The occurrence of multiple endocrine disorders in veterinary patients has occasionally been described in single reports or small case series as well as anecdotally in textbooks, but is not a well-reported phenomenon.

In humans with more than 1 endocrine disorder, a common immune-mediated etiology is usually identified. Autoimmune polyendocrinopathy syndromes are complex and well-documented disorders in human medicine. Contrary to the name, polyendocrine syndromes encompass several autoimmune disorders, and these disorders may or may not be endocrine related. Many of the reported polyendocrinopathy syndromes in humans have been related to 1 or more genetic mutations, likely leading to breakdown in self-tolerance of endocrine and other organs.

There have been occasional case reports of similar suspected autoimmune polyendocrinopathies in dogs. Many endocrinopathies in dogs, such as hyperadrenocorticism, hypothyroidism, and diabetes mellitus, have an underlying immune-mediated etiology. Many of these conditions, such as diabetes mellitus and hyperadrenocorticism, are considered common in dogs. However, some reports of dogs with more than 1 endocrine disorder include endocrinopathies that are not believed to arise from an immune-mediated cause. Among these is simultaneous occurrence of hyperadrenocorticism and diabetes mellitus, which is considered common in dogs.

Although polyendocrinopathies appear to be adequately documented in human medicine, little is known about the occurrence of multiple endocrine disorders in canine patients. Based on previous case reports, it appears that dogs with multiple endocrine disorders do not always have a common immune-mediated etiology. The purpose of the study reported here was to characterize a population of dogs from a tertiary care center with 2 or more endocrine disorders, including the specific disorders and time intervals between diagnosis of each disorder.

**Materials and Methods**

**Criteria for selection of cases**—A computer search of the veterinary medical record database of all dogs examined at the Ontario Veterinary College Teaching Hospital at the University of Guelph between January 1996 and June 2009 was performed and identified patients.
that had 2 or more of the following disorders: diabetes mellitus, central diabetes insipidus, hypothyroidism, hyperadrenocorticism, hypoadrenocorticism, primary hyperparathyroidism, or hypoparathyroidism. Dogs were eligible for inclusion in the study if they had clinical signs that were compatible with the disorders; if they had undergone physical examination, clinico-pathologic testing, and endocrine testing; and if complete medical records were available.

**Procedures**—Data obtained from the medical records of dogs included in the study consisted of signalment; body weight at the time of diagnosis; clinical signs and duration of signs; physical examination findings; concurrent medical conditions or medication administration; results of clinico-pathologic testing including any of the following: CBC, serum biochemical analysis, coagulation testing, urinalysis and bacterial culture of urine samples, endocrine testing, diagnostic imaging, and histologic and cytologic evaluations; treatments; and survival time. When needed, referring veterinarians and owners were contacted to provide additional follow-up data.

**Endocrine testing**—Diabetes mellitus was diagnosed on the basis of compatible clinical signs including polyuria and polydipsia, persistent hyperglycemia after withholding of food (blood glucose concentration, >8 mmol/L or 144 mg/dL), glucosuria, and a high serum fructosamine concentration (>340 μmol/L) when available.

Central diabetes insipidus was diagnosed on the basis of persistent hypotheniuria (urine specific gravity <1.007), ruling out causes of secondary nephrogenic diabetes insipidus, and an appropriate response to a desmopressin acetate therapeutic trial.

Hypothyroidism was diagnosed on the basis of compatible clinical signs and biochemical abnormalities (eg, hypercholesterolemia after withholding food), a low serum total T concentration (<13 nmol/L or 1.0 μg/dL) in conjunction with a low serum free T concentration (<6 pmol/L or 0.47 ng/dL), a high thyroid-stimulating hormone concentration (>0.6 ng/mL), and no evidence of concurrent uncontrolled illness when possible. Dogs with a medical history of treatment with sulfonamides, NSAIDs, phenobarbital, or prednisone (except dogs previously determined to have hypoadrenocorticism receiving physiologic doses of corticosteroids) were excluded, as these medications can interfere with thyroid testing.13

Diagnosis of pituitary-dependent hyperadrenocorticism was based on consistent clinical signs, compatible serum biochemical abnormalities (eg, increased alkaline phosphatase activity), compatible adrenal function testing results from an ACTH stimulation test or an LDDST, and supportive diagnostic imaging results when available. A high post–ACTH stimulation serum cortisol concentration (>600 nmol/L or 22 μg/dL) either 1 hour after administration of synthetic cosynotropin (1.1 U/kg [0.5 U/lb], IV) or 2 hours after administration of corticotropin (2.2 U/kg [1 U/lb], IM) was considered consistent with hyperadrenocorticism. Results from the LDST were considered consistent with hyperadrenocorticism if there was inadequate suppression of cortisol concentration (>40 nmol/L; 1.4 μg/dL) 8 hours after administration of a low dose of dexamethasone (0.01 mg/kg [0.0045 mg/lb], IV). A diagnosis of pituitary-dependent hyperadrenocorticism was based on consistent LDDST results, including a 4-hour serum cortisol concentration >50% suppression from baseline or <40 nmol/L (<1.4 μg/dL), an 8-hour serum cortisol concentration >50% suppression from baseline but >40 nmol/L (>1.4 μg/dL), or compatible abdominal ultrasonographic findings displaying bilaterally symmetric adrenal glands considered to be of normal or increased size. Atypical hyperadrenocorticism was diagnosed in neutered patients with compatible clinical signs and clinico-pathologic findings, including a large increase in serum concentrations of 17-hydroxyprogesterone (>2.63 ng/mL), with or without increases in androstenedione (>29.0 ng/mL), estradiol (>69.4 pg/mL), progesterone (>1.45 ng/mL), or aldosterone (>398.5 pg/mL) after ACTH stimulation. Patients with high serum concentrations of sex hormones received a diagnosis of atypical hyperadrenocorticism when they had a positive response to treatment with mitotane.

Hypoadrenocorticism was diagnosed on the basis of low pre- and 1-hour post-ACTH stimulation serum cortisol concentrations (≤55 nmol/L or 2 pg/dL). Primary hypoadrenocorticism was diagnosed on the basis of compatible ACTH stimulation test results plus hypercalcemia (serum sodium concentrations <140 mmol/L), hyperkalemia (serum potassium concentrations >5.4 mmol/L), or both. Atypical or glucocorticoid-deficient hypoadrenocorticism was suspected on the basis of consistently high serum cortisol concentrations after ACTH stimulation testing, high serum sodium concentrations or serum sodium concentrations within reference limits (reference interval, 140 to 154 mmol/L), and low serum potassium concentrations or serum potassium concentration within reference limits (reference interval, 3.8 to 5.4 mmol/L). Dogs that had a history of corticosteroid treatment within the previous 3 months, or any history of treatment with mitotane, trilostane, or ketoconazole, were excluded from having a diagnosis of hypoadrenocorticism.

Primary hyperparathyroidism was diagnosed on the basis of persistent high serum concentrations of total calcium (>3 mmol/L or >12 mg/dL) and high serum concentrations of ionized calcium (>1.45 mmol/L), low or low-end-of-the-reference-range serum phosphorus concentration (reference interval, 0.90 to 1.85 mmol/L), concurrent high or high-end-of-the-reference-range intact parathyroid hormone concentrations (reference interval, 3 to 17 pmol/L [29 to 162 pg/mL]), 1 or more detectable parathyroid masses on ultrasonography, and no evidence of concurrent disease that could result in hypercalcemia. Hypparathyroidism was diagnosed on the basis of persistent hypocalcemia (serum calcium concentrations <2.5 mmol/L and serum ionized calcium concentrations <1.25 mmol/L), serum phosphorus concentrations >1.85 mmol/L, and concurrent low intact parathyroid hormone concentrations (<3 pmol; 29 pg/mL).

**Diagnostic imaging**—Results of all radiographic and ultrasonographic examinations performed by a board-certified radiologist were recorded for each patient and were used to support endocrine testing results where applicable.

**Data analysis**—Data are reported as mean ± SD values, median and range values, or frequency of occurrences and percentages.
Results

During the study period, 71 dogs with a diagnosis of 2 or more endocrinopathies were identified for potential inclusion in the study. Eighteen dogs were excluded because an endocrinopathy was iatrogenic because of treatment of an endocrine disorder (n = 14), hypophysectomy (2), adrenalectomy (1), or administration of corticosteroids (1). Although 16 dogs had clinical signs and clinicopathologic evidence of a second concurrent endocrine disorder, these dogs did not meet the endocrine diagnostic inclusion criteria and were therefore excluded. Two dogs were erroneously coded as having a second endocrinopathy and were excluded from the study. The remaining 35 dogs were included in the study.

A total of 13,912 dogs were evaluated at the veterinary teaching hospital during the study period, and the dogs in the present study made up 0.3% of the hospital population. Of the 13,912 dogs, 482 (3.6%) were recorded as having hyperadrenocorticism, 477 (3.5%) with hypothyroidism, 308 (2.3%) with diabetes mellitus, 182 (1.3%) with hyperadrenocorticism, 73 (0.5%) with primary hyperparathyroidism, 14 with diabetes insipidus (0.1%), and 9 with hypoparathyroidism (0.06%).

The mean age at diagnosis of the first disorder for all dogs in the study was 7.9 ± 2.6 years (median, 8.5 years; range, 3.1 to 13.2 years). After a diagnosis of the first disorder, the mean time to diagnosis of a second endocrine disorder was 14.5 ± 17.7 months (median, 4 months; range, 0 to 53 months). The mean time to diagnosis of a third endocrine disorder after diagnosis of the first disorder was 31.1 ± 22.6 months (median, 31.5 months; range, 10 days to 79.5 months).

Of the 10 dogs in which hypothyroidism was diagnosed first, the mean age at diagnosis was 7.0 ± 2.1 years (median, 6.3 years; range, 4.4 to 10.7 years). Of the 13 dogs in which diabetes mellitus was diagnosed first, the mean age at diagnosis was 8.4 ± 2.4 years (median, 9 years; range, 3.6 to 12.5 years). Of the 7 dogs in which hyperadrenocorticism was diagnosed first, the mean age at diagnosis was 9.1 ± 2 years (median, 9 years; range, 6.5 to 11.6 years). Of the 4 dogs in which hypoadrenocorticism was diagnosed first, the mean age at diagnosis was 4.9 ± 1.7 years (median, 4.7 years; range, 3.1 to 7 years).

Of the 35 dogs included in the study, 22 (62.9%) were castrated males, 8 (22.9%) were spayed females, and 5 (14.3%) were sexually intact males. There were no sexually intact females included in the study. Nine of 35 (25.7%) dogs were mixed breeds (of which 5 were Poodle crossbred dogs), 7 (20%) were Miniature Schnauzer, 3 (8.6%) each of the following breeds: Jack Russell Terrier, Siberian Husky, American Eskimo Dog, Great Pyrenees, German Shepherd Dog, Bichon Frise, Weimaraner, Irish Setter, English Setter, Cocker Spaniel, Dachshund, Golden Retriever, Toy Poodle, Shih Tzu, Brittany Spaniel, and West Highland White Terrier.

Of the 35 dogs, 28 (80%) had 2 endocrine disorders, and 7 (20%) had 3 endocrine disorders. The most common combination of multiple endocrinopathies was diabetes mellitus and hypoadrenocorticism, which was found for 14 of 35 (40%) dogs. Of these 14 dogs, diabetes mellitus was diagnosed first in 8 dogs, hyperadrenocorticism was diagnosed first in 4 dogs, and the 2 disorders were diagnosed concurrently in 2 dogs.

The next most common combination of endocrinopathies was hypothyroidism and hypoadrenocorticism in 7 of 35 (20%) dogs. Of these 7 dogs, hypothyroidism was diagnosed first in 2 dogs, the 2 disorders were diagnosed concurrently in 3 dogs, and hypoadrenocorticism was diagnosed first in 2 dogs.

Diabetes mellitus and hypothyroidism was diagnosed in 4 of 35 (11.4%) dogs. Of these 4 dogs, hypothyroidism was diagnosed first in 3 dogs, and diabetes mellitus was diagnosed first in the remaining dog.

One of 35 (2.9%) dogs had hypothyroidism and hyperadrenocorticism, in which the hypothyroidism was diagnosed first. One of 35 (2.9%) dogs had a diagnosis of hypothyroidism followed by a diagnosis of primary hyperparathyroidism. Finally, 1 of 35 (2.9%) dogs had diabetes mellitus and hypoparathyroidism, in which diabetes mellitus was diagnosed first.

Seven dogs had 3 endocrine disorders. The most common combination for dogs with 3 concurrent endocrinopathies was diabetes mellitus, hypothyroidism, and hyperadrenocorticism in 5 of 35 (14.3%) dogs. Of the 5 dogs, hyperadrenocorticism was diagnosed first in 3 dogs, and diabetes mellitus or hypothyroidism was diagnosed first in 1 each of the remaining 2 dogs. One of 35 (2.9%) dogs had concurrent diabetes mellitus, hypothyroidism, and hypoparathyroidism, in which hypoadrenocorticism was diagnosed first. Finally, 1 of 35 (2.9%) dogs first had a diagnosis of central diabetes insipidus, then diabetes mellitus, and finally hyperadrenocorticism.

Discussion

To our knowledge, the present study is the largest, most detailed of dogs with naturally occurring multiple endocrine disorders. Clinical findings and clinicopathologic test results at the time of diagnosis of each endocrine disorder (ie, hypothyroidism, diabetes mellitus, hyperadrenocorticism, primary hyperparathyroidism, and hypoparathyroidism) were consistent with previously reported findings.7

The prevalence of multiple endocrine disorders in dogs was low, representing 0.3% of the total canine hospital patients during this time period. Patients with multiple endocrine disorders represented 2.3% of the total canine patients with an endocrinopathy, indicating that this is a rare occurrence.

The reported mean age at the time of diagnosis for dogs with various endocrine disorders is variable. Hyperadrenocorticism, hypothyroidism, and hypoparathyroidism are more common in younger dogs, with an approximate age at onset of 2 to 6 years.5,11 Diabetes mellitus is most common in middle-aged to older dogs with peak prevalence at 7 to 9 years of age.7,9 Hyperadrenocorticism and primary hyperparathyroidism are typically diagnosed in older dogs, with an average age at diagnosis of 11 years.7,14 The mean age at the time of the diagnosis of the first endocrine disorder for dogs in the present study was 7.9 ± 2.6 years. Diabetes mellitus (13/33 [37.1%] dogs) was the most commonly diagnosed first endocrine disorder followed by hypothyroidism (10/35 [28.6%] dogs). The mean age at diagnosis for
dogs in the present study is similar to the age at diagnosis of most dogs with diabetes mellitus and slightly older than most dogs with hypothyroidisms.

There are conflicting reports regarding sex predisposition to developing endocrine disorders in dogs. Most dogs with hyperadrenocorticism, hypoadrenocorticism, hypoparathyroidism, and diabetes mellitus were female in some reports, whereas another study showed an approximately equal distribution of diabetes mellitus among male and female dogs. In the present study, 6 of 35 (22.9%) patients with multiple endocrine disorders were female, and 27 of 35 (77.1%) were male, which does not agree with the available information on sex predisposition for endocrine disorders in dogs. In human medicine, female patients are more likely to develop polyendocrine syndromes than are males, likely attributable to the immune-mediated etiology of these syndromes and the overall predilection of females for immune-mediated disorders in general. In contrast to this study, previously reported cases of dogs with multiple endocrine disorders were predominantly female. During the study period, our hospital's canine population sex distribution was 48.7% female and 51.3% male; the high percentage of affected males in the present study could not be attributed to a predominantly male hospital population. It is unclear why the cases of multiple endocrine disorders were predominantly in male dogs in the present study, but may be related to the relatively small population studied.

Breed predispositions are associated with canine endocrine diseases. The most common breed in the present study was the Miniature Schnauzer (7/35 [20%]). Miniature Schnauzers are reportedly predisposed to developing diabetes mellitus, hypothyroidism, and hypoparathyroidism. During the study period, 2.6% of canine hospital admissions were Miniature Schnauzers. There appears to be an increased proportion of Miniature Schnauzers within the study group, compared with the proportion in the hospital population. There were 9 (25.7%) affected mixed-breed dogs in the present study, similar to the overall canine hospital population (22% mixed-breed dogs).

The time between diagnosis of the first and second endocrine disorder in these dogs was variable, with a mean time of 14.5 months (median, 4 months; range, 0 to 53 months). In dogs with 3 endocrine disorders, the mean time between diagnosis of the second and third disorder was 19.8 months (median, 16.8 months; range, 2 to 47 months) but was also variable. Previous studies and anecdotal information regarding multiple endocrine disorders indicate similar time intervals between subsequent diagnoses, also with a large degree of variation in these time intervals. However, clinicians should remain suspicious of another endocrine disorder when appropriate historical, physical, and clinicopathologic findings are present, regardless of the time interval between diagnoses.

Several combinations of endocrine disorders reported in the present study and previous case reports are similar to those identified in humans with polyendocrinopathy syndromes. Eight of 35 (22.9%) dogs in the present study had concurrent hypoadrenocorticism and hypothyroidism. Additionally, 10 of 35 (28.6%) dogs had diabetes mellitus and hypothyroidism. Furthermore, 1 dog had diabetes mellitus and hypoadrenocorticism, and 1 dog had diabetes mellitus, hypothyroidism, and hypoparathyroidism. Several case reports have documented concurrent hyperadrenocorticism and hypothyroidism in dogs, and this is likely the most commonly recognized polyendocrine failure state in dogs. A previous study showed that 4% of dogs with hyperadrenocorticism had concurrent hypothyroidism. Additionally, concurrent diabetes mellitus and hypothyroidism has occasionally been reported in dogs. A study of dogs with hypothyroidism showed that 1.5% had concurrent diabetes mellitus, whereas a study of diabetic dogs identified concurrent hypothyroidism in 4% of the dogs.

Diabetes mellitus, hyperadrenocorticism, hypothyroidism, and hypoparathyroidism may result from an underlying immune-mediated etiology in dogs. It is possible that the dogs in the present study with combinations of those endocrine diseases were affected by a common immune-mediated etiology in the development of their multiple endocrinopathies, similar to humans affected by polyendocrinopathy syndromes. Only 2 dogs with hypothyroidism in the present study had thyroglobulin autoantibodies measured: 1 was seropositive for thyroglobulin autoantibodies, and 1 was seronegative for thyroglobulin autoantibodies. Autoantibody concentrations were not measured in any of the other dogs and would need to be evaluated to help identify an immune-mediated origin.

Diabetes mellitus and hyperadrenocorticism are the most frequently cited concurrent endocrine disorders in canine patients. Similarly, the combination of diabetes mellitus and hyperadrenocorticism was most commonly identified in the present study, affecting 20 of 35 (57.1%) dogs. Of these 20 dogs with diabetes mellitus and hyperadrenocorticism, 5 dogs also had hypothyroidism, and 1 dog also had diabetes insipidus. It is estimated that 5% to 8% of dogs with hyperadrenocorticism will eventually also receive a diagnosis of diabetes mellitus. Conversely, in a teaching hospital's population of dogs with diabetes mellitus, 23% had hyperadrenocorticism.

The etiology of the diabetes mellitus and hyperadrenocorticism is likely not related in these dogs. Diabetes mellitus in dogs is considered to develop at least partially from immune-mediated pancreatic destruction, whereas hyperadrenocorticism in the dogs of the present study was thought to develop from a pituitary adenoma. In the present report, most of the dogs with concurrent diabetes mellitus and hyperadrenocorticism had diabetes mellitus as their first endocrine disorder. The diagnosis of diabetes mellitus preceded the diagnosis of hyperadrenocorticism by a mean of 12.6 months (median, 4 months; range, 12 days to 49 months). In a previous study of 30 dogs with diabetes mellitus and hyperadrenocorticism, the 2 disorders were diagnosed concurrently in 15 of 30 dogs; diabetes mellitus was diagnosed first in 8 of 15 dogs; hyperadrenocorticism was diagnosed first in the remaining 7 dogs. It is difficult to determine which disease arises first in these patients. However, it is thought that hyperadrenocorticism likely occurs first in most of these dogs and that previously subclinical diabetes mellitus begins to become clinical in these dogs because of the insulin resistance secondary to the hyperadrenocorticism. Diabetes mellitus is usually diagnosed first in these
dogs, which is likely in part attributable to the presence of persistent hyperglycemia and glucosuria being easily detected on a routine minimum database before a clinician pursues specific adrenal function testing in these dogs. However, once the diabetes mellitus becomes difficult to control with routine insulin administration or signs of diabetes (eg, polyuria and polydipsia) persist, further investigation including adrenal function testing is often pursued.

In the present study, 6 dogs had concurrent hyperadrenocorticism and hypothyroidism, whereas 1 dog had concurrent hypothyroidism and primary hyperparathyroidism. Similar to the etiology of pituitary-dependent hyperadrenocorticism, primary hyperparathyroidism is usually due to adenomatous changes in the parathyroid gland and therefore unlikely to be caused by an immune-mediated pathogenesis. Their concurrent incidence is likely coincidental in middle-aged to older dogs.

Seven dogs had 3 endocrine disorders. Five of the 7 dogs had a combination of diabetes mellitus, hyperadrenocorticism, and hypothyroidism. There was also 1 dog each with concurrent diabetes mellitus, hypothyroidism, and hyperadrenocorticism and concurrent diabetes mellitus, hypothyroidism, and hypoparathyroidism. Dogs with 3 concurrent endocrine disorders have rarely been reported in the veterinary literature. The prevalence of dogs with 3 endocrine disorders appears low, representing only 0.5% of the dogs with an endocrine disorder from our hospital population.

The presence of multiple endocrine diseases can present a diagnostic challenge. Clinical signs and clinicopathologic findings can be similar among various endocrine disorders. Additionally, the presence of more than 1 endocrine disorder can affect specific endocrine testing results, especially for hyperadrenocorticism and hypothyroidism.

Along with consistent clinical signs, the diagnosis of hyperadrenocorticism in a dog with another previously diagnosed endocrine disorder relies on an ACTH stimulation test or an LDDST. Caution should be used, as concurrent diseases such as diabetes mellitus can lead to false-positive adrenal function test results. The false-positive result rate of the LDDST can be up to 30% in the presence of other illness or medications. Additionally, the ACTH stimulation test has a false-positive result rate of up to 15%. Adrenal function testing results can be within reference range for patients with well-regulated diabetes mellitus that do not have hyperadrenocorticism. However, many of the dogs that received a diagnosis of hyperadrenocorticism after a diagnosis of diabetes mellitus in the present study were not considered well-regulated diabetics. It is possible that hyperadrenocorticism was overlooked in this population. In light of potential error in adrenal function testing results, each diagnosis of hyperadrenocorticism was based on a combination of supportive findings from the historical information, physical examination and clinicopathologic findings, diagnostic imaging findings when available, and long-term response to treatment.

It is possible that some euthyroid dogs were misidentified as hypothyroid in the present study. Concurrent disease such as hyperadrenocorticism can cause low T4 values. Glucocorticoids can exert negative feedback on the hypothalamus-pituitary-thyroid axis, resulting in decreased total T4 and, to a lesser extent, free T4, as well as variable changes in thyroid stimulating hormone. A recent report showed that 20% of dogs with untreated hyperadrenocorticism had a low total T4 and 11% had a low free T4 concentration. It is possible that some of the dogs with concurrent hypothyroidism and hyperadrenocorticism in the present study were instead showing a normal physiologic response of decreased T4 concentrations in response to excess circulating glucocorticoids. The strongest clinicopathologic evidence for hypothyroidism includes a combination of low total and free T4 plus a high thyroid-stimulating hormone value. These criteria, along with compatible clinical features and appropriate response to treatment (when available), were used to help minimize the false diagnosis of hypothyroidism in euthyroid sick dogs.

The retrospective nature of this study introduces some important limitations to this report. The number of dogs with multiple endocrine disorders may have been underestimated because of improper record coding or incomplete medical records. This study examined only dogs referred to a tertiary care center, which likely led to a differential admission bias. However, it was not the intention of the authors to investigate the true incidence of multiple endocrinopathies in canine patients, but rather to describe the most common combinations of concurrent endocrine disorders in these patients.

The recognition of multiple endocrine disorders in dogs is important for the successful management of these patients. Additionally, clinicians must recognize that the occurrence of multiple endocrine disorders is rare. Diagnosis of multiple endocrine disorders relies on a combination of historical, physical, and clinicopathologic findings. Endocrine testing has limitations, especially when performed in dogs with concurrent disease. Strict diagnostic criteria should be used, and the potential for false-positive test results must be recognized in these patients. Further study in this area is needed and should include investigation of circulating and tissue autoantibodies in dogs with 1 or more endocrine disorders as well as correlation of the presence of these antibodies with development of later disease.

References