993 is found which does not have hypoadrenocorticism and is owned by a different owner. (Note: dogs which live in the same household will be considered to have the same owner.)

Note: If you have any questions, contact Phylis Hilling, LVT or Randy Lynn, DVM at 1-800-447-2391.

Return to: Ciba Animal Health
                Post Office Box 18300
                Greensboro, NC 27419-8300

APPENDIX B

COMPUTATION OF CHI-SQUARE STATISTICS

APPENDIX B

COMPUTATION OF CHI-SQUARE STATISTICS

General 2 x 2 Contingency Table

		Variable A		
		Category 1	Category 2	
Variable B	Category 1	a	b	a + b
	Category 2	c	d	c + d
		a + c	b + d	N = a + b + c + d

$$\chi^2(uncorrected) = \frac{N\,(ad-bc)^2}{(a+b)\,(c+d)\,(a+c)\,(b+d)}$$

APPENDIX C

LOGISTIC REGRESSION

CONTENTS–APPENDIX C

C1. Evaluation of Logistic Regression Models for Presence or Absence of Canine Hypoadrenocorticism Using Age, Breed, Sex, and Body Weight as Independent Variables: All Single Factor Models

Model [*,**]	Factor	Factor Wald chi square (df)[***,79]	Chance probability of Wald chi square	Model LOF[****] chi square (df)	Chance probability of LOF chi square	R^2 [180]
Case =				264.37 (125)	< 0.0001	0.0709
	Age	154.05(1)	< 0.0001			
Case =				None		0.0961
	Breed	178.63 (17)	< 0.0001			
Case =				None		0.0499
	Sex	111.56(3)	< 0.0001			
Case =				466.52 (373)	0.0007	0.0222
	Body weight	50.37(1)	< 0.0001			
Case =				152.42 (124)	0.0423	0.1176
	Age	140.07(1)	< 0.0001			
	Age★Age	94.59(1)	< 0.0001			
Case =				138.51 (123)	0.1605	0.1234
	Age	53.36(1)	< 0.0001			
	Age★Age	26.56(1)	< 0.0001			
	Age★Age★Age	13.60(1)	0.0002			

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Model *,**	Factor	Factor Wald chi square (df)***[79]	Chance probability of Wald chi square	Model LOF**** chi square (df)	Chance probability of LOF chi square	R^2 [180]
Case =				466.80 (372)	0.0006	0.0221
	Body weight	2.52(1)	0.1124			
	Body weight★ Body weight	0.30(1)	0.5870			
Case =				460.62 (371)	0.0010	0.0248
	Body weight	5.20(1)	0.0226			
	Body weight★ Body weight	2.65(1)	0.1037			
	Body weight★ Body weight★ Body weight	2.82(1)	0.0933			

* Case = presence or absence of hypoadrenocorticism in dog.
 Age = dog's age in yr.
 Breed = dog's breed.
 Sex = dog's sex classified as female-intact, female-spayed, male-intact, or male-castrated.

** All models were significant at p < 0.0001.

*** Wald chi square with associated degrees of freedom in parentheses.

**** Lack of fit chi square with associated degrees of freedom in parentheses.

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C2. Evaluation of Logistic Regression Models for Presence or Absence of Canine Hypoadrenocorticism Using Age, Breed, Sex, and Body Weight as Independent Variables: All Two Factor Models with No Interactions

Model [*,**]	Factor	Factor Wald chi square (df)[***][79]	Chance probability of Wald chi square	Model LOF[****] chi square (df)	Chance probability of LOF chi square	R^2 [180]
Case =				440.04 (348)	0.0006	0.1673
	Age	140.96(1)	< 0.0001			
	Breed	170.93(17)	< 0.0001			
Case =				338.52 (218)	< 0.0001	0.0973
	Age	103.51(1)	< 0.0001			
	Sex	60.51(3)	< 0.0001			
Case =				1627.57 (1313)	< 0.0001	0.0958
	Age	147.05(1)	< 0.0001			
	Body weight	71.72(1)	< 0.0001			
Case =				66.04 (49)	0.0526	0.1359
	Breed	162.13(17)	< 0.0001			
	Sex	90.27(3)	< 0.0001			
Case =				688.29 (640)	0.0908	0.1244
	Breed	173.42(17)	< 0.0001			
	Body weight	47.21(1)	< 0.0001			

Model *,**	Factor	Factor Wald chi square (df)***[79]	Chance probability of Wald chi square	Model LOF**** chi square (df)	Chance probability of LOF chi square	R^2 [180]
Case =				784.49 (655)	0.0004	0.0715
	Sex	104.99(3)	< 0.0001			
	Body weight	48.93(1)	< 0.0001			

* Case = presence or absence of hypoadrenocorticism in dog.
Age = dog's age in yr.
Breed = dog's breed.
Sex = dog's sex classified as female-intact, female-spayed, male-intact, or male-castrated.

** All models were significant at p < 0.0001.

*** Wald chi square with associated degrees of freedom in parentheses.

**** Lack of fit chi square with associated degrees of freedom in parentheses.

C3. Evaluation of Logistic Regression Models for Presence or Absence of Canine Hypoadrenocorticism Using Age, Breed, Sex, and Body Weight as Independent Variables: All Two Factor Models with Interactions

Model [*],[**]	Factor	Factor Wald chi square (df)[***][79]	Chance probability of Wald chi square	Model LOF[****] chi square (df)	Chance probability of LOF chi square	R^2 [180]
Case =				418.23 (331)	0.0008	0.1764
	Age	0.16(1)	0.6868			
	Breed	36.92(17)	0.0035			
	Age★Breed	12.20(17)	0.7876			
Case =				330.96 (215)	< 0.0001	0.1005
	Age	84.54(1)	< 0.0001			
	Sex	26.10(3)	< 0.0001			
	Age★Sex	5.49(3)	0.1394			
Case =				1626.18 (1312)	< 0.0001	0.0964
	Age	59.24(1)	< 0.0001			
	Body weight	23.89(1)	< 0.0001			
	Age★Body weight	1.38(1)	0.2393			
Case =				None		0.1626
	Breed	71.18(17)	< 0.0001			
	Sex	0.07(3)	0.9949			
	Breed★Sex	15.06(49)	1.0000			
Case =				660.39 (623)	0.1451	0.1363
	Breed	20.27(17)	0.2604			
	Body weight	0.27(1)	0.6034			
	Breed★Body weight	20.32(17)	0.2583			

Model [*],[**]	Factor	Factor Wald chi square (df)[***][79]	Chance probability of Wald chi square	Model LOF[****] chi square (df)	Chance probability of LOF chi square	R^2 [180]
Case =				777.86 (652)	0.0005	0.0744
	Sex	33.35(3)	< 0.0001			
	Body weight	17.97(1)	< 0.0001			
	Sex*Body weight	6.40(3)	0.0935			

[*]   Case = presence or absence of hypoadrenocorticism in dog.
Age = dog's age in yr.
Breed = dog's breed.
Sex = dog's sex classified as female-intact, female-spayed, male-intact, or male-castrated.

[**] All models were significant at p < 0.0001.

[***] Wald chi square with associated degrees of freedom in parentheses.

[****] Lack of fit chi square with associated degrees of freedom in parentheses.

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C4. Evaluation of Logistic Regression Models for Presence or Absence of Canine Hypoadrenocorticism Using Age, Breed, Sex, and Body Weight as Independent Variables: All Three Factor Models with No Interactions

Model [*],[**]	Factor	Factor Wald chi square (df)[***][79]	Chance probability of Wald chi square	Model LOF[****] chi square (df)	Chance probability of LOF chi square	R^2 [180]
Case =				587.96 (559)	0.1918	0.1873
	Age	100.55(1)	< 0.0001			
	Breed	160.18(17)	< 0.0001			
	Sex	46.47(3)	< 0.0001			
Case =				1598.15 (1444)	0.0027	0.1922
	Age	130.48(1)	< 0.0001			
	Breed	163.50(17)	< 0.0001			
	Body weight	64.83(1)	< 0.0001			
Case =				1784.93 (1519)	< 0.0001	0.1217
	Age	103.33(1)	< 0.0001			
	Sex	59.98(3)	< 0.0001			
	Body weight	69.20(1)	< 0.0001			
Case =				1012.13 (954)	0.0935	0.1646
	Breed	159.20(17)	< 0.0001			
	Sex	87.37(3)	< 0.0001			
	Body weight	47.75(1)	< 0.0001			

[*]   Case = presence or absence of hypoadrenocorticism in dog.
  Age = dog's age in yr.
  Breed = dog's breed.
  Sex = dog's sex classified as female-intact, female-spayed, male-intact, or male-castrated.

[**] All models were significant at $p < 0.0001$.

[***] Wald chi square with associated degrees of freedom in parentheses.

[****] Lack of fit chi square with associated degrees of freedom in parentheses.

C5. Evaluation of Logistic Regression Models for Presence or Absence of Canine Hypoadrenocorticism Using Age, Breed, Sex, and Body Weight as Independent Variables: All Three Factor Models with Two-Way Interactions

Model *,**	Factor	Factor Wald chi square (df)***[79]	Chance probability of Wald chi square	Model LOF**** chi square (df)	Chance probability of LOF chi square	R^2 [180]
Case =				494.22 (488)	0.4132	0.2270
	Age	0.07(1)	0.7940			
	Breed	17.47(17)	0.4227			
	Sex	0.03(3)	0.9984			
	Age★Breed	7.76(17)	0.9715			
	Age★Sex	7.95(3)	0.0470			
	Breed★Sex	13.75(49)	1.0000			
Case =				1542.30 (1409)	0.0072	0.2171
	Age	0.04(1)	0.8491			
	Breed	6.99(17)	0.9837			
	Body weight	0.14(1)	0.7076			
	Age★Breed	14.71(17)	0.6163			
	Age★Body weight	0.11(1)	0.7383			
	Breed★Body weight	17.51(17)	0.4202			
Case =				1769.60 (1512)	< 0.0001	0.1286
	Age	45.84(1)	< 0.0001			
	Sex	11.42(3)	0.0097			
	Body weight	13.11(1)	0.0003			
	Age★Sex	3.72(3)	0.2933			
	Age★Body weight	1.51(1)	0.2184			
	Sex★Body weight	8.76(3)	0.0327			

Model *,**	Factor	Factor Wald chi square (df)***[79]	Chance probability of Wald chi square	Model LOF**** chi square (df)	Chance probability of LOF chi square	R² [180]
Case =				919.26 (883)	0.1929	0.2051
	Breed	13.39(17)	0.7095			
	Sex	3.43(3)	0.3303			
	Body weight	0.09(1)	0.7678			
	Breed★Sex	12.02(49)	1.0000			
	Breed★Body weight	15.63(17)	0.5502			
	Sex★Body weight	6.88(3)	0.0758			

* Case = presence or absence of hypoadrenocorticism in dog.
Age = dog's age in yr.
Breed = dog's breed.
Sex = dog's sex classified as female-intact, female-spayed, male-intact, or male-castrated.

** All models were significant at p < 0.0001.

*** Wald chi square with associated degrees of freedom in parentheses.

**** Lack of fit chi square with associated degrees of freedom in parentheses.

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C6. Evaluation of Logistic Regression Models for Presence or Absence of Canine Hypoadrenocorticism Using Age, Breed, Sex, and Body Weight as Independent Variables: All Three Factor Models with Two- and Three-Way Interactions

Model [*,**]	Factor	Factor Wald chi square (df)[***,79]	Chance probability of Wald chi square	Model LOF[****] chi square (df)	Chance probability of LOF chi square	R^2 [189]
Case =				470.13 (437)	0.1322	0.2372
	Age	< 0.01(1)	0.9966			
	Breed	5.42(17)	0.9963			
	Sex	0.08(3)	0.9946			
	Age★Breed	18.26(17)	0.3729			
	Age★Sex	109.85(3)	< 0.0001			
	Breed★Sex	8.61(49)	1.0000			
	Age★Breed★Sex	107.15(44)	< 0.0001			
Case =				1527.87 (1392)	0.0061	0.2235
	Age	< 0.01(1)	0.9786			
	Breed	9.97(17)	0.9049			
	Body weight	<0.01(1)	0.9460			
	Age★Breed	8.21(17)	0.9618			
	Age★Body weight	0.03(1)	0.8662			
	Breed★Body weight	9.10(17)	0.9371			
	Age★Breed★ Body weight	11.85(17)	0.8090			
Case =				1768.21 (1509)	< 0.0001	0.1292
	Age	37.33(1)	< 0.0001			
	Sex	5.11(3)	0.1640			
	Body weight	11.31(1)	0.0008			
	Age★Sex	2.68(3)	0.4436			
	Age★Body weight	1.61(1)	0.2042			
	Sex★Body weight	0.39(3)	0.9417			
	Age★Sex★Body weight	1.36(3)	0.7153			

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Model *,**	Factor	Factor Wald chi square (df)***[79]	Chance probability of Wald chi square	Model LOF**** chi square (df)	Chance probability of LOF chi square	R² [180]
Case =				895.30 (832)	0.0630	0.2155
	Breed	7.96(17)	0.9675			
	Sex	0.15(3)	0.9857			
	Body weight	< 0.01(1)	0.9969			
	Breed★Sex	17.19(49)	1.0000			
	Breed★Body weight	2260.49 (17)	< 0.0001			
	Sex★Body weight	74.17(3)	< 0.0001			
	Breed★Sex★ Body weight	8226.35 (42)	< 0.0001			

* Case = presence or absence of hypoadrenocorticism in dog.
  Age = dog's age in yr.
  Breed = dog's breed.
  Sex = dog's sex classified as female-intact, female-spayed, male-intact, or male-castrated.

** All models were significant at p < 0.0001.

*** Wald chi square with associated degrees of freedom in parentheses.

**** Lack of fit chi square with associated degrees of freedom in parentheses.

C7. Two Logistic Regression Models Fit for Presence or Absence of Canine Hypoadrenocorticism Using Age, Breed, Sex, and Body Weight as Independent Variables

Model *,**	Factor	Factor Wald chi square (df)***[79]	Chance probability of Wald chi square	Model LOF**** chi square (df)	Chance probability of LOF chi square	R^2 [180]
Case =				1612.14 (1578)	0.2692	0.2418
	Age	82.51(1)	< 0.0001			
	Age★Age	51.96(1)	< 0.0001			
	Breed	148.12(17)	< 0.0001			
	Sex	40.27(3)	< 0.0001			
	Body weight	46.06(1)	< 0.0001			

		Estimate
Parameter estimates:		
Intercept		-5.71413
Age		0.67965
Age★Age		-0.03073
Breeds		
	Airedale Terrier	1.37241
	Basset Hound	2.72231
	Bearded Collie	2.26271
	Boxer	-6.86806
	Cocker Spaniel	0.68076
	Dalmatian	-7.15408
	German Shorthaired Pointer	1.72756
	Great Dane	3.18304
	Lhasa Apso	-0.95415
	Pit Bull Terrier	-7.18512
	Pomeranian	-0.01101
	Poodle	2.54412
	Shetland Sheepdog	-0.43610
	Shih Tzu	0.48986
	Springer Spaniel	2.62266
	West Highland White Terrier	3.60843
	Yorkshire Terrier	0.00000
	Other	0.93638
Sexes		
	Female-intact	-0.05424
	Female-spayed	0.53356
	Male-intact	-0.55904
	Male-castrated	0.00000
	Body weight	0.03585

Model *, **	Factor	Factor Wald chi square (df)***[79]	Chance probability of Wald chi square	Model LOF**** chi square (df)	Chance probability of LOF chi square	R² [180]
Case =				1590.04 (1574)	0.3833	0.2516
	Age	80.25(1)	< 0.0001			
	Age★Age	60.18(1)	< 0.0001			
	Breed	143.08(17)	< 0.0001			
	Sex	13.03(3)	0.0046			
	Body weight	25.84(1)	< 0.0001			
	Age★Body weight	12.85(1)	0.0003			
	Sex★Body weight	8.49(3)	0.0370			

		Estimate
Parameter estimates:		
Intercept		-6.84159
Age		0.88919
Age★Age		-0.03638
Breeds		
	Airedale Terrier	1.35685
	Basset Hound	2.80167
	Bearded Collie	2.29040
	Boxer	-6.80605
	Cocker Spaniel	0.73518
	Dalmatian	-7.01512
	German Shorthaired Pointer	1.87936
	Great Dane	2.57387
	Lhasa Apso	-0.96808
	Pit Bull Terrier	-7.07281
	Pomeranian	-0.11475
	Poodle	2.54819
	Shetland Sheepdog	-0.55209
	Shih Tzu	0.47110
	Springer Spaniel	2.67659
	West Highland White Terrier	3.80993
	Yorkshire Terrier	0.00000
	Other	0.95373
Sexes		
	Female-intact	0.73018
	Female-spayed	0.32866
	Male-intact	-0.64710
	Male-castrated	0.00000
	Body weight	0.06772
	Age★Body weight	-0.00527
	Female-intact★Body weight	-0.03871
	Female-spayed★Body weight	0.01112
	Male-intact★Body weight	0.00631
	Male-castrated★Body weight	0.00000

* Case = presence or absence of hypoadrenocorticism in dog.
  Age = dog's age in yr.
  Breed = dog's breed.
  Sex = dog's sex classified as female-intact, female-spayed, male-intact, or male-castrated.

** Both models were significant at p < 0.0001.

*** Wald chi square with associated degrees of freedom in parentheses.

**** Lack of fit chi square with associated degrees of freedom in parentheses.

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APPENDIX D

CAUSALITY: A COMPLEX ISSUE

APPENDIX D
CAUSALITY: A COMPLEX ISSUE

Melissa called her husband George at his office at three o'clock in the afternoon. Their six-month-old son Jason had a terrible case of diaper rash, and her last can of medicated diaper powder had become thoroughly soaked and useless when a pipe above the bathroom medicine cabinet leaked. Would George stop by the store on the way home and pick up some more powder? George, good husband and father he, said he would.

George—after a long delay in his usual five o'clock departure because he was forced to listen as his boss bloviated endlessly about a myriad of hopelessly inane topics—left his office, got in his car, and drove toward the store. About a mile before the store, George heard a thumping noise from the right rear of the car. Recognizing that he had a flat tire, George pulled over, threw open the door, and stepped out of the car directly into the path of an oncoming truck. George was killed instantly. Question: What *caused* George's death?

The issue of causality is a complex one which philosophers and scientists have been struggling with for centuries. Epidemiologists are often inclined to quickly and, as it turns out, facilely dismiss the issue as simple and self-evident. For example, asked the question posed in Chapter 5 whether age, breed, sex, and body weight *cause* canine hypoadrenocorticism, many epidemiologists would

condescendingly respond assertively in the negative. Age, breed, sex, and body weight may be *associated* with canine hypoadrenocorticism, they would say, but to speak of *causation* would be naive. This appendix demonstrates that, while these epidemiologists may or may not be correct, questions of causality are definitely *not* answered simply. Put by another:

> . . . it is apparent that some of the main philosophical problems of causation do not yield to any easy solution. The idea of a necessary connection between cause and effect may be, as Hume thought, an *esoteric and metaphysical one, but it is doubtful whether anyone can render an adequate analysis of the causal relation without it* [Italics added].[21]

The author will, risking nihilism, assert that, given the present state of human knowledge and understanding, assertions that such and such is or is not the *cause* of something else are virtually always naive. This will be based on the premise that such assertions are usually at variance with human understanding of the physical universe.

This discussion of causality in epidemiology must be preceded by the disclaimer that it *does not* pretend to be comprehensive, and its author *acknowledges* up-front that he is a rookie philosopher of the rawest sort. Nevertheless, as appropriate in an interdisciplinary endeavor like the Comparative and Experimental Medicine Program, the author attempts in his probably hopelessly puerile way to, in the spirit of the first Ph.D. granted in "General" by The University of Tennessee in 1886 (see Preface), grapple with this thorny issue. His purpose is not to settle the issue of what is and what is not a *cause*, but to

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establish that the issue is a complex one not given to flip, pat pronouncements. The fact that a well-known and respected epidemiologist has seen fit to devote an entire section in his epidemiology text to causation,[165] and to edit another entire book on the subject,[169] testifies to the issue's complexity. Indeed, he says, "We know from Hume, Popper, and others that causal inference is at best tentative and is still a subjective process."[170] In addition, his book on causation says the following about whether or not the epidemiologist, as a scientist, is *obliged* to consider the philosophic complexity of this issue:

> Thus it is in good conscience that one may recommend to the empirical scientist to stand back occasionally and engage in philosophical reflection upon the ultimate nature and significance of his enterprise. He should find it worthwhile to study philosophical literature, for it contains matters of substance that may provide insight and intellectual satisfaction.[185]

Finally, if Aristotle, David Hume, John Stuart Mill, Immanuel Kant, Isaac Newton, and Bertrand Russell cannot sort out the causality issue, only an act of incredible hubris would lay claim to having done so. The author makes no such claim.

Western culture and thought about the physical universe have gone through three major eras: Aristotle's rationalism, Locke's and Newton's empiricism and determinism, and Planck's and Einstein's quantum and relativity theory. Each of these eras was characterized by a different view of *cause* (and, of course, some individuals in each of these eras naively asserted the absolute "rightness" of these different views).

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Aristotle, whose thought about causes prevailed until the Renaissance, defined four kinds of causes,[18,77] and, most important, he felt that rational thought rather than empiricism was the most reliable method for obtaining truth. The doctrine of rationalism held that "scientific knowledge accumulated through reason and intuition rather than by empirical observation."[164] Indeed, Aristotle's ontology suggested that reason was "far more real and trustworthy . . . than the fleeting and undependable experience of the senses."[204] Aristotle, for example, might well have asserted the superiority of his rationally-reasoned belief that a large rock falls faster than a small one *even*, had the results been available to him, in the face of Galileo's empirical experiment.[204] In other words, rational thought was supreme. A corollary of rationalism was the preeminence of mathematics as the "highest form of knowledge."[164]

John Locke rejected Aristotelian rationalism in favor of empiricism. He claimed that the human mind was a *tabula rasa* (blank tablet) at birth and that experience dictated knowledge.[205] Locke's philosophic position led naturally to the empiricism and determinism of the scientific method and the new physics of Isaac Newton. Rationalism and reason were not entirely rejected, of course, but they were accepted only within the "well-defined activities of calculation and logic."[205] Put more succinctly:

> With Newton, the world was not only thought of as a *machine*, but was exhibited in detail as a function of mechanical laws—a system of the world. *All* matters of celestial and terrestrial mechanics, scattered and disconnected

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in Kepler, Copernicus, Huygens, Halley, Wren, Hook, and Galileo, were unified into a grand system of *mathematical-mechanical laws* [Italics added].[mm,84]

According to this view, the world was a giant machine, the components of which, having already been set in motion, would interact in wholly predictable ways in accordance with the "laws" of physics. Newton's universal law of gravity and his laws of thermodynamics exemplified these laws, and science has, since the time of Newton, been largely engaged in finding and refining these laws--all the while, of course, assuming that such laws existed, and that they could be systematically described, principally using mathematics.[oo] This belief in definable physical laws has been described as follows:

> Nonetheless, the notion arose in the eighteenth century that "all sufficiently smooth Newtonian systems were *exactly* and *meaningfully* solvable. In consequence, one no longer spoke of unsolvable systems, only those not yet solved [Italics added]."[56]

In other words, *everything* can be explained by the new physics, and, if something appears *not* to be explainable, it is not because there is no mechanistic explanation, the mechanism simply has not yet been discovered and defined.[pp] (This, arguably,

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[mm]It is a paradox that, while rejecting Aristotelian rationalism, Newtonian physics heavily emphasized mathematics, a discipline which, as mentioned above, was, according to the rationalists, the "highest form of knowledge."[220]

[oo]Newton, in fact, had to specifically develop differential calculus in order to explain this new physics.

[pp]This view of the universe led naturally to the deistic theologic assertion by the French philosophes (and Thomas Jefferson) that the universe was like a giant clock which had been wound up by God, and then abandoned by Him to tick on

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could be described as the ultimate in human hubris: the assertion that the human mind was capable of comprehending *everything* which goes on in the universe.) This worldview largely underpins late twentieth-century science, and, within the scientific community at least, remains, rightly or wrongly, largely unchallenged. The late nineteenth- and early twentieth-century thought of men like Max Planck and Albert Einstein challenged some of the tenets of this worldview.

What will be called here "modern physics" (emphatically recognizing that Newtonian physics is *very much alive* today in all sorts of real-world applications) includes quantum mechanics which began with Max Planck's quantum theory in 1900,[248] relativity theory which began with Albert Einstein's special theory of relativity in 1905,[248] and chaos theory which began with men like Mitchell Feigenbaum in the 1970s.[99,63] Each of these (quantum mechanics, relativity, and

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in perpetuity. This view, mirrored to some extent by the fatalism of Calvinism, led inevitably (and sadly) to a determinism which denied human volition.

This view similarly led to much of the conflict over the centuries between the religious and scientific communities—dating from the house arrest of Galileo in the seventeenth century, including the Scopes "monkey trial" in Dayton, Tennessee in 1925, and (amazingly!) also including the current debate in the Tennessee legislature (this is written on 7 March 1996) about the teaching of evolution in schools.

[99]The author acknowledges here that the lumping together of quantum theory, relativity, and chaos into "modern physics" is wholly arbitrary and is done for two reasons: convenience, and the author's nearly overwhelming ignorance of these fields. The author recognizes that these are three *different* kinds of physics as explained in the following: "The most passionate advocates of the new science [chaos theory] go so far as to say that twentieth-century science will be remembered for just three things: relativity, quantum mechanics, and chaos.

chaos) challenges the Newtonian mechanistic view of the universe. An example of each challenge follows.

Newtonian physics says that, given the position and momentum of an object moving in space, it is simple to compute the position and momentum of the object at a future time. Quantum mechanics, on the other hand, has demonstrated that sub-atomic particles do not behave in this way. Not only can the future position and momentum of a sub-atomic particle not be predicted from its present position and momentum, it is *impossible* to accurately measure both the present position and momentum of the sub-atomic particle in the first place. The particle's position *or* its momentum can be accurately measured, but *not both*. This is Heisenberg's uncertainty principle, and it has been empirically verified by many experiments. Since both the particle's position and momentum cannot be determined, quantum mechanics, in contrast to Newtonian physics, cannot predict specifically where the particle will be at some future instant, but can predict the *probability* that the particle will be at a particular position with a particular momentum.[249] This illustrates one of the essential differences between the Newtonian and quantum mechanical worldviews: the Newtonian world is *precisely* predictable--always

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Chaos, they contend, has become the century's third great revolution in the physical sciences. Like the first two revolutions, chaos cuts away at the tenets of Newton's physics. As one physicist put it: 'Relativity eliminated the Newtonian illusion of absolute space and time; quantum theory eliminated the Newtonian dream of a controllable measurement process; and chaos eliminates the Laplacian fantasy of deterministic predictability.'"[64]

measurable and certain; the quantum mechanical world is *probabilistically* predictable--often immeasurable and uncertain.ᵖ So the Newtonian worldview is imperfect.

Relativity also challenges Newtonian physics. Indeed, Einstein's "proof" that light is composed of photons (recognizing that *no* theory of physics has satisfactorily explained the wave-particle duality of light), coupled with Thomas Young's double-slit experiment conducted in the early nineteenth century, leads to the strong, but very unsettling, possibility that light has consciousness.[250] Indeed, to quote from a book on physics: "We have little choice but to acknowledge that photons, which are energy, *do appear to process information and to act accordingly* [Italics added]."[251] Ironically, Einstein himself would probably have totally rejected this possibility. He is quoted as saying:

> . . . I should not want to be forced into abandoning strict causality without defending it more strongly than I have so far. I find the idea quite intolerable that an electron exposed to radiation should choose *of its own free will*, not only its moment to jump off, but also its direction. In that case, I would rather be a cobbler, or even an employee in a gaming house, than a physicist [Italics in original].[38]

Nevertheless, photons of light and electrons may be conscious.

Relativity, as is well-known (tritely so, perhaps), says that *time itself* is relative; e.g., a cigarette smoked by an astronaut moving through space burns

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ᵖOne philosopher tries to reconcile this conflict between precise and probabilistic predictability.[240]

longer (literally!) than a cigarette smoked by an earthbound astronaut.[252] This relativity of time has been empirically verified by flying atomic clocks around the world.[ss,253] The strange nature of relativity can be described as follows:

> The physical theories of Einstein, and the variants developed by others, which have each been called the "theory of relativity" are so named because they have relativized some of the attributes and relations (spatial distance, time interval, mass) which the Newtonian theory had asserted to be invariant (absolute).[67]

Finally, chaos theory has been defined as "the qualitative study of unstable aperiodic behavior in deterministic nonlinear dynamical systems."[90] It is schizophrenic in that it at once confirms that chaotic systems[tt] are in principle predictable, but that they are, due to "sensitive dependence on initial conditions," almost wholly unpredictable as a practical matter.[88] In other words, specifying initial conditions is well nigh impossible, and the ability to compute results does not exist even if the initial conditions were known. For example, what does watching two bits of foam floating side by side at the bottom of a waterfall tell about where they were at the top? "Nothing. As far as standard physics [is]

[ss]It is an interesting conundrum that, although belief in things like "conscious photons" and "relative time" seems intuitively based more in faith and spirituality than in science, the "proof" of these beliefs *still*, to be satisfying, must rest on empirical evidence. This may be a measure of just how powerfully the Newtonian way of thinking has been hammered into our twentieth-century brains.

[tt]Which "can appear in the context of exceedingly simple and entirely Newtonian equations of motion"[88]; i.e., chaotic systems are easily and everywhere to be found.

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concerned, God might just as well have taken all those water molecules under the table and shuffled them personally."[65] This leads to the humbling paradox that the universe is at the same time deterministic, but not deterministic in the sense of a Newtonian timepiece. This has been better said:

> The curious nature of chaotic unpredictability also raises questions about scientific determinism. These systems with sensitive dependence on initial conditions produce random or chancy behavior, the *opposite* of what we would expect from a picture of the universe as strictly determined clockwork. Yet chaos theorists consistently describe their models as "deterministic." . . . Not only does chaos theory suggest that predictability should be considered *separately* from determinism, but in conjunction with quantum-mechanical considerations it raises *serious doubts about the viability* of the doctrine of determinism in the context of modern physics [Italics added].[uu,89]

This alludes to the conundrum of "causation without determinism," a seemingly oxymoronic phrase which philosophers have, in light of modern physics, recently been grappling with.[146] It may also allude to problems sometimes introduced into philosophic arguments "as a consequence of customary linguistic usage."[220] In other words, there is a point at which these arguments become moot because they depend on the *limited* ability of humans to communicate with words. At that point, and it is impossible to determine precisely where that point is, further argument becomes meaningless.

[uu]In other words, "predictability" and "determinism" are separate ideas. What? (The author confesses that he is now at or beyond the edge of his intellectual capability.)

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Finally, contemporary scientific training emphasizes an epistemology which at best ignores and at worst is openly hostile to the apparently disorderly conduct of chaotic nonlinear systems. In other words, though we live in a decidedly nonlinear world (as defined by Aristotle *or* Newton *or* Einstein), the contemporary training of and practice by scientists tries to force the world to be linear. This bias against the nonlinear has been succinctly described:

> . . . the professional training of scientists . . . diverted attention away from areas where chaos might have been discovered and studied. By training students to disregard apparently disordered behavior, to focus attention on linear models, and to seek simple exact solutions, scientific education screened off chaos. . . . Education in the natural sciences created the impression that linear and solvable systems were the only ones (or at least the only important ones)--an impression that came very close to being a prejudice in favor of systems as regular and predictable as clockwork. . . . Professional instruction rendered chaos less visible in two ways: on the one hand, students were indirectly steered away from nonlinear systems (the only systems in which chaos is possible) by being taught that they were uninteresting or exceptional cases. On the other hand, when apparently bizarre or even chaotic behavior was found in these nonlinear systems, it was dismissed as mere noise or experimental error . . .[91]

In other words, scientists are taught to shun results which they cannot understand in favor of those which fit their (often preconceived) idea of how the world *ought* to work.ʷThis is a very *unscientific* attitude!

ʷHow many times have you heard a scientist say, "The experiment *did not work*"? Amazing! According to Newtonian thought, which shapes most contemporary scientific thought, experiments *always* work; i.e., the molecules *always* do what they are supposed to. The problem is human understanding, not molecular incompetence.

So, what does all this have to do with the question of whether or not age, breed, sex, and body weight *cause* canine hypoadrenocorticism? The answer is, recognizing the possibly just accusation of nihilism, unknown and unknowable given contemporary human understanding of how the world works.[ww] How can causality be conclusively determined if the physical world is as yet ill-defined? It cannot. Assertions to the contrary are naive and symptomatic of contemporary hubris among scientists.

So, back to Melissa and George: What *caused* George's death? The answer is unknown and unknowable. On the macro-, non-scientific level, one could argue that the *causes* were the plumbing problem at George's house; the baby Jason's diaper rash; Melissa's call to George; George's delay leaving work while his boss blathered on; the manufacturer of George's tires; the person who dropped the object on the road which punctured George's tire; George's carelessness in getting out of his car; and so on. On the micro-, scientific level, one could argue that the *causes* were being hit by a truck (the forensic pathologist's view); the sudden collapse of the cranium with its incumbent near-instantaneous cessation of all ordered neural activity in the brain (the neuropathologist's view); a failure to

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[ww]The question could, trivially, be answered yes.[4,19,100,121,124,137,145,166,167] (Each of these nine references--with specific page numbers cited--is a work of either philosophy or epidemiology in which the definition of causality leads to the answer yes. The author recognizes that *other* references could be found in which the definition of causality leads to the answer no.)

breathe accompanied by sudden, irrevocable cardiovascular collapse (the cardiologist's view); the necrosis of tissues and cells due to massive hemorrhage and near-complete interruption of blood supply (the histopathologist's view); the necrosis of tissues and cells due to profound alterations in their cellular milieu (oxygen tension, pH, electrolyte concentrations, etc.) (the biochemist's view); and so on.[x] Therefore, the question of causality remains puzzling in even seemingly simple situations.

So, what is the point? It is that the epidemiologist should *neither* fall prey to the *post hoc ergo propter hoc* fallacy *nor* be too quick to cavalierly dismiss factors associated with diseases as *surely not* causally related. The epidemiologist should, recognizing just how complex the causality issue is, avoid both errors—in most cases by recognizing that what *causes* something is usually unknown and unknowable.

Finally, a spiritual, mystical element has crept into this discussion. This was deliberate, and while some scientists dismiss appeals to the supernatural as primitive superstition, some of the world's best scientific thinkers do not. So, lest the author's thoughts about science generally and causality specifically—and their possible relationship to the spiritual—be casually dismissed, the reader is referred to the words of Stephen Hawking, a mathematician and physicist who has (unlike

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[x]This reasoning parallels almost exactly that used in a well-known textbook of epidemiology.[99]

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the author) thoroughly understood Aristotelian rationalism, Newtonian physics, and modern physics; who has in fact filled the same professor's position at Cambridge University once filled by Isaac Newton; and who has been described[175] as a "legend" and a "worthy successor" of Newton by Carl Sagan:

> However, if we do discover a complete theory [of the universe] it should in time be understandable in broad principle by everyone, not just a few scientists. Then we shall all, philosophers, scientists, and just ordinary people, be able to take part in the discussion of the question of why it is that we and the universe exist. If we find the answer to that, it would be the ultimate triumph of human reason--for then we would know the mind of God.[74]

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VITA

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Vita

William James Kelch was born in Jersey City, New Jersey, on July 5, 1945. He attended public schools in Newton Falls, Ohio, and Royal Oak, Michigan, where he graduated from the Kimball High School in June, 1963. He attended the Michigan State University where he was awarded the Bachelor of Science in Veterinary Science in December, 1966, and the Doctor of Veterinary Medicine in June, 1968. He immediately entered the United States Army Veterinary Corps after graduation, and served 20 years until his retirement in the grade of Lieutenant Colonel. His military career included assignments in the United States in Alabama, Illinois, Kansas, Maryland, Massachusetts, Oklahoma, Oregon, and Texas, as well as overseas in Japan and Yugoslavia. During his military service he received several military awards, including the Army Commendation Medal and three awards of the Meritorious Service Medal. He was also the Honor Graduate of the United States Army Medical Service Veterinary School in August, 1968, and an Honor Graduate of the United States Army Command and General Staff College in June, 1981. While on active duty he obtained the Master of Administrative Science from the University of Alabama in Huntsville in May, 1975; the Master of Science in Food Science and Technology from the Oregon State University in June, 1977; and the Master of Military Art and Science from the United States Army Command and General Staff College in June, 1981. He

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became a Diplomate in the American College of Veterinary Preventive Medicine in July, 1978, and graduated from the Army War College in August, 1986.

Since retiring from the United States Army, he has resided in Tennessee. He attended the Walters State Community College where he received the Outstanding Student Award in History in May, 1988, and The University of Tennessee which awarded him the Master of Science in Statistics in May, 1994. He is a runner, triathlete, karateka, and military historian. His plans include learning to speak Spanish, completing an ironman distance triathlon, pursuing the blackbelt in karate, writing about the use of dogs by military forces, and establishing a private consulting firm in epidemiology, toxicology, and public health.