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DR. SCHAER MICHAEL

Acute Adrenocortical Insufficiency
Canine Hyperadreno Corticism (Cushing's Syndrome)
Diabetes Insipidus (DI)
Diabetic Ketoacidosis - Pathophysiology, Diagnosis and Medical Management
Growth Hormone and Acromegaly
Pituitary Dwarfism in German Shepherds
Treatment of Diabetes Mellitus in the Cat and Dog
10. DR. SCHAER MICHAEL

10.1 ACUTE ADRENOCORTICAL INSUFFICIENCY

Etiology

Adrenocortical insufficiency can result from the following causes: iatrogenic adrenocortical atrophy from glucocorticoid administration, o,p'DDD-induced adrenocortical destruction, hemorrhage or infarction of the adrenal glands, mycotic or neoplastic involvement, surgical adrenalectomy, anterior pituitary gland insufficiency, and, primary hypoadrenocorticism. An additional rare cause is bilateral adrenal hemorrhage that occurs within a few days following an ACTH injection for the evaluation for Cushing’s. This is thought to result from possible hypertension in the adrenal arteries caused by the ACTH (JVIM 19;2005). Primary hypoadrenocorticism typifies canine Addison’s syndrome and is pathologically characterized as a bilateral adrenocortical atrophy. Most of the veterinary literature applies an idiopathic cause for the majority of cases of canine Addison’s disease; however, an autoimmune destruction of the adrenal cortices has also been described in the dog. This autoimmune process might very well be the initial cause of what eventually becomes bilateral adrenocortical atrophy and fibrosis.

Pathophysiology

The pathophysiologic consequences of primary adrenocortical insufficiency are a direct result of glucocorticoid and aldosterone deficiencies. Glucocorticoid depletion results from impaired function of the zona fasciculata. The hypocortisolemia causes impaired gluconeogenesis and glycogenolysis, decreased sensitization of blood vessels to catecholamines, impaired renal water excretion, and decreased vitality as characterized by poor appetite, lethargy and impaired cerebration.

Aldosterone is a mineralocorticoid hormone that plays an important role in sodium and potassium homeostasis. Hypoaldosteronism occurs from impaired function of the zona glomerulosa and causes renal sodium and chloride ion wasting and potassium and hydrogen ion retention. The clinical and pathophysiologic effects of hyponatremia include lethargy, mental depression, nausea, hypotension, impaired cardiac output and renal perfusion, and hypovolemic shock. Hyperkalemia causes muscle weakness, hyporeflexia, and abnormal cardiac excitation and conduction. The Addisonian crisis most often occurs in the setting of moderate to marked hyponatremia (serum sodium < 132 mEq/L) and hyperkalemia (serum potassium > 7.0 mEq/L).
The hypoaldosteronism is the chief reason for the hyperkalemia. The hyponatremia, which occurs mostly with glucocorticoid deficiency, is caused by elevated arginine vasopressin levels and the resulting increased free water retention, decreased sodium pump activity and the resulting shift of extracellular sodium into cells, and decreased delivery of filtrate to diluting segments of the nephron as a result of decreased glomerular filtration rates.

**Differential Diagnosis**

The differential diagnosis of hypoadrenocorticism includes any illness that can characterize as vomiting, depressed appetite, weight loss, muscular weakness, or acute collapse. Some of the more common differentials include gastrointestinal disorders, renal failure, various intoxicants, liver disease, and cardiac disorders.

**Diagnosis**

A tentative diagnosis of acute adrenocortical insufficiency can be made on the basis of the history and physical examination findings. Historically, the dog might have had a chronic period of weight loss, vomiting and/or diarrhea, and lethargy. Polydipsia and polyuria are rarely present in some patients. The chronicity might vary from weeks to months duration and then suddenly culminate in an acute hypotensive state of collapse. On the other hand, the addisonian crisis can occur acutely without any prior signs of illness.

The physical examination findings of the acutely decompensated patient will depict a generally ill patient that is either hypo- or normothermic. Hydration varies from normal to varying degrees of dehydration. The mentation is dull, and muscle weakness is usually marked. The respiratory rate can be normal or rapid, the latter due to either shock and/or attempted compensation for a metabolic acidosis. The mucous membranes are usually pink, but the capillary refill time is prolonged. Cardiac auscultation can detect either normal sinus rhythm or arrhythmias, especially bradyarrhythmias. The pulse quality is weak, and the rate varies from normal to slow.

The electrocardiogram is a useful diagnostic tool for the detection of the various conduction and complex abnormalities that are associated with hyperkalemia. The most common abnormalities include flattened P-waves, increased positive or negative deflected T-waves, broadened QRS complexes, bradycardia, sinoventricular complexes, and atrial standstill. These electrocardiographic abnormalities do not occur until the serum potassium exceeds 7.5 mEq/L, but they can occur at 7.0 mEq/L when the serum sodium is < 130 mEq/L.
The tentative clinical diagnosis of Addison's disease is based on clinicopathologic test results. The hallmark findings include hyperkalemia and hyponatremia (Na/K < 20:1). Atypical addisonian patients can have hyponatremia with normokalemia or hyperkalemia with normonatremia. Other causes of hyponatremia with hyperkalemia have to be differentiated from adrenocortical insufficiency. These include renal failure, gastroenteritis, decompensated diabetes mellitus, ascites and chylothorax. Some addisonians might have normal electrolytes yet have hypocortisolemia. Additional associated clinicopathologic abnormalities include mild to moderate hypochloremia, azotemia, hyperphosphatemia, metabolic acidosis, and rarely hypothyroidism. Mild hypercalcemia is oftentimes present, but of no clinical significance. Hypoglycemia occurs rarely, but may be the only presenting abnormality in an atypical addisonian.

Although the above historical, physical, clinicopathological and electrocardiographic abnormalities are strongly suggestive of acute hypoadrenocorticism and usually constitute the basis for the clinical diagnosis and the need for immediate therapy, the absolute diagnosis depends on the demonstration of absent or minimal adrenocortical response to an injection of corticotropin (ACTH). The following procedure is recommended soon after the patient's admission in order to avoid any unnecessary delay of therapy for the sake of performing a diagnostic test.

(1) Draw blood for hemogram, serum biochemistry and basal cortisol determinations.
(2) Begin the intravenous fluids and give 2-5 mg/kg of dexamethasone sodium phosphate intravenously.
(3) Immediately give 0.25 mg of alpha 1-24 cosyntropin (dogs) (Cortrosyn-Organon) intramuscularly or intravenously. Cats should receive 0.125 mg.
(4) Withdraw a second blood sample for plasma cortisol determination 45-60 minutes later.

The patient will derive the benefit of immediate treatment while simultaneous confirmatory diagnostic tests are performed with the above technique. The post ACTH injection cortisol blood level will barely increase above the basal value in typical hypoadrenocorticism. Blood levels of < 1.0 Φg/dl are typical, while those stimulating to only 2-3 Φg/dl also suggest hypoadrenocortical function.

A recent study by E.M. Lennon, et al, reports on the diagnostic value of the basal serum cortisol concentration (JAVMA, Aug 1, 2007). Basal values of <1 ug/dL had an excellent sensitivity of 100% and a specificity of 98.2% for detecting dogs with hypoadrenocorticism. For basal cortisol concentrations of < 2.0 ug/dL, sensitivity was 100% and specificity was 78%. This
population was initially screened for prior glucocorticoid and mitotane use.

**Treatment**

Treatment should begin immediately whenever the index of suspicion is strong for diagnoses of an addisonian crisis. The therapeutic objectives include (1) intravascular volume resuscitation, (2) correcting the hyponatremia and hyperkalemia, (3) providing glucocorticoids, and (4) recognizing and reversing any life-threatening cardiac arrhythmias.

Sodium chloride 0.9% is the fluid of choice and should be delivered through an indwelling intravenous catheter. The saline should be infused at a rate of approximately 75 ml/kg body weight during the first 1 to 2 hours of treatment if the dog is markedly hypotensive. Care should be taken to avoid an iatrogenic intravascular fluid overload because of the addisonian patient's theoretical intolerance to acute water loading. Central venous pressure determinations should be done in order to safeguard against this complication. For the remaining 24-hour period, the isotonic saline can be evenly infused at a maintenance rate of approximately 60 ml/kg body weight so long as the serum sodium concentration does not increase by more than 8-12 mEq/L (or 0.5 to 1.0mEq/L per hour) during the first 24-hours if the initial serum Na⁺ was < 125 mEq/L. The intravenous fluids are discontinued when hydration, urine output, serum electrolytes, the BUN levels are restored to normal (usually following 48 to 72 hours of treatment), and the patient begins eating.

Although intravenous saline will help correct the hyponatremia and hyperkalemia, the patient must also receive a mineralocorticoid drug that will enhance renal distal tubular sodium reabsorption and potassium excretion. When desoxycorticosterone acetate (DOCA) was available the dose ranged from 1.0 mg for a small dog to 5.0 mg for a large dog and was given once daily intramuscularly. In many patients, the subsequent daily doses of DOCA was decreased to approximately one-half of the initial dose due to the synergistic effects of fluids, DOCA and glucocorticoid medications. Currently DOCP (2.2 mg/kg IM) can be used in its place although its rate of onset is slower than DOCA.

When DOCA or DOCP are unavailable, fludrocortisone acetate (Florinef; Bristol-Meyers Squibb Company) should be given orally at an initial dosage 0.1 mg/5 kg body weight per day. Re-assessment of the serum electrolyte levels will serve as a helpful treatment guide for further dosage adjustments.

The glucocorticoid deficiency is best corrected with rapid-acting drugs such as prednisolone sodium succinate or dexamethasone.
phosphate. These glucocorticoid drugs should be given intravenously once initially at doses of 5-10 mg/kg and 2-5 mg/kg body weight, respectively for prednisolone sodium succinate and dexamethasone phosphate. Subsequent glucocorticoid requirements are fulfilled by administering 1 mg/kg body weight of prednisolone orally, intramuscularly, or intravenously every 12 hours through the second day and then reducing the dose to 0.25 to 0.5 mg/kg body weight every 12 hours for the remainder of hospitalization.

Hydrocortisone sodium succinate can be given for glucocorticoid replacement taking advantage of the fact that this particular glucocorticoid contains some mineralocorticoid activity. The emergency dose for shock is 20-25 mg/kg body weight IV every 6 hours. There has been no proven advantage with the use of hydrocortisone sodium succinate.

Serum potassium concentrations greater than 7.0 mEq/L can cause progressive abnormalities in myocardial excitation and conduction. The degree of hyperkalemic myocardial toxicity ranges from mild to severe based on the electrocardiographic changes, and only with severe changes is special therapy warranted. In such cases treatment should consist of 10% calcium gluconate, sodium bicarbonate, and/or insulin-dextrose solutions. Ten percent calcium gluconate solution is given at a dose of 0.5 to 1.0 ml/kg body weight intravenously over a 5- to 10-minute period, accompanied by continuous electrocardiographic monitoring. It directly antagonizes the myocardial toxic effect of hyperkalemia, but it will not lower the serum potassium level. Calcium gluconate takes it affect within minutes. To accomplish this latter effect, sodium bicarbonate solution is given at a dose of 1-2 mEq/kg body weight intravenously over a 5-to 10-minute period. Bicarbonate takes its effect after approximately 15 minutes. Regular crystalline insulin at an intravenous dose of 0.25 unit/kg body weight will also lower the serum potassium level. Two to three grams of dextrose per unit of insulin administered should also be given by intravenous push in order to avoid the anticipated hypoglycemic effects of insulin. The insulin dextrose treatment will lower the serum K+ after approximately 30 minutes. The above emergency measures for the treatment of myocardial toxicity are required only once and need not be repeated.

Complications

The majority of dogs with Addison's disease have an excellent prognosis for a normal quality of life. Early complications that might alter a favorable outcome include acute renal failure resulting from renal ischemia associated with protracted hypotension and cardiac dysfunction. If the patient is oliguric or anuric following the initial period of intravascular volume expansion, mannitol should be given intravenously at a dose of 0.5 gm/kg body weight in order to promote
an osmotic diuresis. Furosemide (1-2 mg/kg IV) and dopamine (2-5 \( \text{\textmu} \text{g} / \text{kg/minute} \)) can also be used to counteract oliguria. An indwelling urethral catheter should be inserted to quantitate the urine output until it is deemed adequate.

Iatrogenic complications include pulmonary edema resulting from excess parenteral fluid administration during the initial phase of intravascular volume resuscitation and hypokalemia as a consequence to excess mineralocorticoid treatment. Pulmonary edema can be avoided by closely observing the patient for signs of respiratory distress and by not exceeding the recommended volume of fluid delivery (20 to 40 ml/kg body weight) during the first 2 hours of therapy. Hypokalemia can occur on the second or third days of therapy and is mostly due to the combined effects of the saline infusion and excess amounts of mineralocorticoid. Daily monitoring of the patient's serum sodium and potassium levels will provide objective criteria for making any necessary treatment adjustments.

Central pontine myelinosis can occur as a result of too rapid correction of the serum sodium concentration. The parenchymal central nervous system tissue changes associated with this condition can cause signs of seizures, behavioral changes and paresis. The mechanism involves an osmotic dysequilibrium between the brain parenchyma and the plasma that occurs when the onset of hyponatremia is over 24 hours duration and is corrected at a rate exceeding 0.5 to 1.0 mEq/L per hour. The serum sodium concentration should not be allowed to increase by more than 8-12 mEq/L over the first 24-hours in order to avoid this complication.

| SERUM Na\(^+\) AND K\(^+\) LEVELS IN HYPOADRENOCORTICISM |
|---------------------------------|-----------------|
| **TYPICAL**                     | **ATYPICAL**    |
| Na\(^+\) 9, K\(^+\) 8           | Na\(^+\) normal, K\(^+\) 8 |
|                                  | Na\(^+\) 9, K\(^+\) normal |
|                                  | Na\(^+\) normal, K\(^+\) normal |

<table>
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<th>DIFFERENTIATING ACUTE RENAL FAILURE (ARF) FROM ADDISONS</th>
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If a dog is going to be maintained on Florinef, it is essential to know that it has up to five times the glucocorticoid activity as hydrocortisone. Therefore, larger doses of Florinef (3-5 tablets bid) can make the addisonian dog appear cushingoid.

10.2 CANINE HYPERADRENOCORTICISM (CUSHING'S SYNDROME)

Etiologies

Pituitary-induced bilateral adrenocortical hyperplasia also known as pituitary-dependent Cushing's disease (PDH) accounts for about 85% of all cases of spontaneous hypercortisolism in the dog. It results from either an adenohypophyseal ACTH-secreting micro- or macroadenoma or from excess pituitary ACTH secretion due to over secretion of corticotrophin releasing factor (CRF) by the hypothalamus. The end result of both processes is hypersecretion of ACTH causing bilateral adrenocortical hyperplasia and subsequent hypercortisolism.

Adrenal tumors consist of either functional adenomas or adenocarcinomas of the adrenal cortex. These comprise 10-15% of all causes of spontaneous Cushing's syndrome in dogs.

Iatrogenic hypercortisolism is by far the most common cause of the "Cushingoid" dog. It is caused by over-treatment with glucocorticoid drugs.


Cortisol: 700-800 ug/kg/day = 0.7-0.8 mg/kg/day
Corticosterone : 300-400 ug/kg/day
Desoxycortisol: 80-90 ug/kg/day
Deoxycorticosterone: 5-10 ug/kg/day
Aldosterone: 5-10 ug/kg/day
Total adrenal steroid rate = 1.2 mg/kg/day

Breeds, Age, Sex

Endogenous Cushing's disease is commonly reported in poodles, dachshunds, and terriers. It can be seen in any breed and mixed breeds as well. The average reported age is 8 years, but can
range from very young (3 years) to very old (>12 years). There is no particular sex predilection.

**Clinical Signs**

1. **Polydipsia and polyuria** (PD/PU) are very common complaints. The hypothetical mechanisms include: (1) increased renal free water clearance as a result of increased renal blood flow and (2) inhibition of ADH release and its effect on the renal collecting ducts. A small percentage of dogs (10%) do not show PD and PU.

2. **Polyphagia** is a very common sign. It may be the main complaint along with a tendency toward obesity. The cause is unknown.

3. **Pendulous abdomen** has a high incidence. It results from abdominal muscle weakness, hepatomegaly and intraperitoneal fat deposition and is commonly mistaken for ascites.

4. **Bilateral symmetrical alopecia** typically has truncal distribution and results from atrophy of the pilosebaceous apparatus. There is a variable incidence of skin pathology while a number of dogs do not have any changes whatsoever.

5. **Other skin abnormalities** include hyperpigmentation, comedone formation, thin skin (especially noted in inguinal area), calcinosis cutis (dry or inflammatory forms), tendency toward ecchymosis following venipuncture and superficial bacterial skin infections.

6. **Hepatomegaly** is due to steroid hepatopathy as a result of hepatic glycogen deposition. It does not usually cause significant hepatic dysfunction, however.

7. **Anestrus and testicular atrophy** probably result from inhibition of gonadotropin release.

8. **Muscle dysfunction and weakness - Myotonia** characterized with a stiff gait is a rare complication. Muscle weakness results from the generalized catabolic effects of hypercortisolemia.

9. **Pulmonary calcification** is a rare complication associated with the dystrophic effects of prolonged hypercortisolism. Symptomatic severe respiratory impairment can result.

10. **Systemic hypertension** occurs in dogs with Cushing=s. Excess cortisol concentrations elevates plasma renin substrate, the circulating protein upon which renin acts to release angiotensin I. Therefore, the hypertension may be partly produced by angiotensin-mediated vasoconstriction.

11. **Central nervous system** signs of stupor, seizures, circling,
ataxia, blindness, or Horner's syndrome in a patient with HAC suggests an enlarging pituitary tumor which can be present in as many as 8-13% of dogs with PDH.

**Thromboembolism**

Cushing's syndrome is associated with a hypercoagulable state in both dogs and humans. One study (Jacoby RC, et al, Arch Surg, 2001 Sept;136(9):1003-6) showed that levels of procoagulation factors II, V, VII, IX, X, XI, and fibrinogen were significantly increased in dogs with Cushing=s. In addition, the natural antithrombotic antithrombin was significantly decreased. Sites of involvement can include lungs, brain, bowel as well as others. Providing heparin during surgical procedures should be considered.

**Clinicopathological Laboratory Changes**

The typical abnormalities are provided below:

1. **Hemogram** - Typical findings include mature neutrophilia, eosinopenia, and lymphopenia. Polycythemia (PCV in low 50’s) is sometimes present (due to 17-ketosteroid excess). Some dogs lack these hemogram changes.

2. **Serum liver enzyme elevation** - is usually characterized with an elevated alkaline phosphatase level (from steroid-induced hepatic isoenzyme induction). ALT, AST, and BSP retention can also be slightly to moderately elevated. Serum bilirubin and albumin levels are always normal in Cushing's.

3. **Glucose** varies from normal to overt diabetic range. Diabetes mellitus occurs in 10 to 20% of dogs with endogenous hypercortisolism.

4. **Plasma lipids** - hypercholesterolemia and hypertriglyceridemia can occur and cause the blood to become lipemic.

5. Serum electrolytes are usually normal. Hypernatremia and hypokalemia are rarely, if ever, seen.

6. **Urinalysis** - often dilute, but kidneys retain ability to concentrate. Bacteriuria due to lower urinary tract infection is common. Glomerulopathy with proteinuria also occurs and may or may not resolve with treatment for Cushing=s. It is thought to be due to an antigen overload (R. Nelson, UCD).

7. **Thyroid function** - usually normal despite low T₃ and T₄ blood levels. The latter is due to ability of cortisol to inhibit thyroid hormone protein binding. A normal TSH
response test might be necessary to substantiate euthyroidism.

**Radiographic Abnormalities**

There are several radiographic changes that characterize some dogs with Cushing's syndrome. These include: (1) soft tissue mineralization, that can involve skin, muscles, lungs, and blood vessels, (2) hepatomegaly and pendulous abdomen, and (3) osteoporosis, especially involving the vertebrae.

Approximately one-half of the adrenal adenomas and adenocarcinomas will calcify and subsequently be seen on plain abdominal radiographs. They are visualized cranial and slightly medial to the anterior pole of the kidneys (VD view especially important). An IVP (especially nephrogram phase) can "highlight" the tumor, but selective abdominal arteriography can be more specific. Remember to take thoracic radiographs in suspect neoplasia cases in order to detect pulmonary metastasis. Abdominal ultrasound and abdominal CAT-scan are newer helpful diagnostic procedures. PDH characterizes as bilaterally enlarged adrenal cortices. Contrary to previous descriptions functional adrenocortical tumors often show one enlarged gland with a tumorous bulge while the contralateral adrenal gland can be either of normal or atrophic proportions. Such normal sized contralateral glands can still show atrophy on histopathological examination.

**Adrenal Function Tests**

Today, there is considerable controversy surrounding the optimal endocrinologic tests for diagnosing canine hyperadrenocorticism. The descriptions of these tests are provided:

A. Urinary steroids - requires a 24-hour urine collection and is, therefore, not very conducive for the practitioner. It is best to assay for 17-ketogenic steroids (normal: 1.13 to 3.67 mg/24 hours) or 17-hydroxycorticosteroids (average normal: 3.7 mg/m² per 24 hours).

B. Basal plasma cortisol levels - One basal value usually not dependable due to the fluctuating and overlapping blood levels that occur in normal and cushingoid dogs. Normal unstressed dogs range between 1.9 to 2.5 micrograms/dl (by RIA). **NOTE**: values reported in nanograms/ml can be converted to micrograms/dl by moving the decimal point one place to the left.

C. ACTH stimulation test - assesses the adrenocortical response to exogenous adrenocorticotropic. It will accurately diagnose endogenous hyperadrenocorticism approximately 70-80% of the time, but will not
distinguish between pituitary-induced Cushing's and functional adrenocortical tumors. Cortisol and aldosterone are 11-hydroxy corticosteroids, but the sex corticoid (17-ketosteroids) will also respond to the ACTH adrenocortical stimulators.

Some functional adrenal tumors are autonomous and therefore do not hypersecrete cortisol subsequent to ACTH stimulation. The reasons for a tumor’s poor response include 1) the production of a different hormone such as 17-hydroxyprogesterone, 2) lack of receptors for ACTH, and 3) some aberrant biosynthetic pathway for cortisol synthesis. However, recent findings show that approximately 50% will hypersecrete cortisol similar to pituitary-induced adrenal hyperplasia patients.

The typical pituitary-induced Cushing dog will hypersecrete cortisol to levels in excess of 17.0 micrograms/dl following ACTH injection. There are some who respond to levels ranging 8 to 15 μg/dl, however. (A very low to minimal response to ACTH in a cushingoid dog suggests either iatrogenic disease due to prior glucocorticoid treatments or the presence of an adrenal tumor.) The ACTH stimulation test technique is performed as follows:

1. using ACTH gel
   a. collect basal plasma cortisol sample  
   b. give ACTH gel IM at dose of 1 unit/lb body weight  
   c. after 2 hours collect the post-ACTH plasma cortisol sample  

2. using Cortrosyn (cosyntropin, Organon Inc., West Orange, NJ)
   a. collect basal plasma cortisol sample  
   b. inject 0.25 mg Cortrosyn IV or IM for dogs > 5.0 kg; give 0.125 mg for dogs < 5.0 kg. An alternative dose is 5 µgm/kg iv.  
   c. after 1 hour collect post-ACTH plasma cortisol sample  

3. low-dose Cortrosyn
   - can dose Cortrosyn at 5 μg/kg and give this either IM or IV – both routes equally effective.  
   - take baseline and 60 minute (postinjection) samples
A recent study shows that 17-hydroxyprogesterone (OHP) along with certain other 17-ketosteroids respond almost the same as cortisol with the ACTH stimulation test. These other steroids include progesterone, testosterone, and androstenedione. There are some dogs with PDH that will have a minimal cortisol response to ACTH, while simultaneously having an exaggerated 17-ketosteroid response. It is therefore important to measure these other hormones when there is a questionable cortisol response. See Hill KE, et al, JAVA (2005);226:556-561.

Since adrenal tumors can also hypersecrete OHP and other 17-ketostepoid hormones with the ACTH stimulation test, it is important to rule out this diagnosis by using other diagnostic tests such as abdominal ultrasound, CAT scan, and by measuring ACTH plasma levels.

Results of the ACTH stimulation test are positive for hyperadrenal function when the OHP level exceeds 1.32 ng/ml (4 nmol/L) but this value will vary between labs. Our adrenal steroid panel is done at the University of Tennessee.

D. Low-dose dexamethasone suppression test.

1. In the normal dog, dexamethasone will suppress pituitary ACTH secretion by negative feedback inhibition and thereby suppress adrenocortical cortisol secretion. This test is 90-95% reliable for diagnosing endogenous hypercortisolism.

2. Technique (from Peterson). Inject 0.01 mg/kg dexamethasone phosphate IM or IV and collect plasma cortisol sample 8 hours later.

3. Interpretation (from Peterson ME. Hyperadrenocorticism. Vet Clin N Am 14:739, 1984). Suppressed cortisol levels to levels < 1 μg/dl rule out endogenous Cushing's. No suppression indicates Cushing's but does not differentiate adrenal tumors from pituitary-induced adrenal hyperplasia. About 27% of dogs with chronic illnesses (e.g., diabetes mellitus, hepatic and renal disease) fail to "adequately" suppress. In diabetic dogs treated with insulin, the effect of a blood glucose of less than 65 mg/dl may over-ride the suppressive effects of dexamethasone and result in...
inadequate suppression that may suggest hyperadrenocorticism to the unwary. The stress of the hospital environment uncommonly causes inadequate suppression.

Dogs with spontaneous hyperadrenocorticism are usually resistant to low dose dexamethasone suppression (i.e., they have "inadequate suppression"). The test is approximately 94% accurate in distinguishing normal from spontaneously hyperadrenal dogs. Using a slightly higher dose of dexamethasone (0.015 mg/kg), five patterns of suppression are reported:

a. In 80% of dogs with adrenal-dependent and in 25% of dogs with pituitary-dependent hyperadrenocorticism, there is no suppression.

b. Cortisol decreases by about 50% but is still above 1 \( \mu \)g/dl in 15% of dogs with adrenal-dependent and in 15% of dogs with pituitary-dependent hyperadrenocorticism (i.e., inadequate suppression).

c. Cortisol decreases by about 50% in 2 to 4 hours but returns to resting values at 8 hours in 5% of adrenal-dependent and in 25% of pituitary-dependent hyperadrenocorticism patients (i.e., inadequate suppression).

d. Cortisol decreases to expected values (i.e., less than 1 \( \mu \)g/dl) at 2 to 6 hours but increases back to resting values at 8 hours in 30% of pituitary-dependent hyperadrenocorticism patients (i.e., inadequate suppression).

e. Cortisol decreased to less than 1 \( \mu \)g/dl in 5% of dogs with early pituitary-dependent hyperadrenocorticism (i.e., normal or adequate suppression). This group usually develops abnormal test results when retested 2 to 4 months later.

Note: Remember that the ACTH stimulation test is the preferred screening test for iatrogenic hyperadrenocorticism.

4. This is the most accurate screening test for diagnosing endogenous hypercortisolism. (The 1-2
hour ACTH Stimulation test might be more convenient for the client, however.)

E. Hi-dose dexamethasone suppression test

1. Autonomous cortisol secreting adrenal tumors are independent of the ACTH inhibition caused by high doses of dexamethasone. On the other hand, dogs with pituitary-dependent hyperadrenocorticism ideally will show suppressed cortisol secretion subsequent to hi-dose dexamethasone-induced ACTH inhibition thereby differentiating the pituitary-induced form from functional adrenal tumors.

2. Technique (from Peterson ME: Hyperadrenocorticism. Vet Clin N Am 14:741, 1984): Collect basal plasma cortisol samples. Give dexamethasone phosphate (dose range, 0.1-1 mg/kg b.w.) IM or IV. Collect 8 hour post injection sample.

3. Interpretation: When using 0.1 mg/kg dexamethasone (high dose), "adequate suppression" is defined as the serum cortisol decreasing to less than 50% of the resting value. In many dogs with pituitary-dependent hyperadrenocorticism, adequate suppression occurs, whereas dogs with adrenal-dependent disease do not have adequate suppression. Hence, if adequate suppression occurs, pituitary-dependent hyperadrenocorticism is diagnosed, but inadequate suppression is inconclusive because 25-50% of pituitary-dependent patients have this finding.

When using 1.0 mg/kg (megadose), careful patient selection is required. Adequate suppression is defined as serum cortisol decreasing to less than 1.5 μg/dl, which is diagnostic of pituitary-dependent hyperadrenocorticism. Four patterns of plasma cortisol responses are seen:

1. In 80% of dogs with pituitary-dependent hyperadrenocorticism but in no dogs with adrenal-dependent disease there is adequate suppression.

2. In 5% of dogs with pituitary-dependent but in no dogs with adrenal-dependent disease, there is adequate suppression at 2 to 4 hours but inadequate suppression by 8 hours.
3 and 4. In 15% of dogs with pituitary-dependent disease, there is inadequate suppression. These dogs oftentimes go on to develop large pituitary chromophobe tumors.

Additional testing is indicated to differentiate pituitary-dependent from adrenal-dependent disease when inadequate suppression occur in the high dose dexamethasone suppression tests because 15% to 25% of pituitary-dependent cases do not "adequately" suppress. Abdominal radiographs and abdominal ultrasound will help detect an adrenal mass; the majority of adrenal tumors are calcified, but calcification does not indicate malignancy. If a mass is found, exploratory surgery is indicated; large adrenal masses are usually adenocarcinomas. In the absence of a mass, several choices are available. Measurement of endogenous plasma ACTH concentrations will assist in separating pituitary from adrenal-dependent disease. If ACTH measurement is not available, exploratory laparotomy and adrenal biopsy can be done.

F. Technique for the combined ACTH stimulation and hi-dose dexamethasone suppression test for the out-patient.

1. Collect basal cortisol sample
2. Inject dexamethasone phosphate (0.1 mg/kg b.w.) IV
3. After two hours, collect post-dexamethasone suppression plasma cortisol sample. Then give Cortrosyn (0.25 mg) IV or IM or ACTH gel (1 unit/lb IM).
4. After 1-2 hours (depending on whether you use Cortrosyn or ACTH gel respectively) collect the post-ACTH stimulation plasma cortisol sample.

G. Plasma ACTH levels (by RIA) - useful for differentiating pituitary dependent Cushing's from functional adrenal tumors. Levels less than 20 pg/ml suggest adrenocortical neoplasia. Levels exceeding 40 pg/ml suggest pituitary-dependent Cushing's. Intermediate levels (between 20-40 pg/ml) are non-diagnostic.

H. Urine cortisol:creatinine ratio

1. Urine cortisol measured by RIA
2. Urine creatinine measured by Jaffe reaction
3. Values expressed in μmol/L and all ratio values expressed as $10^{-6}$
4. Interpretation:
   a. Test results $> 10 \times 10^{-6}$ suggests Cushing's
   b. Test results $< 10 \times 10^{-6}$ rules out Cushing's
5. Some overlap exists between Cushing's and other polydipsia-polyuria syndromes
6. This test is simple and inexpensive to run. Because of overlap, confirmation of Cushing's in a dog with a positive c:c should be made with an additional test; i.e. ACTH stimulation, lo-dose dexamethasone suppression.

**Treatment**

Adrenalectomy is the treatment of choice for focal nonmetastatic adrenocortical carcinoma with a 50:50 incidence of adenomas and adenocarcinomas. Perioperative mortality is reported to range from 9 to 60% with infection, thromboemboli, and wound dehiscence being common complications. The average survival period for those that survive surgery is 141 weeks.

**Adrenocortical Adenomas and Adenocarcinomas:** If surgical removal of the abnormal gland is elected, the contralateral adrenal will be atrophic due to prior inhibition of ACTH secretion. During surgery and for 2 days post-operatively, large doses of prednisolone are necessary (1 mg/kg per day) followed by a tapering dose over the subsequent 3-4 weeks (use alternate-day steroids during the 3rd and 4th weeks). A repeat ACTH stimulation test should be done 4-6 weeks postoperatively in order to assess the function of the remaining adrenal gland (discontinue steroids 2-3 days prior to test).

Mitotane (Op'-DDD) is indicated if gross metastatic disease is evident prior to surgery, if the tumor is unresectable or if the owner refuses surgery. Initially, mitotane is given daily. Maintenance therapy is begun if and when serum cortisol levels have decreased to undetectable to low values.

Treatment is initiated at a dosage of 50 to 75 mg/kg/day in divided doses for 10 to 14 days and prednisone, 0.2 mg/kg/day, is given concurrently. The effectiveness of this initial treatment period is evaluated with a ACTH stimulation test. Prednisone supplementation must be withheld on the morning of the test. If the basal and post-ACTH cortisol concentrations decrease but remain within or above the normal resting range, daily mitotane should be continued (50 to 75
mg/kg/day) and ACTH stimulation testing repeated at seven to 14 day intervals until cortisol concentrations fall to below the normal resting range (< 1.0 µg/dl or < 30 nmol/L). If the serum cortisol response to ACTH remains greatly elevated or unchanged from pretreatment test results, the daily dosage of mitotane should be increased to 100 mg/kg/day and ACTH stimulation testing continued at 7 to 14 day intervals. If cortisol concentrations remain greatly elevated, the dose should be increased by 50 mg/kg/day increments (at 7 to 14 days, if necessary) until ACTH stimulation testing reveals that the serum cortisol concentrations have decreased to at least some extent or until intolerance to the drug develops, which is not uncommon at dosages exceeding 100 mg/kg/day. If these incremental increases in drug dosage have partially lowered cortisol concentrations, but not to undetectable to low levels, daily mitotane is continued at the previous week's dosage and ACTH stimulation testing continued at 7 to 14 day intervals until circulating cortisol values fall below normal resting range (< 1.0 µg/dl or < 30 nmol/L. If direct drug toxicity develops (not a result of low serum cortisol concentration) daily therapy is continued at the highest tolerated dose until cortisol levels have fallen. Maintenance mitotane therapy is begun once serum cortisol levels falls to undetectable to low values.

An initial maintenance dose of 100 to 200 mg/kg/week, in divided doses, together with daily maintenance prednisone (0.2 mg/kg/day) should be given. An ACTH stimulation test should be repeated one to two months after initiation of maintenance therapy to ensure that serum cortisol concentrations remain suppressed to desired levels. If basal and post-ACTH serum cortisol concentrations remain at undetectable to low values at the time of follow-up evaluations, the previous maintenance dosage is continued. If, however, cortisol concentrations have risen into the normal resting range (1-4 µg/dl or 25-125 nmol/L) the weekly maintenance dose is increased by 50 per cent. If cortisol concentrations rise above normal resting range, daily mitotane is reinstituted (50-100 mg/kg/day) until cortisol concentrations fall to low or undetectable values; the weekly maintenance dose is then increased by 50 per cent. Weekly doses of 300 to 400 mg/kg or greater may eventually be necessary. These adjustments in dosage should be assessed by repeat ACTH stimulation testing in one month to ensure an adequate response to the new maintenance dose. Subsequent dosage adjustments are based on periodic ACTH stimulation tests at three to six month intervals, as well as the dog's tolerance of the medication itself (M. Peterson, Animal Medical Center). The mean survival time of 32 dogs with adrenal tumor treated with O,p'-DDD was 65 weeks, ranging from 20 days to 5.1 years (Kintzer and Peterson, 1994).

**Pituitary-dependent Cushing's Disease** can be treated surgically or medically. Bilateral adrenalectomy or hypophysectomy
are technically difficult and require life-long hormonal supplementation.

Medical therapy with drugs such as cyproheptadine and bromocriptine have been tried in the dog with minimal success. These work centrally to inhibit CRF secretion by the hypothalamus.

O,p'-DDD (mitotane), commercially known as Lysodren and marketed by Bristol, is my medical treatment of choice. At the prescribed dose, it hopefully causes selective destruction of the zona fasciculata and zona reticularis while simultaneously sparing most of the function of the zona glomerulosa (thereby preserving the mineralocorticoid secreting capacity). O,p'-DDD is initially administered in a loading dose. The general treatment protocol is as follows:

1. **Loading** - give Lysodren at a dose of 50 mg/kg orally once daily for first 7 days. Prednisolone (0.3 mg/kg per day) is also administered during this period in order to counter toxic side effects.

2. **Maintenance** - beginning approximately 3 to 7 days after completion of the loading doses, give Lysodren at dose of 25 mg/kg every 3 days thereafter.

3. **Re-assessment** - An ACTH stimulation test should be repeated 1-3 weeks after the loading period. No medication should be given for 48 hrs prior to the test. If the test result is still abnormally elevated (usually accompanied by persistent Cushing’s signs) the loading regimen should be reinstituted for approximately one additional week. The treatment goals include cessation of Cushing’s signs and a post-ACTH stimulation serum cortisol level ranging between 3-6 µg/dl. A level of 10 µg/dl or more calls for re-loading with O,p^-DDD.

Complete remission occurs in most dogs with the above protocol. Usually polyuria, polydipsia, and polyphagia abate within the first few weeks. Hair regrowth may begin within the first several weeks or require several months (one of my patients required 18 months). Many treated Cushing's dogs eventually "break away" from therapeutic control at some time during the first year necessitating re-loading followed by an increased (25 to 50%) maintenance dose. Rarely, some dogs acquire high tolerance for Lysodren and require 2-3 X the original maintenance dose. This is particularly prevalent in dogs receiving phenobarbital where induction of the hepatic microenzyme system increases the metabolism of Lysodren thereby allowing for drug resistance.

Treatment failure should be expected after 14 to 21 days without response. Reasons for this include an undiagnosed tumor, poor drug potency, an incorrect diagnosis, the rare dog with pituitary-
dependent hyperadrenocorticism and epilepsy that requires 30 to 60 days of O,p'-DDD therapy and concurrent anticonvulsant therapy.

All A controlled@ dogs should be retested with the ACTH stimulation test every 4-6 months in order to assess the adequacy of treatment. As stated above, those with post ACTH cortisol values between 3-6 μg/dl are adequately controlled. Values > 10 μg/dl will soon require a re-load with Lysodren. Simply increasing the maintenance dose has not proved to be successful in my experience, thus justifying the need for reload. Patients with serum cortisol levels < 1 μg/dl should be closely observed; they might be candidates for dosage reduction or temporary discontinuation. Prednisone treatment is necessary if signs of hypocortisolemia occur.

The following principles apply to the use of O,p'-DDD for the aged (> 12 years) dog:

1. Use lower doses for dogs 12 years of age and older.
2. Use similar loading protocol, but adjust the Lysodren dose to 25-35 mg/kg/day.
3. Use similar maintenance protocol, but dose at 12-16 mg/kg every 3 days.

**O,p'-DDD in the Diabetic Dog**

The guidelines include:

1. Loading dose of Lysodren is 25-35 mg/kg per day along with simultaneous prednisolone (0.3 mg/kg/day) for 7 days.
2. Maintenance dose is 12-16 mg/kg every 3 days.
3. Anticipate increased insulin sensitivity and tendency toward hypoglycemia after the 2nd day of the loading regimen. This occurs from the decreased gluconeogenesis and peripheral insulin resistance associated with lowered plasma cortisol levels. The insulin dose should therefore be empirically decreased by approximately 50% following the 3rd day of Lysodren loading. The insulin dose must subsequently be titrated on an as-needed basis. Weakness can occur from either hypoglycemia or hypocortisolemia. Weakness associated with moderate glycosuria suggests hypocortisolemia and necessitates prednisolone supplementation. In the absence of glycosuria, the dog should receive carbohydrates and prednisolone.
4. Recurrent hypercortisolemia is evidenced by subsequent increased insulin requirements and a return of Cushing’s signs. Note that recurrent PD, PU, and polyphagia in the
presence of minimal (trace to +1) glycosuria suggest hypercortisolemia.

O,p'-DDD Toxicity

O,p'-DDD toxicity can cause hypocortisolemia, but the drug can be directly toxic itself. The toxic signs usually occur within the first 2-3 weeks of Lysodren treatment, but can occur at any time. The most common signs include anorexia, depression and weakness. Vomiting and diarrhea can also occur. The owners should be informed of these potential side effects and be advised to stop Lysodren, give prednisolone (½-1.0 mg/lb) orally immediately, and call their veterinarian for further advice. Should the dog not recover within a few hours or if vomiting precludes oral prednisolone treatment, the dog must then receive prompt parenteral prednisolone treatment.

A repeat ACTH stimulation test and serum sodium and potassium levels should be done (stop prednisolone 24-36 hours prior to serum cortisol assessment). If the cortisol levels are less than 1 µg/dl, the Lysodren should be temporarily discontinued until repeated testing shows serum cortisol levels at 2.0-5.0 µg/dl after ACTH injection. If the signs of hypocortisolemia persist the dog should be given daily prednisolone treatment (0.3 mg/kg per day) thereafter. This latter situation may persist indefinitely or perhaps be interrupted in the future by recurrent hypercortisolism requiring repeated Lysodren loading and maintenance at the lower dose schedule (see Rx of the aged dog). If hyponatremia and/or hyperkalemia occur, fludrocortisone (Florinef) or DOCP and prednisone should be administered.

In my experience, whenever I had a dog that lost both aldosterone and cortisol production capability from O,p=-DDD toxicity, it became Addisonian forever. If the hyponatremia occurs before the hyperkalemia take heed that the crisis is not too far off and that treatment should commence in order to avoid a full blown crisis. Taking these dogs off treatment for Addison=s is ill advised.

On the other hand, when O,p=-DDD causes only hypocortisolism while maintaining normal serum electrolytes, the dog should only receive prednisone along with close follow-up. If the electrolytes become abnormal, then treat them as Addison=s forever. If sodium and potassium levels remain normal, there is a possibility that the ongoing ACTH hypersecretion will eventually cause recurrent hyperadrenocorticism over the ensuing 1-2 years.

There are more rare complications of O,p'-DDD toxicity. These include:

1. Addison’s disease - a small percentage of dogs might acquire destruction of the entire adrenal cortex thereby
requiring long-term mineralocorticoid (Florinef, Squibb or DOCP, Ciba) treatment.

2. Rapidly expanding pituitary tumor - known as Nelson's syndrome. This has occurred in approximately 5-7% of all pituitary-dependent Cushing's dogs treated by the author. It was once thought to occur from cessation of negative feedback inhibition caused by lowered plasma cortisol levels that subsequently allows increased trophic factor release from the hypothalamus which in turn causes a microadenoma to enlarge to macroscopic clinical proportions. However, it is now thought that the tumor will grow by itself without trophic factor stimulation. This complication can occur between 1 week and several months following the commencement of Lysodren treatment. The most common signs include dementia, circling, and weakness. At necropsy, most of the tumors are chromophobe adenomas and show considerable invasion into the hypothalamus and thalamus.


**Ketoconazole Treatment (Nizoral; Janssen)**

This drug is an imidazole derivative that has antifungal properties. It also has the ability to interfere with gonadal and steroid synthesis in vitro and in vivo. It has been shown to effectively suppress serum cortisol concentrations and the adrenocortical response to ACTH, as well as serum levels of testosterone, progesterone and estrogen in the dog.

This drug provides a viable means of treating canine Cushing's disease due to its low incidence of toxicity, reversible inhibition of adrenal steroidogenesis and negligible effects on mineralocorticoid production. The indications for treatment include:

1. Palliative medical treatment for dogs with nonresectable malignant adrenal tumors.
2. Initial therapy prior to adrenalectomy.
3. Treatment option for pet owners refusing surgery.
4. Use as test therapy for dogs with equivocal diagnosis.
5. Primary therapy for dogs that are intolerant to O,p'-DDD.

The final dosage is 15 mg/kg BID. It is best to begin with 5 mg/kg BID for 7 days, then 10 mg/kg BID for 7 days, and then maintain on 15 mg/kg BID. Discontinue the ketoconazole if adverse signs of vomiting, anorexia, depression, diarrhea, or weakness occur.
Glucocorticoid treatment might be necessary to counteract the hypocortisolemia. It is recommended to assess the patient's response to the ACTH stimulation test approximately every 4 months.

**L-Deprenyl** (Anipryl - Novartis) is a drug belonging to the monoamine oxidase inhibitor group that is used to treat canine cognitive dysfunction. In healthy dogs, ACTH secretion from the pars distalis is stimulated by corticotropin releasing hormone (CRH) from the hypothalamus, while secretion of ACTH from the pars intermedia is under negative control by dopamine. Experimentally induced chronic dopamine inhibition unmasks CRH-stimulated release of ACTH, and it has been hypothesized that dopamine depletion may play a role in pituitary dependent Cushing’s disease (PDH). Dopamine is metabolized by monoamine oxidases (MAO), and L-deprenyl is a specific inhibitor of MAO-B. Therefore, administration of L-deprenyl to dogs with PDH may ameliorate dopamine depletion, and in turn promote normalization of pituitary ACTH regulation and secretion. This may lead to normalization of cortisol secretion and resolution of the clinical signs and laboratory abnormalities associated with hyperadrenocorticism.

The recommended dose of L-deprenyl is 2 mg/kg orally every 24 hours. Clinical response is assessed by remission of signs as well as an improved low-dose dexamethasone response test. One of the advantages of L-deprenyl is the absence of drug induced adrenocorticocytolysis as seen with the use of O,p-DDD. Expense, variable response rate, and the need for daily treatment might be limiting factors to its use in dogs. It is important to note that the true clinical efficacy of L-deprenyl has yet to be established. Drug efficacy trials are currently underway (1997). Until these results are known, the recommendations for using this drug to treat canine PDH can only be given with reservations. I have not recommended nor have used this drug to treat Cushing’s in the dog because of all of the treatment failures I have witnessed over the years.

**Trilostane** - A synthetic orally active steroid analog. Currently licensed for veterinary use in UK where it is sold as Vetoryl (Arnolds Pharmaceuticals, UK). It acts as a competitive inhibitor of the 3β hydroxysteroid dehydrogenase system and thereby inhibits several steroids including cortisol and aldosterone. Unlike O,p-DDD it is not a cytotoxic agent but it will interfere with cortisol and aldosterone synthesis. Available in 60 mg capsules.

**Dosing:** The earlier literature used a dose of 5-10 mg/kg/day but subsequent use and more recent literature recommend a starting dose of approximately 2.0 mg/kg bid and titrate to effect over the following weeks (Vaughn MA, et al, JAVMA 2008, 232 (9): 1321-1328). Another paper by Alenza in J Am Anim Hosp. Assoc 2006;42:269-276 reports on the efficacy of an average dose of 3.1 mg/kg q12h initially and an average maintenance dose of 3.2 mg/kg.
q12h on a daily basis. Some lethargy and decreased appetite can occur during the first few days of treatment. Hypoadrenalism can occur as a side effect calling for adequate monitoring and any necessary medical emergency measures. My review of the papers describing trilostane and comparing it to O,p'-DDD cause me to find little advantage to using trilostane based on ease of administration, anticipated effects, and the fact that adrenocortical insufficiency is still a potential complication with both drugs.

Monitoring is done using the ACTH stimulation test at days 10 to 14, 30 days and 90 days after starting. Using protocols where trilostane is given once daily the test is conducted 4-6 hours after the morning dose with the optimal cortisol ranging between 0.7-0.9 µg/dl. Periodic serum chemistry profiles should be done as well in order to assess serum electrolyte status. When trilostane is given twice daily, the acceptable post-ACTH stimulation test results should range from 5 to 10 µg/dl.

An abstract by Sieber-Ruckstuhl in the 2005 ACVIM Proceedings hypothesizes that there can be an incomplete inhibition of the beta-hydroxysteroid dehydrogenase enzyme with an additional inhibition of the 21-hydrolase or the 11-beta-hydroxylase. This might explain the typical increased steroid intermediate concentrations, as determined on the patient’s steroid profile, when trilostane is used to treat PDH.
10.3 DIABETES INSIPIDUS (DI)

**Physiology of Antidiuretic Hormone (ADH, Vasopressin):**

The main action of ADH in the body is to inhibit the excretion of excess amounts of water by the kidney. In the absence of ADH or its effects, voluminous amounts of very dilute urine (polyuria) will be excreted. This condition is called diabetes insipidus.

Hypovolemia and plasma hyperosmolality are the primary stimuli for endogenous ADH secretion. Plasma osmolality is monitored by osmoreceptor cells in the hypothalamus. With increased plasma osmolality, the hypothalamic osmoreceptors located in the supraventricular and paraventricular nuclei are stimulated to produce and secrete antidiuretic hormone, which in turn is transported down the neurohypophyseal stalk to the posterior pituitary gland from where it is released into the systemic circulation. Hypovolemia stimulates angiotensin II secretion which in turn can directly stimulate the hypothalamus to produce and secrete ADH.

At the kidney, the primary action of ADH is to conserve body fluid by reducing the rate of urine production. This antidiuretic effect is achieved by promoting the reabsorption of solute-free water from the renal distal tubules and the collecting duct into the hypertonic renal medullary interstitium. Nephrogenic diabetes insipidus (NDI) occurs when the kidneys do not respond to normal or increased amounts of ADH.

Those factors that will stimulate ADH secretion include increased plasma osmolality, hypovolemia, pain, exercise and certain drugs that include nicotine, morphine, barbiturates and chlorpropamide. Those that inhibit ADH secretion include hypothermia, plasma hyposmolality, hypervolemia, and certain drugs that include alcohol, phenytoin, and opiate antagonists (butorphanol and oxilorphan).

**Incidence:**

Diabetes insipidus has no breed or age predilection. Both cats and dogs can be affected by either congenital or acquired forms of this disease. The central (CDI) form can be either complete or partial.

**Etiology:**

CDI results from pathology involving the hypothalamo-neurohypophyseal tract. The various causes can include tumors, granulomas, trauma, or infarction. Oftentimes the etiology is listed as idiopathic.

NDI has been reported rarely as a congenital primary disorder. Usually it is an acquired (secondary) disorder from conditions that cause diffuse renal tubular dysfunction. These include renal fibrosis, pyelonephritis, hypercalcemia, and hypokalemia. The acquired form can be associated with hyperadrenocorticism, pyometra, hyperthyroidism and hepatic failure.
**History and Physical Examination Findings:**

The most common historical complaints are polydipsia/polyuria (PD and PU) and sometimes nocturia. In CDI there is an absence of signs related to other organ systems. So long as the animal has free access to water, it should otherwise be well.

The physical examination findings are usually normal so long as free choice water is available and the animal can imbibe as needed. Gross signs of interstitial fluid deficits will not occur until late in the course of fluid restriction because the hypertonic extracellular fluid space will attract water from the cellular space, thereby providing for adequate interstitial water. Cellular dehydration will be profound, however, and this will become clinically apparent with brain dysfunction. However, should the animal be water deprived for a protracted time period it can very well lapse into a life-threatening status characterized by hypovolemia and renal failure, as well as hypernatremic encephalopathy (coma and seizures).

**Differential Diagnosis:**

Diabetes insipidus is usually considered after other causes of PD and PU have been eliminated from the differential diagnosis. These conditions include chronic renal disease, hypercorticism, hypoadrenocorticism, diabetes mellitus, pyometra, chronic liver disease, pituitary neoplasia, hypercalcemia, hypokalemia, iatrogenic drug induced (diuretics), and psychogenic.

**Diagnostic Criteria for Recognition:**

The history of PD and PU, normal physical examination findings, and normal serum biochemical findings (especially creatinine, liver enzymes, proteins, glucose, Na, K, and Ca) should prompt the clinician to strongly consider a diagnosis of CDI or NDI. A complete urinalysis should be normal except for a characteristically low specific gravity (< 1.008) and hypo-osmolality (< 400 mosm).

Polydipsia is present when water intake exceeds 100 ml/kg/day. In DI the PD ranges from 130 to 700 ml/kg/day. Normal water intake in the dog ranges from 32-50 ml/kg/day. That in the cat ranges 0-45 ml/kg/day.

Polyuria is defined as a urine output exceeding 90 ml/kg/day with hypothenuria (urine s.g. < 1.008) or isosthenuria (urine s.g. with fixed range of 1.008-1.012). In DI, polyuria ranges from 100-600 ml/kg/day. The normal urine output in dogs and cats ranges between 10-25 ml/kg/day and 20-40 ml/kg/day, respectively.

Direct measurements of plasma ADH levels are being done in human medicine using a radioimmunoassay technique. This procedure, however, is not yet widely available in veterinary medicine.
**Diagnostic Criteria for the Differentiation of the Main Variants of the Syndrome**

**Water Deprivation Test:**
This test measures the ability of the hypothalamo-neurohypophyseal system to produce vasopressin under the stress of dehydration. The animal must be fully hydrated and have had free access to water prior to the test. The procedure is as follows:

1. Obtain serum for osmolality determination and urine for osmolality and specific gravity determinations prior to the test.
2. Weigh animal and place it in a metabolic cage deprived of food and water until a weight loss of 3-5% of the initial body weight is reached (8-24 hrs.).
3. Empty the bladder every 2-3 hours if the patient does not urinate.
4. Stop the deprivation when the required weight loss is reached. Collect serum and urine samples for osmolality and specific gravity determinations.
5. Compute urine output during the test (ml/kg/hr.).

**Interpretation:**

a. before water deprivation:

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Diabetes Insipidus</th>
<th>Psychogenic Polydipsia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine concentration (U)</td>
<td>500-800 osm</td>
<td>&lt; 400 osm</td>
<td>Low</td>
</tr>
<tr>
<td>Serum osmolality (P)</td>
<td>280-310 osm</td>
<td>N or 8</td>
<td>Low</td>
</tr>
<tr>
<td>U/P</td>
<td>2-3</td>
<td>&lt; 1</td>
<td>&gt; 1</td>
</tr>
</tbody>
</table>

b. following water deprivation:

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>DI</th>
<th>Psychogenic PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine concentration (U)</td>
<td>8</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>Serum osmolality (P)</td>
<td>N or slight 8</td>
<td>8</td>
<td>N or slight 8</td>
</tr>
<tr>
<td>U/P</td>
<td>&gt; 3</td>
<td>&lt; 1</td>
<td>&gt; 1-2</td>
</tr>
</tbody>
</table>

**Vasopressin Test:**
This procedure measures the kidney’s ability to respond to vasopressin and concentrate urine. It can be done using aqueous vasopressin. The vasopressin procedure should follow the water deprivation test after a 24-hr. period of access to food and water. The technique is described below:
1. Collect urine and serum samples for osmolality and specific gravity determinations.
2. Empty the urinary bladder.
3. Inject 0.5 units/kg (not to exceed 5 units) units of vasopressin IM. Can also use 2 μg of DDAVP nasal drops SQ or IV or 20 μg (4 drops) of nasal drops topically conjunctivally.
4. Maintain initial body weight by weighing dog at hourly intervals and replacing measured urinary losses with equivalent amounts of water.
5. Measure urine osmolality or specific gravity and serum osmolality levels every 2 hrs for 6 to 10 hours when using DDAVP or for 1 to 2 hours when using aqueous vasopressin.
6. Determine the final urine osmolality or specific gravity and serum osmolality values.
7. Urine output is calculated.

**Interpretation:**

<table>
<thead>
<tr>
<th></th>
<th>DI</th>
<th>Nephrogenic DI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine concentration (U)</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Serum osmolality (P)</td>
<td>Normal</td>
<td>Normal or 8</td>
</tr>
</tbody>
</table>

The test is now complete, and the dog or cat is then offered small amounts of water over the next few hours. Further increase in urine osmolality or urine specific gravity after administration of aqueous vasopressin or DDAVP greater than 10% is suggestive of central DI or partial nephrogenic DI. Increase in urine osmolality or urine specific gravity less than 10% is suggestive of a vasopressin-resistant disorder (i.e., complete nephrogenic DI).

**Combined Water Deprivation - Aqueous Vasopressin Test:**

1. Empty the urinary bladder and determine and record the patient's body weight, BUN, serum and urine osmolalities, and urine specific gravity.
2. Repeat #1 every 2 hours and discontinue the water deprivation when the patient loses 5% of its body weight or if the BUN exceeds 30 mg/dl.
3. Assuming the absence of urinary concentration capability, give the patient 2 to 5 units (or 0.5 units/kg) of aqueous ADH IM, empty the urinary bladder, and provide limited access to water (20 ml/kg body weight). Can also use DDAVP in place of aqueous vasopressin at dosage provided on previous page.
4. Repeat #1 two hours later.

Most animals with CDI will concentrate their urine with this test. Failure to do so might be due to the presence of NDI or perhaps to
prior renal medullary washout. This latter condition can interfere with a CDI patient's ability to respond to ADH. It can be corrected by providing for a gradual 10% reduction of water intake per day for 3-5 days prior to doing the water deprivation test. One method is to begin water restriction three days before abrupt water deprivation. The patient is allowed twice its normal daily water requirement (120 to 150 ml/kg), divided into six to eight small portions during the initial 24 hr. Over the next 48 hrs., the animal is given gradually decreasing amounts of water until normal maintenance requirements are reached (60 ml/kg).

**The ADH Trial:**

As an alternative to the modified water deprivation test, or in cases where this test fails to establish a definitive diagnosis, a closely monitored therapeutic trial with DDAVP can be performed. The pet owner should measure the animal's 24-hour water intake 2 to 3 days before the therapeutic trial with DDAVP is initiated, allowing free-choice water intake. The intranasal preparation of DDAVP is administered in the conjunctival sac (1 to 4 drops every 12 hours) for 5 to 7 days. A dramatic reduction in water intake greater than 50% during the first treatment day would strongly suggest a vasopressin deficiency and a diagnosis of central DI or partial nephrogenic DI.

**Cushings vs. DI:**

Occasionally, results obtained from the water deprivation test or a therapeutic trial with DDAVP are incorrectly interpreted. Factors that may alter proper interpretation include renal medullary washout, enhanced antidiuretic response to low levels of ADH in patients with central DI, and abnormally elevated osmolar set points for ADH release. One of the most common causes of misinterpretation is the unsuspected case of hyperadrenocorticism. These patients may show (1) complete ability to concentrate urine after dehydration (suggesting psychogenic polydipsia) or (2) incomplete ability to concentrate urine after dehydration followed by a further increase of 10 to 50% in urine concentration after aqueous vasopressin or DDAVP injection (suggesting central DI or partial nephrogenic DI) or (3) an increase in urine concentration greater than 50% after a therapeutic trial with DDAVP (suggesting central DI or partial nephrogenic DI). Misdiagnosis of hyperadrenocorticism is most easily avoided by screening for this disorder (e.g., using ACTH stimulation or low dose dexamethasone testing) prior to initiating the water deprivation test or response to DDAVP supplementation.

**Treatment of CDI:**

Desmopressin is available for clinical use intranasally, intravenously, and subcutaneously. The intranasal preparation (DDAVP® - Aventis Pharmaceuticals) is supplied in 2.5 and 5 ml bottles containing 100 μg/ml of DDAVP. One drop of nasal solution...
corresponds to 1.5 to 4.0 μg of DDAVP. A tuberculin syringe may be used for more accurate dosing. Although administration of medication to dogs and cats via the intranasal route is possible, it is not tolerated in many cases. Drops placed in the conjunctival sac are a more suitable alternative. The recommended initial dose is 1-2 drops intraconjunctivally once or twice daily.

Two parenteral preparations, differing only in size, are also available: DDAVP Injection® (1 ml snap-top ampules or 10 ml multi-use vials; Aventis Pharmaceuticals). Both contain 4 μg/ml of DDAVP. Parenteral administration of DDAVP is most useful in patients that will not tolerate or absorb the drug by the intranasal or conjunctival routes. The initial dose is 0.5-2 μg SQ once or twice daily. Since the cost of parenteral DDAVP is 20 times higher per μg than the intranasal preparation, the intranasal form of DDAVP, although not designed for parenteral use, has been given by injection with no adverse effect to both dogs and cats. Clinically, the intranasal and injectable preparations of DDAVP produce indistinguishable responses when administered intravenously or subcutaneously. The monthly cost for DDAVP treatment will exceed $100 in most cases.

DDAVP (0.1 mg and 0.2 mg) tablets are now available. A child’s dose begins at 0.05 mg. Adults receive 0.1 to 0.2 mg divided every 8-12 hours. The DDAVP tablets have been shown to be effective in dogs where the starting dose is 0.1 mg orally every 8 hours and titrated to effect.

**Treatment of NDI:**

Therapeutic benefits with ADH resistant polyuria (nephrogenic DI) and central DI has been achieved with the use of the thiazide diuretics hydrochlorothiazide (Hydrodiuril, Merck Sharp & Dohme) and chlorothiazide (Diuril, Merck, Sharp & Dohme). Thiazides reduce total body sodium concentration by inhibiting sodium reabsorption in the distal tubule and connecting segment. Resultant decreased plasma sodium and osmolality inhibit the thirst center, thereby reducing water consumption. This leads to extracellular fluid volume contraction, decreased glomerular filtration rate, increased proximal tubular sodium and water reabsorption, and decreased delivery of water to the distal tubule. The net effect is a reduction in urine volume.

The dose of these drugs must be individualized for each patient. Suggested dosages for hydrochlorothiazide and chlorothiazide are 2.5 to 5.0 mg/kg b.i.d. and 20 to 40 mg/kg b.i.d., respectively. Side effects are rare but may include occasional hypokalemia.

**10.4 DIABETIC KETOACIDOSIS - PATHOPHYSIOLOGY, DIAGNOSIS AND MEDICAL MANAGEMENT**

Diabetic ketoacidosis (DKA) in the dog and cat can present as an acute metabolic derangement that requires prompt diagnosis and
treatment. The problem usually occurs in the middle aged to older pet animal, oftentimes after a variable period characterized with polydipsia, polyuria and weight loss. This review will discuss the pathophysiology, clinical signs, and medical management of this interesting and challenging metabolic disorder.

PATHOPHYSIOLOGY

Hyperglycemia and ketoacidosis occur when there is an absolute or relative deficiency of insulin. Consequently, there is overproduction and under-utilization of both glucose and ketoacids. Insulin deficiency results in decreased glucose use and increased release of glucose precursors and free fatty acids by peripheral tissues. Hepatic gluconeogenic pathways become activated, and the extraction of glucogenic substrates becomes more efficient.

Although increased availability of free fatty acids continues to be a critical requisite for ketogenesis, intrahepatic processes and the disposition of the incoming fatty acids are important. Insulin deficiency not only alters peripheral metabolism favoring ketogenesis, but it may also activate certain ketogenic pathways in the liver. Hepatic ketogenesis is regulated by the rate of fatty acid transport across the mitochondrial membrane and then subsequent β-oxidation. The enhanced hepatic capacity for ketone production is due to activation and increased activity of carnitine acyltransferase, an enzyme responsible for the mitochondrial uptake of fatty acids. There is a bihormonal hypothesis for the pathogenesis of diabetic ketoacidosis where hypoinsulinemia is responsible for the accelerated lipolysis in adipose tissue, the provision of adequate substrate, and stimulation of ketogenesis; whereas glucagon is responsible for accelerated hepatic ketogenesis and additional gluconeogenesis.

Hepatic overproduction of β-hydroxybutyrate and acetoacetate is primarily responsible for the organic metabolic acidosis. Acetone is also produced but does not function as an acid. Acidosis ensues when the body buffer base is reduced and respiratory compensation is unable to maintain a normal pH. In most diabetic ketoacidotic patients, both β-hydroxybutyrate (B) and acetoacetate (A) are produced in varying proportions, although in some patients the B/A ratio can be excessively high.

Plasma, serum and urinary ketones are detected and semiquantitated by using the nitroprusside reaction (Ketostix®, Acetest® tablet). The ketone reagent pad found on most urine dipstick tests can also be used. This test does not react with β-hydroxybutyrate but will detect acetone and acetoacetate. This has clinical importance in situations where shock-like states promote the production of 3-hydroxybutyrate thereby disallowing the clinical detection of ketoacidosis.

After institution of insulin treatment, the B/A ratio will decrease due to the conversion of β-hydroxybutyrate to acetoacetate. Although
the acetoacetate level will eventually decrease, the shifting B/A ratio explains the clinical paradox where the initial negative detection of the patient's ketone levels converts to positive on the second and third day of treatment despite their actual clinical improvement.

Plasma acetone concentrations are markedly elevated in the diabetic ketoacidotic patient. Acetone is formed by the decarboxylation of acetoacetate. These can be detected by some individuals as a Juicy Fruit® odor. Acetone is also detected with the nitroprusside test. The plasma acetone concentration may remain elevated for one to two days after the plasma glucose, β-hydroxybutyrate and acetoacetate levels have returned to normal. This might also explain the persistent ketonuria that can occur during successful therapy.

In summary, the DKA condition is characterized by: (1) increased hepatic glucose production, (2) impaired peripheral tissue glucose utilization, (3) lipolysis, and proteolysis. The hyperglycemia eventually exceeds the renal tubular threshold maximum for glucose reabsorption (cat>300 mg/dl; dog>200 mg/dl) causing glycosuria and an osmotic diuresis that allows for the loss of large quantities of water and essential electrolytes such as sodium, potassium, chloride and phosphorus. The resulting polyuria causes plasma hypertonicity and thirst stimulation (polydipsia).

The increased organic ketoacid production will be buffered by plasma bicarbonate causing a base deficit and the characteristic metabolic acidosis and the rate and/or depth of respiration will increase in an attempt to get rid of “volatile acid” in the form of CO₂. The resulting sodium-ketone salts will be excreted in the urine.

**Hormonal Changes**

As mentioned earlier, the pathogenesis of DKA involves the interplay of hypoinsulinemia and hyperglucagonemia. Other hormones that have varying contributing roles include epinephrine, growth hormone, and cortisol. Epinephrine stimulates gluconeogenesis and glycolysis in the liver. It also stimulates lipolysis and hepatic ketogenesis. Growth hormone causes insulin resistance that results causes impaired peripheral tissue utilization of glucose. Growth hormone may also play a key role in ketogenesis because it can markedly increase circulating levels of free fatty acids and ketone bodies. Cortisol promotes gluconeogenesis and impaired peripheral tissue glucose utilization; it too promotes peripheral lipolysis and increases the supply of free fatty acids entering the liver for ketogenesis (Table 1). Although the majority of gluconeogenesis occurs in the liver, a respectable amount also takes place in the kidney.

**DIAGNOSIS**

**History and Physical Examination**
The history can be acute and characterized by a sudden onset of anorexia, depression, weakness, and vomiting of only several days duration. On the other hand, it can be more chronic and characterized with polydipsia, polyuria, polyphagia, and weight loss of several weeks to months’ duration.

A complete physical examination should be done in order to thoroughly assess the patient's initial status as well as to detect other disorders that might be simultaneously present. The examination can show an entire spectrum of findings ranging from an essentially normal animal to one that is prostrate and moribund. Severe muscle weakness can be caused by hypokalemia. In cats this can be shown as ventral cervical posturing. Limb weakness can also be caused by diabetic neuropathy. An increased respiration rate can be due to the compensatory hyperventilation used to counteract the metabolic acidosis. The term "diabetic coma" is frequently used to describe the ketoacidotic condition, but only a small percentage of patients actually present with a profound state of altered consciousness. Table 2 provides a list of other disorders that have been known in the author's experience to coexist with DKA in the dog and cat. It is therefore essential to diagnose these other disorders in order to provide the best possible therapeutic efforts and hopefully attain a successful patient outcome.

**Clinical Pathology**

The clinicopathological definition of DKA can be characterized as blood glucose > 250 mg/dl, pH < 7.3, bicarbonate < 15 mEq/L, ketonemia, ketonuria, and glucosuria. Other abnormalities that can occur with varying frequencies are shown in Table 2.

Since hepatic production of glucose is high in all patients with this disease and rarely causes the blood glucose to exceed 300-400 mg/dl by itself, it is likely that higher degrees of hyperglycemia are determined primarily by the severity of volume depletion. Therefore, extreme levels of hyperglycemia tend to occur only when extracellular fluid volume has decreased to a point that urine flow is impaired; ie, where glycosuria is diminished.

As stated earlier, the metabolic acidosis is primarily due to the formation of ketoacids. However, acidosis can also occur from renal failure and lactic acid production. The metabolic acidosis caused by these various factors is the anion gap (AG) type which can be calculated with the following formula:

\[ AG = (Na^+ + K^+) - (HCO_3^- + Cl^-), \]

where AG values in excess of 30 mEq/L are especially significant.

Diabetic ketoalkalosis can occur when the patient has repeated vomiting allowing for an excessive loss of H^+ and Cl^- . This is resulting base excess state is furthered with hypokalemia.

Hyponatremia can be factitious (due to hypertriglyceridemia) or real (due to urinary or gastrointestinal sodium ion loss). Factitious
hyponatremia, or pseudohyponatremia is suspected when the plasma sample is grossly lipemic, although this does not rule out a true sodium deficit. The factitious hyponatremia occurred when serum electrolytes used to be determined using the flame photometry laboratory methodology. Spurious hyponatremia can occur when high plasma glucose levels draw water into the extracellular space thereby diluting the serum sodium concentration. Neither of these two causes reflects true sodium loss, however.

True hyponatremia can occur from the osmotic diuresis induced by glucosuria and the renal excretion of sodium ketone salts. Sodium loss can also occur with the vomiting that accompanies DKA. There is evidence available that shows that insulin deficiency may also cause sodium loss through a lack of renal tubular reabsorption.

Hypokalemia is the most important electrolyte disturbance in DKA and reflects a substantial reduction in the total body potassium stores. Even those patients with normokalemia might very well have a considerable total body potassium deficit since ninety-eight percent of the total body potassium is located within the intracellular space. The major causes of potassium depletion include: (1) lean tissue breakdown; (2) hypoinsulinemia, allowing cellular potassium to enter the plasma and be lost in the urine; (3) secondary hyperaldosteronism, in response to hypovolemia; (4) gastrointestinal loss from vomiting and anorexia.

Metabolic acidosis does not cause hyperkalemia because the acidosis is of the organic type which does not create an electrochemical gradient across the cell membrane. However, severe azotemia can cause hyperkalemia.

Phosphorus is an integral component of the lean body mass, and enhanced catabolism of muscle tissue in DKA results in increased urinary phosphorus excretion and phosphorus wasting. Hypophosphatemia in ketoacidosis is multifactorial and is due to impaired glucose utilization and cellular phosphorous uptake, increased renal excretion consequent to metabolic acidosis, as well as to increased tissue catabolism. Any clinical signs of hypophosphatemia usually occur at serum concentrations <2.0 mg/dl. Hyperphosphatemia occurs with decreased renal perfusion and renal failure.

Elevated serum liver enzyme levels (ALT, AST, alkaline phosphatase) are commonly due to the hepatic lipidosis that occurs in DKA as a result of the massive fatty acid influx into the liver and their subsequent conversion to triglycerides. This hepatic change is completely reversible in most dogs and cats, and the serum liver enzyme levels will normalize following successful treatment. However there have been rare instances where the hepatic lipidosis takes on a more aggressive role that progresses to overt hepatic failure.

Azotemia can be pre-renal associated with dehydration or primary renal in origin. In pre-renal azotemia, the patient retains its
ability to concentrate its urine specific gravity to > 1.012, although its true maximum concentrating capability might be hindered by the solvent drag that accompanies glycosuria. Pre-renal azotemia readily resolves with adequate rehydration. Extensive primary renal dysfunction characterizes with isosthenuria (fixed urine specific gravity ranging 1.010-1.012) in the setting of dehydration. The accompanying azotemia does not resolve as readily as compared with the pre-renal type.

Some diabetics can have “diabetic kidney disease” characterized by the formation of glycoprotein deposits throughout the glomerular basement membrane which impairs glomerular and eventually renal tubular function. In humans this is a common cause of renal failure calling for the need of lifelong hemodialysis.

Hyperamylasemia can occur with acute pancreatitis or be consequent to impaired renal function. The diagnosis of acute pancreatitis is made after considering all of the available diagnostic information that is compatible with this particular diagnosis. One of the guidelines used in humans for relating hyperamylasemia to acute pancreatitis is when the serum amylase concentration exceeds the reference range by a factor of 5.

**TREATMENT**

**Fluid and Electrolytes**

Disturbances in hydration and electrolyte balance are of great importance in diabetic ketoacidosis and require expedient correction when present. The calculated isotonic fluid requirements include the patient's dehydration deficits, the 24-hour maintenance needs, and extra losses that result from vomiting or diarrhea. The dehydration status is approximated on a scale ranging from a mild (5%) to extreme (12%). The needed isotonic replacement volume is calculated by either of the following two methods:

1. Dehydration volume deficit (ml) =  
   % dehydration x kg body wt x 1000
2. Dehydration volume deficit (ml) =  
   % dehydration x lb body weight x 500

The 24 hour maintenance volume is roughly estimated (assuming adequate urine output) at 60 ml/kg (30 ml/lb). Therefore, the initial first 24 hour total fluid volume is the sum of the dehydration and the maintenance volumes so long as urine output is adequate (1-2 ml/kg/hr).

If the animal is 8-12% dehydrated, ½ of the estimated dehydration deficit should be administered intravenously over the first 2-4 hour period of hospitalization with the remaining replacement and maintenance volumes given over the following 20-22 hour period.
It is important to remember that hydration alone can be used to decrease blood glucose and certain counter-regulatory hormone concentrations. Most investigators believe that the main mechanism of lowering the blood glucose by hydration is caused by increased osmotic diuresis and glucosuria, but decreases also occur by the dilution caused by adding crystalloid solution to the plasma space. It is suggested that prior hydration will make the response to insulin more predictable and that rehydration alone can lower the blood glucose level from 18-80%. This author prefers to correct hypovolemia with isotonic solutions such as lactated Ringer’s or 0.9% saline. Acetated solutions, on the other hand, are not recommended since they may theoretically result in increased ketone body production. Recommended maintenance solutions include 0.45% saline or ½-strength lactated Ringer’s solution. Dextrose solutions (2½-5%) are reserved for use when the patient’s blood glucose declines to 250 mg/dl or less in the setting of continued insulin administration.

Hyponatremia is corrected with intravenous 0.9% saline solution in order to avoid any plasma hypoosmolality that might occur when the hyperglycemia is reduced with insulin treatment. Plasma hypoosmolality can cause a reversal of osmotic gradients and overexpansion of the intracellular compartment, particularly the nervous system, with resultant cerebral edema. This can be avoided by correcting the hyponatremia slowly over a period of 24-36 hours.

As mentioned earlier, hypokalemia is the most common and probably most important serum electrolyte disorder in DKA. The reasons for potassium loss have already been provided; however, this loss is further complicated by additional losses that are known to accompany therapy. This further decline in serum potassium levels occurs owing to: (1) serum dilution from rehydration; (2) continued urinary losses brought about by sodium ion delivery to the distal renal tubule; (3) correction of acidosis and the accompanying cellular influx of potassium ions; and (4) increased cellular uptake of potassium due to insulin.

Potassium supplementation is best provided with potassium chloride (KCl) solution, which is added to the parenteral fluids. If concurrent hypophosphatemia is present, potassium phosphate solution can be added as well. Potassium supplementation is best begun after the first 2 hour period of fluid replacement when hydration, blood pressure, and urine output are improved. If the patient is initially hypokalemic, KCl can be added to the hydrating solution, but the infusion is slowed down to where one-half of the dehydration replacement volume is delivered over an additional 1- to 3-hr period. The maximal rate of potassium chloride infusion should not usually exceed 0.5 mEq/L per hour, but in extreme situations (serum K⁺ < 2.0) the rate can be increased to 1.5 mEq/kg per hour along with EKG monitoring. The recommended amount of potassium
supplementation to be administered over a 24-hour period is as follows:

1. **Mild hypokalemia** (serum $K^+ = 3.0-3.5$ mEq/L): give 2-3 mEq KCl/kg or add 20-30 mEq KCl/liter IV fluids
2. **Moderate hypokalemia** (serum $K^+ = 2.5-3.0$ mEq/L): give 3-5 mEq KCl/kg or add 30-40 mEq KCl/liter IV fluids.
3. **Severe hypokalemia** (serum $K^+ = < 2.5$ mEq/L): give 5-10 mEq KCl/kg or add 40-60 mEq KCl/liter IV fluids.

Daily serum electrolyte determinations and the necessary treatment adjustments are made until normal values are obtained. The intravenous fluids are discontinued when serum biochemistries are normal, euhydration is present, and the patient is able to eat.

Hypophosphatemia is known to occur in some patients with DKA. Its multifactorial origin was described earlier. Although plasma phosphate may fall to levels that are experimentally shown to be associated with altered consciousness, rhabdomyolysis, muscle weakness, impaired cardiac function, hemolysis, and respiratory failure, phosphate depletion in DKA is usually clinically silent and shows up only in clinical measurements. Nevertheless, if the clinician is concerned about severe hypophosphatemia that is present before treatment, phosphate supplementation can be given with potassium phosphate solution at the recommended dose of 0.01 to 0.03 mmol of phosphate/kg/hr followed by repeat serum phosphorus and calcium determinations every 6 hours in order to detect hyperphosphatemia-induced hypocalcemia.

Sodium bicarbonate treatment is another matter of controversy in treating DKA. The advocates of treatment express their concern that severe acidosis can adversely effect cardiac function, as seen experimentally, while opponents of bicarbonate therapy base their concerns on its cause and effect relationship with paradoxical central nervous system acidosis. The use of sodium bicarbonate is often restricted to those patients with a blood pH $< 7.1$. During most treatment courses, the metabolic acidosis will reverse due to: (1) the cessation of ketogenesis; (2) metabolic conversion of ketones to bicarbonate following commencement of insulin treatments; (3) improved renal function, and (4) conversion of the lactate in lactated Ringer's solution to bicarbonate. In severe metabolic acidosis, where the anion gap $> 30$ mEq/L and the arterial pH $< 7.1$, sodium bicarbonate can be given at the following dose schedule:

$$\text{amount NaHCO}_3 = \text{base deficit} \times 0.3 \times \text{body weight kg}$$

The base deficit equals the difference between the desired serum bicarbonate level and the measured level. Subsequent alkali treatment will depend on the results of repeated plasma pH measurements; it should be discontinued when the blood pH is restored to a level of 7.2 or greater.
**Insulin**

Regular crystalline insulin is used when the patient has signs of depression, dehydration, anorexia, and vomiting. The advantages of regular insulin include: (1) various routes of administration (IV, IM and SQ); (2) rapid onset of action; and (3) short duration of action. These properties allow adequate insulin titration throughout the day according to the animal's needs. The clinician must remember that blood glucose levels decline much earlier than ketone levels and must therefore anticipate the persistence of some ketonemia and ketonuria for the first 48-72 hr.

Bolus intravenous doses of insulin offer the advantage of an immediate onset of action for the critically hypotensive patient, but this technique is rarely used anymore. The recommended dose for a medium-sized to large dog is 1-2 units/kg. In the small dog and cat, the dose is reduced to 0.5 units/kg. Subsequent doses are given at the same amount every 2-3 hr until the blood glucose levels decrease to less than 250 mg/dl, at which time the patient is switched over to subcutaneous regular insulin injections given approximately every 6 hr. The disadvantages of this technique include the need for intensive care monitoring with frequent (every 1-2 hr) blood glucose determinations, the likelihood of hypoglycemia and hypokalemia, and the possibility of cerebral edema resulting from a too-rapid fall in blood glucose levels. Mannitol is the preferred treatment should this complication occur. The maximal rate of blood glucose decline should not exceed 75-100 mg/dl per hour.

When laboratory facilities are unavailable, blood glucose reagent strips (Chemstrip bG reagent strips, Boehringer Mannheim Inc. or Dextrostix reagent strips, Bayer Corp.) can be used for approximate blood glucose determinations. Several reflectance colorimeters are now commercially available to enhance the accuracy of these reagent strips. More accurate determinations are obtained using in-house serum or blood chemistry devices such as the I-Stat.

To circumvent the occurrence of the aforementioned side effects, a continuous low-dose insulin infusion can be used. One successfully applied technique in the dog involves the addition of 5 units of regular insulin to a 500 ml bottle of lactated Ringer's solution (insulin concentration of 0.01 unit/ml) after the first 2 hr of rehydration and adjusting the infusion set whereby 0.1 unit/kg/hr is delivered to the patient. This dose is reduced to 0.05 unit/kg/hr when the blood glucose level decreases to < 250 mg/dl. This can be accomplished by infusing the insulin containing solution through a separate intravenous catheter. Blood glucose determinations should be made every 1-2 hr while taking heed to avoid excessive blood loss.

Low-doses of regular insulin can also be given intramuscularly. Initially 1-2 units are given into the thigh muscles of cats and dogs weighing less than 10 kg. For dogs weighing more than 10 kg, the initial dose is 0.25 unit/kg. Subsequent hourly injections of 1 unit for
cats and small dogs and 0.1 unit/kg for larger dogs are given until the blood glucose level is less than 250 mg/dl, at which time the subcutaneous route can be used on an every 6 hr or as needed basis. The low doses used in this technique can be accurately measured with low-dose insulin syringes using U-100 regular insulin.

Subcutaneous regular insulin treatment is a suitable alternative to the intravenous and intramuscular methods when intensive care monitoring is unavailable. It is only an efficacious route of regular insulin administration when the patient has reasonably adequate peripheral perfusion (patient alert and able to ambulate). The initial dose is 0.5 unit/kg followed by subsequent doses every 6-10 hr depending on need (Tables 4 and 5).

The patient is regarded as stable and able to receive intermediate action (NPH (Humulin-N), Vetsulin) or ultralong-acting (for the cat - PZI, Glargine) insulin when normal hydration is restored, blood glucose levels are below 350 mg/dl, serum or urine ketones are minimal to absent, and oral feedings are accepted.

**Complications**

A list of complications, causative factors, and possible corrective measures is provided in Table 6. Many of these problems are avoidable with meticulous medical management and frequent patient monitoring.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>The Contributing Roles of Hormone Changes in Diabetic Ketoacidosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hormonal Change</td>
<td>Effects</td>
</tr>
<tr>
<td>1. Hypoinsulinemia</td>
<td>Activates lipolysis; increases free fatty acid plasma concentrations, gluconeogenesis, proteolysis, ketogenesis. The major contributor to DKA.</td>
</tr>
<tr>
<td>2. Hyperglucagonemia</td>
<td>Promotes glycogenolysis, gluconeogenesis, accelerated ketogenesis.</td>
</tr>
<tr>
<td>3. Growth hormone</td>
<td>Causes peripheral insulin resistance. Promotes lipolysis and ketogenesis.</td>
</tr>
<tr>
<td>4. Cortisol</td>
<td>Causes peripheral insulin resistance, promotes gluconeogenesis, and causes lipolysis and ketogenesis.</td>
</tr>
</tbody>
</table>
Table 2  Some Disorders That Can Coexist with DKA in the Dog and Cat

<table>
<thead>
<tr>
<th>Acute or chronic pancreatitis</th>
<th>Cardiac disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyelonephritis</td>
<td>Pyometra</td>
</tr>
<tr>
<td>Chronic renal insufficiency</td>
<td>Cholecystitis</td>
</tr>
<tr>
<td>Lower urinary tract infections</td>
<td>Pneumonia</td>
</tr>
<tr>
<td>Abscesses</td>
<td>Pyoderma</td>
</tr>
<tr>
<td>Septicemia</td>
<td>Cushing's syndrome</td>
</tr>
<tr>
<td>Hepatic lipidosis</td>
<td></td>
</tr>
<tr>
<td>Liver abscess</td>
<td></td>
</tr>
</tbody>
</table>

Table 3  Clinicopathological Abnormalities That are Known to Occur in Diabetic Ketoacidosis

<table>
<thead>
<tr>
<th>Serum</th>
<th>Hemogram</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperglycemia</td>
<td>Leukocytosis (a mature neutrophilia up to (20 \times 10^3) can result from dehydration or stress).</td>
</tr>
<tr>
<td>Hyperketonemia</td>
<td>Higher levels with or without a left shift requires a search for infection.</td>
</tr>
<tr>
<td>Hypobicarbonatemia</td>
<td>Anemia - due to chronic disease or to repeated phlebotomy</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td></td>
</tr>
<tr>
<td>Hypokalemia</td>
<td></td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td></td>
</tr>
<tr>
<td>Elevated liver enzymes</td>
<td></td>
</tr>
<tr>
<td>Elevated BUN</td>
<td></td>
</tr>
<tr>
<td>Decreased pH</td>
<td></td>
</tr>
<tr>
<td>Hyperamylasemia</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Urinalysis</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycosuria</td>
<td></td>
</tr>
<tr>
<td>Ketonuria</td>
<td></td>
</tr>
<tr>
<td>Hematuria</td>
<td></td>
</tr>
<tr>
<td>Pyuria</td>
<td></td>
</tr>
<tr>
<td>Bacteriuria</td>
<td></td>
</tr>
<tr>
<td>Urine Glucosea</td>
<td>Urine Ketones</td>
</tr>
<tr>
<td>---------------</td>
<td>---------------</td>
</tr>
<tr>
<td>2% (4+) or 1% (3+)</td>
<td>Large-small</td>
</tr>
<tr>
<td>0.5% (2+)</td>
<td>Large-small</td>
</tr>
<tr>
<td>2% (4+) or 1% (3+)</td>
<td>Trace-negative</td>
</tr>
<tr>
<td>0.25% (1+), 0.1% (trace), negative</td>
<td>Large-negative</td>
</tr>
<tr>
<td>2% (4+) or 1% (3+)</td>
<td>Negative</td>
</tr>
<tr>
<td>0.5% (2+) or 0.25% (1+)</td>
<td>Negative</td>
</tr>
<tr>
<td>Negative</td>
<td>Negative</td>
</tr>
</tbody>
</table>

aBecause simultaneous measurements of urine and blood glucose levels can differ, the clinician should determine the blood glucose concentration whenever an exact assessment is deemed necessary.

bForced feeding is not attempted if the animal is vomiting.

cWhen the animal is minimally or negative ketonuric, one of the longer-acting insulins is given at a dose amounting to two-thirds of the average total 24 hr requirement of regular insulin or 0.5 unit/kg body weight.
Table 5  Sliding Scale Technique for Subcutaneous Regular Insulin Administration in the Ketoacidotic Cat and Dog Following the Initial Injection - Blood Monitoring

<table>
<thead>
<tr>
<th>Blood Glucose</th>
<th>aUnits of Regular Insulin Every 6-10 Hours</th>
<th>IV Drip Supplement</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 400 mg/dl</td>
<td>-Increase 1-2 units above the previous dose (cat and small dog)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>-Increase 2-4 units above the previous dose (medium or large dog, respectively)</td>
<td>-</td>
</tr>
<tr>
<td>240-400 mg/dl</td>
<td>-Repeat previous dose (cat and small dog)</td>
<td>2.5% dextrose when blood glucose &lt; 250 mg/dl</td>
</tr>
<tr>
<td></td>
<td>-Increase 1-2 units above previous dose (medium and large dogs, respectively)</td>
<td>2.5% dextrose</td>
</tr>
<tr>
<td>180-240 mg/dl</td>
<td>-Decrease 2 units from previous dose (cat and small dog)</td>
<td>2.5% dextrose</td>
</tr>
<tr>
<td></td>
<td>-Decrease 4 units from previous dose (medium and large dogs)</td>
<td>2.5% dextrose</td>
</tr>
<tr>
<td>&lt; 180 mg/dl</td>
<td>-Omit insulin for 4-6 hrs</td>
<td>2.5-5% dextrose</td>
</tr>
</tbody>
</table>

*These insulin dosages are only empirical recommendations. The clinician should adjust subsequent doses according to each individual patient's response.
<table>
<thead>
<tr>
<th>Complication</th>
<th>Causative Factors</th>
<th>Prophylaxis and/or Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoglycemia</td>
<td>-Insulin overdose</td>
<td>Give 50% dextrose 1 ml/kg by IV push followed by maintaining the patient with a 2.5-5% dextrose infusion. Refractory cases require 0.5 – 13.0 ng/kg/min.</td>
</tr>
<tr>
<td></td>
<td>-Failure to accurately measure blood glucose levels</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-Failure to provide dextrose when the blood glucose level falls below 250 mg/dl</td>
<td></td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>-Failure to determine and monitor serum potassium levels</td>
<td>-Monitor serum potassium levels at least once daily</td>
</tr>
<tr>
<td></td>
<td>-Insulin overdose</td>
<td>-Provide potassium chloride as described in the text</td>
</tr>
<tr>
<td></td>
<td>-Inadequate potassium supplementation</td>
<td>-Use sodium bicarbonate only when metabolic acidosis is severe</td>
</tr>
<tr>
<td></td>
<td>-Excess bicarbonate administration</td>
<td></td>
</tr>
<tr>
<td>Cerebral edema</td>
<td>-Too rapid decline of the blood glucose level, causing an osmotic gradient shift of water into the brain parenchyma</td>
<td>-Lower the blood glucose level gradually over a 6- to 12-hr period. Avoid lowering the blood glucose at a rate exceeding 100 mg/hr</td>
</tr>
<tr>
<td>Metabolic alkalosis</td>
<td>-Excess bicarbonate use</td>
<td>-Avoid excess bicarbonate use</td>
</tr>
<tr>
<td></td>
<td>-Continuous vomiting</td>
<td>-Correct the hypokalemia</td>
</tr>
<tr>
<td></td>
<td>-Hypokalemia</td>
<td>-Stop the lactated Ringer's and switch to 0.9% saline solution</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-Give antiemetics if necessary</td>
</tr>
<tr>
<td>Paradoxical CSF acidosis</td>
<td>-Excessive and rapid bicarbonate administration</td>
<td>-Avoid excess bicarbonate use</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-No treatment because sudden death ensues</td>
</tr>
<tr>
<td>Sepsis</td>
<td>-Urinary or intravenous catheter contamination</td>
<td>-Maintain strict catheter aseptic techniques</td>
</tr>
<tr>
<td></td>
<td>-Failure to thoroughly assess patient</td>
<td>-Culture any body fluid or site of suspected infection</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-Use bactericidal antibiotics according to results of sensitivity testing</td>
</tr>
</tbody>
</table>
10.5 GROWTH HORMONE AND ACROMEGALY

Growth Hormone:
Growth hormone (GH), also known as somatotropin, is normally produced and secreted by the anterior pituitary gland. It has both anabolic and catabolic effects on the body. Its secretion from the pituitary gland is stimulated by hypothalamic growth hormone releasing factor (GHRF) which in turn is stimulated by many factors some of which include stress, hypoglycemia, protein needs, alpha-adrenergic agonists and beta-adrenergic antagonists.

The catabolic effects include increased lipolysis and hyperglycemia through growth hormone's interference with insulin at the peripheral tissue level and its ability to increase hepatic glucose output. The net effects of GH on carbohydrate metabolism are hyperglycemia and peripheral insulin resistance.

GH activates peripheral tissue hormone-sensitive lipase within adipocytes thereby causing lipolysis. The released fatty acids can act as a substrate for ketone body formation, especially in the setting where the insulin resistance eventually promotes the onset of diabetes mellitus. Paradoxically most acromegalic acts rarely become ketoacidotic.

Most of the anabolic actions of growth hormone are mediated through the formation of insulin-like growth factors (IGF) or somatomedins that are mainly produced in the liver. The somatomedins (especially IGF-1) exert their anabolic effect by increasing chondrogenesis, skeletal growth, protein synthesis and cell proliferation.

Acromegaly in the Cat
Cause:
Pituitary tumors are the primary cause of acromegaly in the cat.

Signalment:
In cats, acromegaly tends to affect the geriatric patient. Most of the cases reported thus far have involved the male domestic short-hair.

Clinical Signs:
The most common signs in the cat include inspiratory stridor (due to pharyngeal soft tissue proliferation), polydipsia and polyuria (associated with diabetes mellitus), large body size and head, prognathia inferior, renomegaly, cardiomyopathy, and arthropathy. Signs referable to an expanding pituitary mass include lethargy, mental depression and disorientation and circling. Seizures are rare. Other signs in the cat include cardiomyopathy, heart failure, degenerative arthropathy, and diabetes mellitus.
The most commonly recognized clinical manifestation of acromegaly in the cat is insulin-resistant diabetes mellitus. Growth hormone, especially in carnivores (especially cats and dogs), displays powerful diabetogenic activity and appears to provoke hyperglycemia mainly by inducing peripheral insulin resistance. Excessive GH has been shown to decrease insulin receptor numbers, decrease receptor-binding affinity and induce a post-receptor insulin defect similar to that observed with cortisol-induced insulin antagonism. All cats with acromegaly thus far reported have exhibited severe, persistent hyperglycemia, which was relatively refractory to insulin therapy and could be controlled only with extremely large doses of exogenous insulin (20 to 130 U/day of an intermediate- or long-acting insulin). Despite the presence of such uncontrolled diabetes mellitus, the development of ketoacidosis is rare in cats with acromegaly.

**Laboratory and Radiographic Findings:**

The most common clinicopathologic abnormalities include elevated serum alkaline phosphatase and alanine aminotransferase (ALT) levels, mild hyperphosphatemia, hyperglycemia, and anemia (or rarely polycythemia). The elevated alkaline phosphatase can occur from the direct effects of GH on bone metabolism. On the other hand, the elevated liver enzymes can be due to secondary hepatic lipidosis. Glycosuria will accompany overt diabetes mellitus.

The diagnosis of acromegaly would usually depend on documenting increased serum growth hormone (GH) concentration, but unfortunately this assay is not available for veterinary purposes in this country. An alternative screening test is the Insulin Growth Factor-1 (IGF-1) assay. IGF-1 is produced by the liver, and this is stimulated by GH and insulin levels in the portal system. It has been shown in humans and now in cats that IGF-1 is an indication of GH secretion. It is also elevated in some cats without pituitary tumors that have been treated with insulin for several months. Therefore, it is important to know that elevated IGF-1 concentrations are not an absolute diagnostic test for acromegaly in the cat, but it is a reliable indicator for further evaluation with diagnostic imaging when the serum IGF-1 concentration is elevated along with clinical signs of acromegaly.

The typical radiographic changes include increased oropharyngeal soft tissue mass, broadening of the metaphalangeal bones, soft tissue swelling of the head and limbs, and calvarial hyperostosis. Special radiographic procedures utilizing nuclear magnetic imaging is an effective way of diagnosing pituitary tumors in the cat.
Treatment:

Pituitary tumors are oftentimes too large to respond to surgical removal by the time they are diagnosed in the cat. Radiation therapy is a feasible alternative to surgery; however, its availability is limited. Medical therapy of pituitary tumors with bromocriptine, a dopamine agonist, has been used in man to control the signs of acromegaly. The drug, however, does not reduce the size of the tumor. Currently there is no effective medical treatment for pituitary tumors in the cat. The somatostatin analog, octreotide, has an inhibitory effort on growth hormone secretion. It has shown only a limited effect in humans but has not yet been shown to be of any benefit of the cat.

Prognosis:

The outcome for patients with pituitary tumors is grim. The severity of clinical signs and clinical course of acromegaly in cats are related to both the rise in circulating GH concentrations and the duration of GH hypersecretion. The short-term prognosis for feline acromegaly appears to be relatively good. Severe insulin-resistant diabetes mellitus can generally be satisfactorily controlled using large doses of insulin in divided daily doses, as described above. In some acromegalic cats, combinations of short-acting insulin (regular insulin) with NPH insulin at a 1:2 ratio help control hyperglycemia. Mild to moderate cardiac disease responds well to diuretic therapy. Despite the possibility that acromegaly may have been diagnosed late in the natural course of the disease, survival times for the cats with acromegaly that have been reported have ranged from 4 to 42 months (mean survived almost 2 years). However, all of the cats do eventually die or are euthanized because of the development of severe congestive heart failure, renal failure, or an expanding pituitary tumor (Peterson, M.). Pituitary irradiation treatment has been shown to be moderately successful in some acromegalic cats. This should be done before the tumor reaches an advanced stage.

10.6 PITUITARY DWARFISM IN GERMAN SHEPHERDS

Clinical Findings:

This is a rare syndrome with a genetic predisposition primarily in German shepherd dogs. Other breeds (Weimaraner, Spitz, Toy pinscher, Carnelian bear) and the cat have a much lower incidence. It is thought to be transmitted by simple autosomal recessive inheritance. The characteristic clinical signs include short stature, hyperpigmentation and fragility of the skin, deficiency of primary guard hairs, retention of puppy hair coat and partial or total alopecia. Alopecia usually develops over time and will affect the entire body except the head.

The growth rate usually diminishes a few weeks after birth.
Growth plates may be open or closed. The dog's activity level is normal.

**Laboratory Diagnosis:**

Routine laboratory test results are usually normal. The characteristic special endocrine test results are as follows:

4. Basal plasma growth hormone - low (normal 1.5 " 1.2 ng/ml)
5. After clonidine stimulation - low
6. Insulin-like growth factor (IGF) - low
7. Basal T₄ - low
8. Post TSH T₄ - will stimulate to normal or below normal level
9. Basal cortisol - normal
10. Post ACTH cortisol - normal
11. Marked sensitivity to insulin
12. Gonadotropin - impaired release
13. Prolactin - low

**Pathology:**

Has been attributed to a cystic Rathke's pouch. An alternative hypothesis provides that the embryonic craniopharyngeal ectoderm of Rathke's pouch fails to differentiate into normal tropic hormone-secreting cells.

**Treatment:**

The recommended dose of growth hormone (GH) in dogs is 0.3 IU/kg/week or 2 units every second day for 4-6 weeks. Human, porcine and bovine sources can be used, although porcine GH is preferred. Since most dogs are evaluated after or near the time of growth plate closure, increased growth should not be expected. Instead, the only visible effects might be hair regrowth and thickening of the skin.

Recent findings (year 2000) show a growth response to medroxyprogesterone (MPA) at a dosage of 2.5-5.0 mg/kg at 3 and then 6 week intervals. Side effects include pyoderma, cystic endometrial hyperplasia, mucometra, and acromegaly.

Thyroid hormone should be replaced at 0.01 mg/lb (20 μg/kg) once daily for the entire life.

**10.7 TREATMENT OF DIABETES MELLITUS IN THE CAT AND DOG**

Diabetes mellitus is not a rare disease in the dog and cat. It results either from an inability of the pancreatic beta cells to synthesize and release adequate amounts of insulin or from a peripheral antagonism to the effects of insulin. Most of the time the cause is idiopathic, but some associated known predisposing factors include pancreatitis,
glucocorticoid abuse, prolonged use of megestrol acetate, and acromegaly.

Diagnosis is made on the basis of history and clinicopathologic abnormalities as will be described in further sections. The practitioner should be aware that the cat often shows a transient hyperglycemia during times of stress where the blood glucose levels can elevate to 200-300 mg/dl. Therefore, it is important to interpret the laboratory values within the context of the patient. When the significance of the hyperglycemia is questionable, the clinician should repeat the test and check for the presence of glycosuria.

The medical management of the diabetic pet will be divided into two sections. The first will discuss treatment in the non-ketoacidotic diabetic, and the second will discuss treatment for ketoacidosis.

THE NON-KETOACIDOTIC PATIENT

History and Physical Examination Findings

The history usually denotes polyuria, polydipsia, and weight loss with a gradual occurrence over a period of weeks to months. Polyphagia is sometimes evident. The usual physical examination abnormalities include evidence of weight loss and slight hepatomegaly. Dogs can get a rapid onset of diabetic cataracts.

Diagnosis

Persistent hyperglycemia and glycosuria are the classic clinicopathologic abnormalities. Occasionally the liver serum enzyme tests (ALT, AST, and alkaline phosphatase) are elevated due to hepatic lipidosis.

Treatment

Most of the time, these patients are initially treated as outpatients following a special consultation session with the owner that provides specific instructions regarding insulin injection technique, feeding, insulin dosage adjustments, and the actions needed to counter any hypoglycemic reactions.

NPH or Lente (“Vetsulin”) insulins are the initial drugs of choice in the compensated dog. These same insulins can be used in the cat, but PZI given divided twice daily is a commonly used product as well. These insulins are initially dosed at $\frac{1}{2}$ unit/kg and should only be given subcutaneously. In man the activity of NPH insulin is characterized as follows: onset of action - 3 to 4 hours, peak action - 8 to 12 hours, and duration of action 18-24 hours. In the cat and some dogs, however, experience has shown that the onset and peak action times of NPH can occur as early as a few hours following the injection thereby predisposing the animal to life-threatening episodes of hypoglycemia. To circumvent this misfortune, the insulin dose can be split where one-half of the total is given in the morning, and the other half is given 8-12 hours later. This split-dose method provides the patient's total daily insulin requirement yet lessens the risk of hypoglycemic reactions. In situations where the animal is receiving
only one dose of insulin per day, the clinician should suspect the need for splitting the dose when the following signs are present: (a) symptoms of hypoglycemia in the late morning or early afternoon accompanied by minimal glycosuria and (b) hyperglycemia and excess glycosuria on the following morning's blood and/or urine sample(s). The reasons explaining this reaction include the Somogyi reaction, shortened duration of insulin effect, and possibly the owner's administration of excessive carbohydrates on the preceding day to counter the hypoglycemic episode. When "split-dosing" is inconvenient, PZI can be tried subcutaneously once daily at an initial dosage of ½ unit/kg. NPH, PZI, or Lente given Bid had been my preferred insulin for the compensated diabetic cat until the development of the insulin glargine insulin (see below).

Using Glargine in Diabetic Cats

These instructions for using glargine are based on a small number of cats, and caution should be exercised with the insulin until it has been used in a larger number of cats. Because glargine is very long-acting, there is the potential for prolonged hypoglycemia if overdosed.

Basic Information
• Insulin glargine must not be diluted or mixed with anything because the prolonged action is dependent on its pH.
• Insulin glargine should be kept refrigerated to prolong its life.
• Insulin glargine has a shelf-life of 4 weeks once opened and kept at room temperature. Opened vials stored in the refrigerator can be used for > 6 months.
• If using an insulin pen, the manufacturer recommends that the pen and cartridge be kept at room temperature and not refrigerated. This is to reduce the changes in volume of insulin dispensed associated with changes in temperature.
• When performing a blood glucose curve, samples probably only need to be taken every 4hrs over 12 hr in many cats (ie. 0h [before morning insulin], 4h, 8h and 12h after morning insulin)
• Dose changes should be made based on pre-insulin glucose concentration, nadir (lowest) glucose concentration, daily water drunk, and urine glucose concentration.
• Better glycemic control is achieved with twice daily dosing rather than once daily.

Starting Cats on Glargine
• If blood glucose conc. > 360mg/dL (20mmol/L) begin glargine at an initial dose of 0.5U/kg ideal body weight twice daily (BID)
• If blood glucose conc < 360mg/dL (20mmol/L) begin at 0.25U/kg ideal body weight BID
Perform a 12hr glucose curve with samples taken every 4hrs
- DO NOT increase dose for the first week.
- Decrease dose if biochemical or clinical hypoglycemia occurs
- It is suggested that cats stay in hospital for 3 days to check the initial response to insulin, or home glucose curves are obtained for the first 3 days
- Recheck at 1, 2, 3 and 4 weeks after the cat is sent home, and then as required.
- Many cats have negligible glucose lowering effect in the first 3 days (do not increase dose), although by day 10 after beginning insulin, most cats have good glycemic control.
- Until experience is gained in ketoacidotic cats, these should be treated initially with a shorter-acting insulin.

ADJUSTING INSULIN DOSE

1. Indications for increasing dose of glargine
   - If pre-insulin glucose conc. is \( \geq 360 \text{mg/dL} \) (20mmol/L), then increase dose by 0.5U/injection
     AND / OR
   - If nadir glucose conc. is \( >180 \text{mg/dL} \) (10mmol/L) then increase dose by 0.5U/injection

2. Indications for maintaining the same dose
   - If pre-insulin glucose conc. \( >240-<360 \text{mg/dL} \) (\( >15-<20 \text{mmol/L} \))
     AND / OR
   - If nadir glucose conc. 90-180mg/dL (5-10mol/L)

3. Indications for decreasing dose of glargine
   - If pre-insulin glucose conc \( \leq 180 \text{mg/dL} \) \( \leq 10 \text{mmol/L} \)
     decrease 0.5U
   - If nadir glucose conc \( <54 \text{mg/dL} \) \( <3 \text{mmol/L} \) decrease 1U
     If clinical signs of hypoglycemia develop, then reduce dose by 50%

   Insulin dose may be maintained or decreased depending on the water intake, urine glucose, clinical signs and length of time the cat has been treated with insulin
   - If pre-insulin glucose conc. 198- 252 mg/dL (11-14 mmol/L)
   - If nadir 54 – 72 mg/dL (3 - 4 mmol/L)

Determining if in Remission
   After a minimum of 2 weeks of insulin therapy, if the pre-insulin blood glucose is \( < 200 \text{mg/dL} \) (12mmol/L) insulin should be withheld and a 12hr glucose curve performed. If at the next due dosing time the blood glucose is \( >200 \text{mg/dL} \) (12mmol/L) then insulin can be administered at 1U BID. If blood glucose is \( <200 \text{mg/dL} \) then continue to withhold insulin and discharge with a follow-up visit in 1 week.
Some cats may have a pre-insulin glucose concentration below 12mmol/L within 2 weeks, but insulin therapy should be maintained for a total of 2 weeks to give beta cells a better chance at recovery from glucose toxicity. Use 0.5-1U BID or once daily until insulin is withdrawn.

**Urine Glucose**

With the long duration of action of glargine, there should be minimal periods when blood glucose is >14mmol/L (240mg/dL), and hence cats should almost always be 0 or 1+ for urine glucose. A value 2+ or greater likely indicates that an increase in dose is required.

**THE DIABETIC KETOACIDOTIC PATIENT**

The diabetic ketoacidotic pet is usually a medical emergency requiring immediate therapy based on the understanding of the underlying pathophysiology. The amount of knowledge regarding the pathogenesis of ketoacidosis has increased considerably over the past several years. An overview is provided in the following section.

**KETOGENESIS**

The development of hyperketonemia has previously been reviewed as a process that was entirely triggered and regulated by the rate of mobilization of free fatty acids (FFA) from adipose tissue. Over the past several years, studies have shown that alterations in liver metabolism independent of fatty acid delivery are equally important in the regulation of ketogenesis.

Hypoinsulinemia results in augmented lipolysis in adipose tissue. This is due to lack of the normal inhibiting effect of insulin on the hormone-sensitive lipase in adipose tissue. In addition, decreased glucose uptake by fat cells results in a deficiency of glycerol-3-phosphate, which is needed for in situ re-esterification of fatty acids. However, the increase in fatty acid mobilization is not of itself sufficient to bring about hyperketonemia. When FFA levels are markedly increased in normal subjects, hyperketonemia fails to develop.

In addition to increased fatty acid mobilization, the development of hyperketonemia requires an increase in the ketogenic capacity within the liver. The metabolic site within the liver that is responsible for this activation of ketogenesis has been suggested to reside at the mitochondrial carnitine acyltransferase reaction. This enzyme catalyzes the transfer of long-chain fatty acids across the mitochondrial membrane. Since beta-oxidation of fatty acids occurs solely within the mitochondria, accelerated transfer of free fatty acids across the membrane results in augmented fatty acid oxidation and acetyl CoA production. The marked increase in acetyl CoA availability exceeds the capacity for its oxidation to CO₂ via the Krebs cycle, resulting in condensation of acetyl CoA molecules to form the ketone.
acid, acetylacetate. The mechanism whereby insulin deficiency leads to augmented activity of the carnitine acyltransferase reaction is believed to involve augmented transfer of carnitine from extrahepatic sites to the liver as well as a fall in intrahepatic levels of malonyl CoA, the first committed intermediate in the biosynthesis of fatty acids. Malonyl CoA has been demonstrated to be a potent inhibitor of the carnitine acyltransferase reaction. Since insulin lack interferes with fat synthesis, a deficiency of malonyl CoA is an expected finding.

An elevation in glucagon concentration as well as insulin lack will markedly accelerate the ketogenic capacity of the liver. Hyperglucagonemia increases the level of carnitine, decreases the concentration of malonyl CoA, and increases the activity of carnitine acyltransferase in excess of that attributed to insulin deficiency alone. Consequently pancreatectomized patients that lack both insulin and glucagon will show less hyperketonemia as compared with patients that have pancreatic glucagon secreting ability.

In addition to increased ketone production, hyperketonemia in diabetes is a consequence of decreased utilization of these organic acids by muscle tissue. Even in patients with mild insulin lack, a diminution in the ability to dispose of ketones is demonstrable.

The formation of hyperketonemia can therefore be viewed as a three-pronged process involving adipose tissue, the liver and muscle. Insulin lack causes lipolysis in adipose tissue leading to increased delivery of FFA to the liver. Within the liver increased carnitine levels (resulting from insulin lack) and the activation of acylcarnitine transferase (resulting from glucagon excess) stimulate the beta-oxidative pathway and augmented ketogenesis. The ketones released by the liver cannot be metabolized at normal rates by muscle tissue and thus accumulate within the blood. The ketone acids (acetoacetate and beta-hydroxybutyrate) neutralize blood bicarbonate resulting in an increased anion gap-type of metabolic acidosis.

The predominant blood ketone acid is beta-hydroxybutyrate which is present at a ratio of 3:1 as compared to acetoacetate. Acetone is formed as a result of decarboxylation of acetoacetate (this is not a ketone acid). Acetone can be detected on the patient's breath as a fruity odor due to its low vapor pressure and pulmonary excretion. By using the Acetest® nitroprusside reagent test, ketones can be detected in the serum (or plasma) and urine. Since acetoacetate causes a strong reaction, acetone - a mild reaction, and beta-hydroxybutyrate - no reaction, it is conceivable that ketoacidosis in patients with only beta-hydroxybutyrate in the blood can produce a negative nitroprusside test result.

**History and Physical Examination Findings**

The history can be acute and characterized by a sudden onset of anorexia, depression, weakness and vomiting of only several days duration. In other situations the history is more chronic as
characterized by polydipsia, polyuria, and weight loss of several weeks or months duration with the subsequent onset of weakness, depression and vomiting which finally arouses the pet owner's concern.

The physical examination can reveal an entire spectrum of findings ranging from an essentially normal animal to one that is prostrate and nearly comatose, extremely dehydrated, and oftentimes cachectic. A smooth symmetrically enlarged liver due to hepatic lipidosis is often detected with abdominal palpation.

**Diagnosis**

Insulin treatment should not be given until the hallmark signs of hyperglycemia and ketonuria or marked glycosuria and ketonuria are substantiated with laboratory tests. In a previously published survey by this author describing the clinicopathologic abnormalities in thirty diabetic cats the following abnormalities were frequently found in the sick ketoacidotic patient: azotemia, hypobicarbonatemia, elevated serum liver enzyme tests, and hypokalemia. Additional clinicopathologic abnormalities included hyponatremia, hypophosphatemia and anemia.

A qualitative assessment of hyperketonemia can be made using the nitroprusside test (Acetest Tables - Ames Division, Miles Laboratories Inc, Elkart, Indiana, 46514) when a urine sample is not initially available. This serum ketone test is first performed on an undiluted sample and then subsequently on serial serum dilutions ranging from 1 in 2 to 1 in 32.

**Treatment**

The type of treatment must be tailored according to each patient's need. A hyperglycemic pet with mild ketonemia that presents with a good appetite and no signs of debilitation can safely receive NPH or Ultralente insulin and be treated as an outpatient as described in the previous section. However, the depressed, dehydrated patient should be hospitalized for more intense treatment and observation. The following sections describe the principles of therapy for the sick ketoacidotic diabetic animal.

(a) **Intravenous Fluid Therapy:**

The calculated fluid requirements include the patient's dehydration deficits, the 24 hour maintenance needs, and extra losses that result from vomiting or diarrhea. The dehydration status is approximated on a scale ranging from a mild (5%) to extreme (10%). The needed isotonic replacement volume is calculated by either of the following two methods:

(1) $\text{dehydration volume deficit (ml) = } \% \text{ dehydration} \times \text{kg body wt} \times 1000$
(2) dehydration volume deficit (ml) = 
\( \% \) dehydration \( \times \) lb body weight \( \times \) 500 

The 24-hour maintenance volume is roughly estimated (assuming adequate urine output) at 30 ml/lb (60 ml/kg). Therefore, the initial first 24-hour total fluid volume is the sum of the dehydration and the maintenance volumes.

If the animal is 8-12% dehydrated ½ of the estimated dehydration deficit should be administered intravenously over the first 2-4 hour period of hospitalization with the remaining replacement and maintenance volumes given over the following 20-22-hour period.

Lactated Ringer's solution (LRS) is the initial fluid of choice, however .9% saline can be given as an alternative or when the patient is significantly hyponatremic. The lactate in LRS is not associated with a H+ and therefore will not promote the onset of lactic acidosis. Acetate-containing parenteral fluids should not be given to the ketoacidotic patients in order to avoid possible increases in acetoacetate blood levels.

(b) Insulin:

Regular crystalline insulin is used when the patient has signs of depression, dehydration, anorexia, and vomiting. The advantages of regular insulin include: (1) various routes of administration (IV, IM and SQ); (2) rapid onset of action; and (3) short duration of action. These properties allow adequate insulin titration throughout the day according to the animal's needs. The clinician must acknowledge that blood glucose levels decline much earlier than ketone levels and so anticipate the persistence of some ketonemia and ketonuria for the first 48-72 hr.

Bolus intravenous doses of insulin offer the advantage of an immediate onset of action for the critically hypotensive patient. The recommended dose for a medium-sized to large dog is 1-2 units/kg. In the small dog and cat, the dose is reduced to 0.5 units/kg. Subsequent doses are given at the same amount every 2-3 hr until the blood glucose levels decrease to less than 250 mg/dl, at which time the patient is switched over to subcutaneous insulin injections given approximately every 6 hr. The disadvantages of this technique include the need for intensive care monitoring with frequent (every 1-2 hr) blood glucose determinations, the likelihood of hypoglycemia and hypokalemia, and the possibility of cerebral edema resulting from a too-rapid fall in blood glucose levels. Mannitol is the preferred treatment should this complication occur.

When laboratory facilities are unavailable, blood glucose reagent strips (Chemstrip bG reagent strips, Boehringer-Mannheim or Dextrostix reagent strips, Bayer) can be used for approximate blood glucose determinations. Several reflectance colorimeters are now commercially available to enhance the accuracy of these reagent strips.
To circumvent the occurrence of the aforementioned side effects, a continuous low-dose insulin infusion can be used. One successfully applied technique in the dog involves the addition of 5 units of regular insulin to a 500 ml bottle of lactated Ringer's solution which produces an insulin concentration of 0.01 unit/ml. After the first 2-4 hr of rehydration, the insulin infusion can be administered at a dosage of 0.1 unit/kg/hr. Care must be taken to avoid intravascular fluid overload in the small animal which might result from the technique. This can be accomplished by infusing the insulin containing solution through a separate intravenous catheter. Blood glucose determinations should be made every 1-2 hr. Reduce the insulin infusion to 0.05 unit/kg per hour when the blood glucose level is reduced to 250 mg/dl.

Low-doses of regular insulin can also be given intramuscularly. Initially 2 units are given into the thigh muscles of cats and dogs weighing less than 10 kg. For dogs weighing more than 10 kg, the initial dose is 0.25 unit/kg. Subsequent hourly injections of 1 unit for cats and small dogs and 0.1 unit/kg for larger dogs are given until the blood glucose level is less than 250 mg/dl, at which time the subcutaneous route can be used on an every 6 hr or as needed basis. The low doses used in this technique can be accurately measured with low-dose syringes (Lo-dose Insulin Syringe, Becton Dickinson, Rutherford, NJ 07070).

Subcutaneous regular insulin treatment is a suitable alternative to the intravenous and intramuscular methods when intensive care monitoring is unavailable. The initial dose is 0.5 unit/kg followed by subsequent doses every 6-10 hr depending on need.

**Dextrose 2.5% or 5% solution is instituted when the blood glucose decreases to < 250 mg/dl.**

The patient is regarded as stable and able to receive intermediate action (NPH, Lente) or ultralong-acting (PZI, Ultralente) insulin when normal hydration is restored, blood glucose levels are below 350 mg/dl, serum or urine ketones are minimal to absent, and oral feedings are accepted.

**Electrolyte Supplementation**

Assessment of the patient's serum electrolyte levels and correction of any abnormalities are extremely important for a successful outcome. As mentioned earlier the most common abnormalities include hypokalemia, hyponatremia and hypophosphatemia. Hypokalemia will be emphasized here because it is the most common and most debilitating serum electrolyte abnormality in the ketoacidotic diabetic.

The major causes of potassium depletion in diabetic ketoacidosis include (1) lean tissue breakdown (nitrogen loss), tissue glycogen depletion and cellular water loss which cause potassium to leave the cell and eventually be excreted in the urine, (2)
hypoinsulinemia allowing cellular potassium to enter the plasma and be lost in the urine, (3) secondary hyperaldosteronism in response to hypovolemia, and (4) gastrointestinal loss from vomiting. To complicate matters even further, the serum potassium level will usually fall after treatment commences via (1) dilution from rehydration, (2) continued urinary losses which are enhanced by excess Na⁺ delivery to the renal distal tubule, (3) correction of acidosis and the cellular influx of K⁺, and (4) increased cellular uptake of K⁺ due to insulin.

A ketoacidotic, dehydrated, normokalemic diabetic usually has significant total body potassium depletion. When hypokalemia is initially present, the total body potassium losses are even more substantial.

Although these patients are acidotic very few are ever found to be hyperkalemic. The onset of hyperkalemia in this setting of metabolic acidosis is offset by the continuing body loss of potassium by the mechanisms shown above. Furthermore the recent literature has shown that hyperkalemia is only rarely associated with an organic anion acidosis as opposed to a predictably higher incidence with an inorganic anion acidosis. Hyperkalemia will more commonly accompany oliguria and anuria.

Potassium supplementation for moderate to severe hypokalemia is best provided with potassium chloride solution which is added to the parenteral fluids. If concurrent hypophosphatemia is present, potassium phosphate solutions are available which can also be added to the intravenous fluid bottle. Potassium supplementation is best begun after the first two hours when rehydration, blood pressure, and adequate urine output are present. When the patient is initially markedly hypokalemic, the potassium can be supplemented in the initial volume of intravenous fluids but care should be taken to slow down the rate of infusion where the replacement of one half of the dehydration deficit is best delivered over an extra 1-3 hour period. The recommended amount of supplemented potassium chloride is provided:

(a) mild hypokalemia (serum K⁺ = 3.0 to 3.5 mEq/L): give 1-3 mEq KCl/kg B.W. over 24 hrs.
(b) moderate hypokalemia (serum K⁺ = 2.5 to 3.0 mEq/L): give 3-5 mEq KCl per kg B.W. over 24 hours.
(c) severe hypokalemia (serum K⁺ = < 2.5 mEq/L.): give 5-10 mEq KCl per kg B.W. over 24 hours.

It is important to recheck the serum electrolyte levels on the following day in order to further adjust electrolyte supplementation. The intravenous fluids and potassium supplementation are usually discontinued when euhydration and normal serum electrolyte levels are restored, and when the patient is able to eat and drink without vomiting.
Acidosis

Diabetic ketoacidosis is metabolic in origin and characterized by the accumulation of organic acid anions (acetoacetate and beta-hydroxybutyrate) which buffer and thereby lower the plasma bicarbonate levels. The body compensates the acidosis quite efficiently by (1) tissue and blood protein buffering (2) increased ventilation rate which blows off CO₂ and (3) renal mechanisms which regenerate bicarbonate and excrete the acid via increased HPO₄²⁻ and NH₄⁺ activity.

The diagnosis of metabolic acidosis in this disorder is characterized by a low blood pH, low total CO₂ level, and the presence of a base deficit and an elevated anion gap. The anion gap is equal to: (Na⁺ + K⁺) - (HCO₃⁻ + Cl⁻). A value greater than 30 mEq/L is clinically significant.

The use of sodium bicarbonate solutions should be reserved for those patients with a blood pH of less than 7.1. The complications of excess sodium bicarbonate therapy include: extracellular fluid hyperosmolarity, cerebrospinal fluid acidosis, intracranial hemorrhage, metabolic alkalosis, hypokalemia, and a left shift of the oxygen-hemoglobin dissociation curve. When the blood pH is between 7.2-7.3, the patient will usually counter the acidosis with its own compensatory mechanisms once the insulin and IV fluids are administered. Furthermore the body will convert acetoacetate and beta-hydroxybutyrate to bicarbonate once adequate amounts of insulin are administered.

When the acidosis is severe (pH < 7.1), sodium bicarbonate treatment should be given. The amount needed is determined by the following formula: mEq NaHCO₃ needed for extracellular replacement = 0.3 x B.W. kg x base deficit in mEq/L. The sodium bicarbonate should be administered slowly, and the blood pH should be re-evaluated a few hours later. When the blood pH returns to levels of approximately 7.25 or greater, the alkaline supplement should be discontinued to avoid the above mentioned side effects.

Feeding

Once the animal is able to hold down food, it should be fed or gently forced fed every 6 hours. A multivitamin supplement should also be given.
# Sliding Scale Technique for Subcutaneous Regular Insulin Administration in the Ketoacidotic Cat and Dog - Blood Monitoring

<table>
<thead>
<tr>
<th>Blood Glucose</th>
<th><em>Units of Regular Insulin Every 6 Hours</em></th>
<th>IV Drip Supplement</th>
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<tbody>
<tr>
<td>&gt; 400 mg/dl</td>
<td>- Increase 1-2 units above the previous dose (cat and small dog)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>- Increase 2-4 units above the previous dose (medium or large dog, respectively)</td>
<td>-</td>
</tr>
<tr>
<td>240-400 mg/dl</td>
<td>- Repeat previous dose (cat and small dog)</td>
<td>2.5% dextrose when blood glucose &lt; 250 mg/dl</td>
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<tr>
<td></td>
<td>- Increase 1-2 units above previous dose (medium and large dogs, respectively)</td>
<td>2.5% dextrose</td>
</tr>
<tr>
<td>180-240 mg/dl</td>
<td>- Decrease 2 units from previous dose (cat and small dog)</td>
<td>2.5% dextrose</td>
</tr>
<tr>
<td></td>
<td>- Decrease 4 units from previous dose (medium and large dogs)</td>
<td>2.5% dextrose</td>
</tr>
<tr>
<td>&lt; 180 mg/dl</td>
<td>- Omit insulin for 4-6 hrs</td>
<td>2.5% dextrose</td>
</tr>
</tbody>
</table>

*These insulin dosages are only empirical recommendations. The clinician should adjust subsequent doses according to each individual patient's response.*