INTRODUCTION
Hypoadrenocorticism (Addison’s disease) results from failure of the adrenal glands to secrete glucocorticoids and mineralocorticoids. Most cases of hypoadrenocorticism are due to primary adrenal failure, resulting in deficiency of usually both cortisol and aldosterone from the adrenal cortex. More rarely, Addison's disease may be due to pituitary dysfunction resulting in a failure of ACTH secretion and pure glucocorticoid deficiency (secondary adrenal failure). In secondary hypoadrenocorticism, mineralocorticoid secretion is expected to be normal.

CLINICAL SIGNS
Signalment: Seventy percent of dogs diagnosed with hypoadrenocorticism are female, and most are young to middle-aged dogs (mean 4 - 5 years). The disease is heritable in the Standard Poodle, Bearded Collie, Portuguese water dog and the Nova Scotia Duck Tolling Retriever (NSDTR) and in these breeds no obvious sex predisposition is evident. In the Standard Poodle, Portuguese Water dog, and NSDTR, the disease appears to be inherited as an autosomal recessive trait. Incidence of hypoadrenocorticism in the NSDTR is estimated to affect 1.4% of the population while in the Standard Poodle 8.6% of poodles in one study were affected.

History and Physical examination: Clinical signs may be either acute or gradual in onset and often wax and wane. Owners may not realize how long their dog has been ill until treatment results in a dramatic improvement in activity level. Since 85-90% of adrenal reserve must be depleted before clinical signs are observed, it may require a stressful event to trigger clinical illness. Clinical signs may be very vague. Anorexia, vomiting, lethargy/depression, weakness, weight loss, diarrhea, shaking/shivering, polyuria, polydipsia, and abdominal pain may be observed. Most of these clinical signs can occur due to glucocorticoid deficiency alone. If mineralocorticoids are also deficient, the clinical signs tend to be more severe and polyuria, polydipsia, hypovolemic shock, collapse and dehydration are often present. Less common clinical signs include acute gastrointestinal hemorrhage, and seizures due to hypoglycemia or electrolyte derangement. The physical examination may be normal or may reveal lethargy, weakness, dehydration, bradycardia, weak pulses, decreased capillary refill time, and other evidence of hypovolemic shock.

DIAGNOSTIC TESTING FOR HYPOADRENOCORTICISM
Clinical Pathology
A complete blood count may reveal a nonregenerative normocytic normochromic anemia; alternatively the hematocrit may be increased due to dehydration. Eosinophilia, neutrophilia or lymphocytosis are found in only 20-30% of dogs with hypoadrenocorticism, but lack of a stress leukogram in a dog with systemic illness is common. A chemistry profile may reveal hyponatremia, hypochloremia, hyperkalemia, hypercalcemia, and hyperphosphatemia. These changes occur due to aldosterone deficiency with a resultant failure of the kidneys to conserve sodium. Other possible serum biochemical abnormalities include hypoalbuminemia, hypocholesterolemia, hypoglycemia, and increased liver enzymes. Specific gravity of the urine is commonly less than 1.030. The changes on the minimum data base in dogs with hypoadrenocorticism may initially mimic other disorders such as renal failure, hepatic disease, gastrointestinal disease, or insulinoma.

Serum electrolyte abnormalities
The majority of dogs with hypoadrenocorticism have the classic electrolyte changes of hyponatremia and hyperkalemia due to aldosterone deficiency.

Na:K ratio
The Na:K ratio is usually low in dogs with hypoadrenocorticism, and this ratio may be useful to guide emergency diagnosis and treatment while waiting for definitive test results.

Imaging studies
Most untreated dogs with hypoadrenocorticism have one or more radiographic abnormalities on thoracic and abdominal radiographs including microcardia, small cranial lobar pulmonary artery, narrow posterior vena cava, or microhepatica. Occasional dogs may have evidence of megaesophagus. Most dogs with hypoadrenocorticism have a measurable reduction in size of the adrenal glands, and sometimes the adrenal glands cannot be identified on ultrasound.

Electrocardiogram
In dogs with hyperkalemia, abnormalities may be present on the electrocardiogram. These include a peaked T wave and shortening of the QT interval in mild hyperkalemia, widening of the QRS complex, decreased QRS amplitude, increased duration of the P wave, and increased P-R interval in moderate hyperkalemia, and loss of P waves and ventricular fibrillation or asystole in severe hyperkalemia.

**Basal cortisol**  
Measurement a basal cortisol of >55 nmol/l (2 microg/dl) is a useful test to exclude a diagnosis of hypoadrenocorticism. Measurement of a basal cortisol concentration is not adequate for confirmation of a diagnosis of hypoadrenocorticism however, because some dogs have a low basal cortisol concentration but have an appropriate response to ACTH administration.

**ACTH stimulation test**  
An ACTH stimulation test is necessary to confirm a diagnosis of hypoadrenocorticism because not all dogs with hypoadrenocorticism have the expected electrolyte changes, and because many other disorders may mimic the characteristic findings of Addison’s disease. In dogs with hypoadrenocorticism, both the pre- and post- ACTH cortisol concentrations are usually less than 27 nmol/l, (1 microg/dl), and both values should be less than the reference range for basal cortisol (usually 55 nmol/l, 2 microg/dl) to confirm the diagnosis.

**ATYPICAL ADDISON’S DISEASE**  
It is now recognized that although most dogs with hypoadrenocorticism have obvious electrolyte changes such as hyponatremia and hyperkalemia, a subset of dogs with hypoadrenocorticism lack these electrolyte changes. In a retrospective study of dogs with hypoadrenocorticism, 24% of dogs lacked hyponatremia and hyperkalemia. In a study of 25 NSDTR, 32% lacked electrolyte abnormalities at the time of diagnosis. Reasons for normal electrolytes include secondary hypoadrenocorticism due to decreased ACTH secretion, selective destruction of the zona fasciculata and reticularis, early stage disease in which there has not yet been complete destruction of the zona glomerulosa, or ability to compensate for sodium wasting by increasing sodium intake. Dogs with glucocorticoid deficient hypoadrenocorticism tend to be older, have a longer duration of clinical signs, and are more likely to be anemic, hypoalbuminemic and hypocholesterolemic than those with electrolyte changes.

**HOW DOES RECOGNITION OF ATYPICAL ADDISON’S DISEASE CHANGE THE DIAGNOSTIC APPROACH?**  
It is important for clinicians to recognize that an absence of the characteristic electrolyte changes of hyponatremia and hyperkalemia does not exclude a diagnosis of hypoadrenocorticism. Clinicians should have a high index of suspicion for hypoadrenocorticism so that this very treatable disease is not missed. Conversely reliance on measurement of electrolytes alone for diagnosis of hypoadrenocorticism can be misleading, because there are many other causes of hyponatremia and hyperkalemia; the diagnosis must be confirmed by endocrine testing. When evaluating any systemically ill dog the possibility of hypoadrenocorticism should always be considered. Useless clues may be the presence of waxing and waning illness, improvement with conservative management, and improvement after administration of glucocorticoids. Lack of a stress leukogram, and identification of small adrenal glands on ultrasound, also increases suspicion for hypoadrenocorticism. In dogs with suspected hypoadrenocorticism measurement of a basal cortisol is useful to exclude the diagnosis without the expense of an ACTH stimulation test.

**ACUTE TREATMENT**  
Rapid treatment of dogs with suspected Addison’s disease is vital especially if profound electrolyte abnormalities are present. Aims of treatment include correction of hypotension/hypovolemia, correction of electrolyte imbalances, provision of an immediate source of glucocorticoids, and correction of acidosis, hypoglycemia, and hypercalcemia. The suggested procedure for dogs presenting with signs of hypovolemia in which Addison’s disease is suspected is detailed below:

Place IV catheter in cephalic or jugular vein, and collect a blood sample for measurement of electrolytes, and cortisol. Synthetic ACTH (5 microg/kg) is then administered IV, and a second blood sample for measurement of cortisol collected 1 hour later. Fluid therapy (0.9% saline IV, 30 - 80 ml/kg/24 hours plus correction for dehydration) should be started immediately. Once the second blood sample has been collected, treatment with glucocorticoids can be begun if there is a high clinical suspicion of Addison’s disease. If animal is in shock, administration of steroids should be at shock doses and this should take precedence over establishing an immediate diagnosis. The choice of mineralocorticoid depends upon the clinical status of patient (oral versus
injectable), product availability, and confidence in diagnosis. In most cases electrolytes normalize with fluid therapy and glucocorticoids alone, and immediate mineralocorticoid supplementation is not necessary. Long-term mineralocorticoid therapy can be initiated once the animal is stable and the diagnosis is confirmed. Other treatments that may be indicated in individual patients include synthetic colloids, blood transfusion, and IV dextrose. Parameters that should be monitored during treatment include serum electrolytes and acid-base status, urine output, ECG, blood pressure, and if possible central venous pressure. IV fluid therapy should be continued until the animal is fully rehydrated and oral intake is possible.

MAINTENANCE THERAPY
Options for long term mineralocorticoid treatment include fludrocortisone (starting dose 0.02 mg/kg/day as a single dose or divided) or desoxycorticosterone pivalate (starting dose 2.2 mg/kg q 25 days). For both of these mineralocorticoids the dose should be titrated to effect. The dose of fludrocortisone typically needs to be increased over time whereas in many cases the final individualized dose of DOCP is < 2.2 mg/kg. Prednisone is typically recommended for glucocorticoid replacement. The starting dose is 0.2 mg/kg per day and the dose should then be tapered to the lowest dose that will control the clinical signs. It is important to avoid excess prednisone supplementation because this may result in manifestations of iatrogenic hyperadrenocorticism. Only 50% of dogs treated with fludrocortisone require supplemental prednisone, whereas most dogs treated with DOCP require prednisone at least every other day.

HOW DOES DIAGNOSIS OF ATYPICAL ADDISON’S DISEASE CHANGE THE DIAGNOSTIC APPROACH?
The main difference between managing dogs with classic Addison’s and those with atypical Addison’s disease is that dogs without electrolyte derangements do not require mineralocorticoid treatment and respond well to treatment with glucocorticoids alone. Treatment costs are therefore much cheaper. Doses of prednisone required to control the clinical signs are typically <0.1 mg/kg/day and some dogs can be managed on every other day treatment. If significantly higher doses of prednisone are required to control the clinical signs the possibility of an alternative diagnosis should be considered.
Dogs with atypical Addison’s should be monitored using clinical signs reported by the owner, physical examination findings (especially weight) and measurement of electrolytes. Serum electrolyte concentrations should initially be monitored frequently because some dogs that present without electrolyte derangements will develop them later. The ACTH stimulation test is not part of the regular monitoring for animals with either classic or atypical Addison’s disease.

REFERENCES