Clinical Approach to Polyuria/Polydipsia
Ellen Behrend, VMD, PhD, DACVIM
Auburn University
Auburn, AL

Case 1
Signalment
12 year-old, castrated male mixed breed dog

History
Polyuria/polydipsia past few weeks; having accidents in the house. Lives in Alabama. Mainly indoors. Up-to-date on vaccines and heartworm preventive. No travel history

Physical examination
Obese

Laboratory data
Complete CBC, profile, urinalysis done. Abnormalities were: Calcium (mEq/L) 11.8 (9.0-11.2); urine specific gravity = 1.009 with 1-2 WBC/hpf and 2-3 RBC/hpf

What is polyuria/polydipsia?
Polydipsia has been defined as water consumption > 100 ml/kg/24 hr in dogs and cats1 but some difference may exist between species and another definition given is > 90 ml/kg/24 hr in dogs and > 45 ml/kg/24 hr in cats.2 Urine production usually follows water intake. Water consumption below these amounts, however, may still be consistent with such a diagnosis. Additional factors need to be considered when deciding if polyuria/polydipsia (pu/pd) are present. Animals that eat canned food drink less than those that eat dry food. Also, normal habits should be assessed. For example, even if water consumption is below 90-100 ml/kg/24 hr in a particular dog, if this is more than twice normal for that pet, a diagnosis of pu/pd may be warranted.

If doubt exists as to whether pu/pd is present, its presence can be verified by quantitating water intake at home; hospitalization can alter drinking habits. Urine specific gravity (USG) assessment may be helpful. If USG is >1.015 on a sample collected at home, pu/pd is unlikely to be present. A USG showing maximal renal concentrating ability (>1.030 in dogs, >1.035 in cats) rules out the possibility of pu/pd.2 If the USG is >1.030 and the owner believes the patient is polyuric, the history should be re-evaluated to ensure the problem is not dysuria, incontinence or a behavioral issue.3

What are the causes of polyuria/polydipsia?
To answer that question, understanding of the mechanisms regulating thirst and urine production is helpful. Anti-diuretic hormone (ADH) is released from the posterior pituitary, with the main function of causing water retention. Without ADH, dilute urine is excreted. When ADH is present, pores open in the membranes of the collecting ducts allowing passive movement of water from the hypotonic tubule lumen to the hypertonic medullary interstitium and concentrated urine is produced.4 Since reabsorption of water in this part of the nephron is passive, the osmotic force responsible, i.e. the concentrated renal medullary interstitium, is crucial. The main stimulus to ADH release is increased extracellular fluid (ECF) osmolality. Below 280 mOsm/kg, serum ADH concentration is very low to non-detectable. Above this point, even a 1% increase in ECF osmolality stimulates ADH secretion. Maximal ADH secretion occurs at an ECF osmolality of 320 mOsm/kg. Anti-diuretic hormone is also released in response to a 10% decrease in circulating blood volume.4

Thus, production of concentrated urine has 3 requirements: 1. Adequate serum ADH concentration and the ability of the kidneys to respond to ADH. 2. Function of at least 33% of total nephron number, i.e. when >2/3 of the nephrons are lost, urine concentrating ability is lost. 3. A concentrated renal medullary interstitium.

Causes of pu/pd can be divided into those causing primary polydipsia vs. primary polyuria (see Table). Primary polyuria is divided into the categories of osmotic diuresis, central diabetes insipidus (CDI), primary nephrogenic diabetes insipidus (NDI) and secondary NDI. CDI is caused by lack of ADH. In NDI, the kidneys’ ability to respond to ADH is compromised. In primary NDI, the problem is intrinsic to the kidneys. With secondary NDI, a non-renal problem interferes with the kidneys’ response to ADH.

<table>
<thead>
<tr>
<th>CAUSES OF POLYURIA/POLYDIPSIA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Polydipsia</strong></td>
</tr>
<tr>
<td>Psychogenic polydipsia</td>
</tr>
<tr>
<td>Liver failure</td>
</tr>
<tr>
<td>Neurological disease</td>
</tr>
</tbody>
</table>

216
Primary Polyuria

Osmotic diuresis
- Chronic renal failure
- Diabetes mellitus
- Primary renal glycosuria
- Post-obstructive diuresis

Central diabetes insipidus

Primary nephrogenic diabetes insipidus

Secondary nephrogenic diabetes insipidus
- Acromegaly
- Drug administration
- Intestinal leiomyosarcoma (paraneoplastic)
- Leptospirosis*
- Liver failure
- Hyperadrenocorticism
- Hypercalcemia
- Hyperthyroidism
- Hypoadrenocorticism
- Hypokalemia
- Hyponatremia
- Portosystemic shunt
- Pyelonephritis
- Pyometra
- Renal medullary washout
- Very low protein diet

*Possible, but not proven

A complete history and physical examination should never be underestimated as an important tool for diagnosis of any disease. For pu/pd, the presence of post-obstructive diuresis or drug administration as a cause can be ruled out on the basis of history. Medications that can cause pu/pd include corticosteroids, phenobarbital, and diuretics. In dogs, use of progestins can lead to acromegaly. The owner should also be asked about any recent diet changes since water content of food is an important water source and low protein diets can lead to low renal medullary tonicity.³ Questions specific to possible differential diagnoses should also be asked.

A CBC, biochemical profile and urinalysis alone can rule out a number of differential diagnoses. If the cause for pu/pd remains unknown after the minimum database has been performed, a urine culture should be submitted regardless of the urine sediment exam to determine if occult pyelonephritis is present. Pyelonephritis is not always accompanied by fever and perinephric pain, and in dilute urine a sediment exam can be misleading. If the cause is then still not apparent, hyperadrenocorticism should be ruled out in dogs by use of an ACTH stimulation test or low-dose dexamethasone suppression test.⁴,⁵ Pu/pd may be the only clinical sign present.

Case summary

Ionized calcium was normal. Urine culture was submitted and an E. coli grew (>100,000 cfu/ml). The dog was placed on an appropriate antibiotic for 4 wks. Cultures were performed 1 wk after starting antibiotics and 1 week after therapy was stopped. Both negative. Pu/pd resolved. Plan: Reculture urine 4 weeks later.

Case 2

Signalment
13 year-old, spayed female miniature Poodle

History
Polyuria/polydipsia past few weeks. Mainly indoors. Up-to-date on vaccines and heartworm preventive

Physical examination
Normal

Laboratory data
Complete CBC, profile, urinalysis done. Abnormalities were: neutrophils 12.5 x 10³/µl (3.0-11.5); lymphocytes 0.7 x 10³/µl (1.0-4.8); ALT: 130 IU/L (10-120); ALP: 322 IU/L (11-210); urine specific gravity = 1.011 with inactive sediment; protein 1+. Urine culture negative.

As with any other diagnostic work-up, look for the more likely and more common causes first before moving on to less likely diseases. In dogs, the 3 most common causes of pu/pd are renal failure, hyperadrenocorticism (HAC) and diabetes mellitus. In cats, the 3 most common causes are renal failure, diabetes mellitus and hyperthyroidism.
Trying to diagnose psychogenic polydipsia, CDI or primary NDI should be the LAST step in a diagnostic work-up for pu/pd. First, psychogenic polydipsia, CDI and primary NDI are very uncommon. Second, in order to correctly interpret the results of the modified water deprivation test (MWDT), a test that can be performed to differentiate these three conditions, all secondary NDI causes must be ruled out first. Secondary NDI can look like primary NDI or partial CDI with respect to results of the MWDT. Last, the MWDT is a time-consuming and potentially expensive test to perform.

In this case, serum ALP activity is not very high and no other signs of hyperadrenocorticism (HAC) besides pu/pd are obviously present. However, Cushing’s needs to be ruled out. Approximately 10% of dogs with HAC have a normal serum ALP activity. In addition, about 66% have proteinuria and/or hypertension. This dog may be proteinuric (1+ protein on urinalysis; a urine protein/creatinine (UPC) ratio is needed to quantify), and blood pressure should be measured. Even if the only abnormality identified (with measurement of liver enzyme activity, UPC, blood pressure, etc.) were pu/pd, HAC should still be ruled out. In cases such as these, I prefer an ACTH stimulation test.

Assessment of hepatic function via measurement of bile acids is not indicated in this case given the (lack of) clinical signs and laboratory findings. However, if liver function is at all questionable or liver enzymes (ALT and/or ALP) are moderately to severely increased, bile acids should be measured before an MWDT is performed.

Case summary
An ACTH stimulation test was performed. Serum cortisol concentration pre-ACTH was 224 nmol/L (reference range 10-160 nmol/L; 8.1 µg/dL, reference range 1-5 mcg/dL) and post-ACTH was 832 nmol/L (reference range 220-560 nmol/L; 30.1 µg/dL reference range 8-20 µg/dL). Systolic blood pressure was 190 mm Hg. UPC was 3.4. A diagnosis of HAC was made.

Case 3
Signalment
4 year-old, FS, Standard Poodle

History
Recurrent vomiting/diarrhea past 1-2 mth. Treated with fluids and antibiotics and always got better but then relapsed. Past 2 days she was anorectic and vomiting ~ 8X/day

Physical examination
Thin, 5% dehydrated

Laboratory data
Complete CBC, profile, urinalysis done. Abnormalities: Hematocrit 35% (37-55); BUN: 50 mg/dl (7-28); Creatinine: 2.0 mg/dl (0.9-1.7); Albumin: 4.7 g/dl (2.7-4.5); Na: 128 mEq/L (145-158); K: 6.2 mEq/L (4.1-5.5); Cl: 95 mEq/L (106-127); USG = 1.015 with inactive sediment.

The most likely differentials for this dog are hypoadrenocorticism and/or renal failure. Care should be taken in evaluating USG in azotemic patients in which a cause for pu/pd other than renal failure may also be present. A combination of inadequately concentrated urine and azotemia does not necessarily denote renal disease. Any cause of CDI or primary or secondary NDI can prevent the kidneys from concentrating urine in the face of prerenal causes of azotemia such as dehydration. If the cause for pu/pd is corrected, the azotemia will resolve if the kidneys are normal

Case summary
An ACTH stimulation test was performed. Serum cortisol concentration pre-ACTH was <14 nmol/L (reference range 14-160 nmol/L; <0.5 µg/dL, reference range 1-5 mcg/dL) and post-ACTH was <14 nmol/L (reference range 220-560 nmol/L; <0.5 µg/dL, reference range 8-20 µg/dL). A diagnosis of hypoadrenocorticism was made and therapy initiated with DOCP and prednisone. At recheck one month after stabilization, serum Na, K, BUN and creatinine concentrations were normal and the USG was 1.032.

Case 4
Signalment
8 yr old FS yellow Labrador

History
For the past 2 weeks she has been lethargic and has had a decreased appetite. Over the past month, she has had some accidents in the house

Physical examination
Normal

Laboratory data
Complete CBC, profile, urinalysis done. No abnormalities on bloodwork. Urine specific gravity = 1.004 with inactive sediment. Urine culture negative. ACTH stimulation test normal. UPC and BP normal.

Now is the time to do an MWDT. If the decision is made to perform a MWDT, decrease the patient’s water consumption slowly e.g. 120 ml/kg/day 72 hrs prior to the test, then 90 ml/kg/day 48 hrs prior and then 60-80 ml/kg/day for the last 24 hours. Prolonged
pu/pd leads to renal medullary washout, and this gradual decrease allows for re-concentration of the renal medulla. The patient should be watched carefully during this time for dehydration.

When the test begins, stop all access to water. At this point the patient needs to be monitored carefully as dehydration can occur quickly. Empty the bladder and obtain an exact body weight. Measure USG and, if possible, a urine and serum osmolality. A BUN should be measured and hydration status assessed. Do not do an MWDT if azotemia, dehydration, hypercalcemia or significant systemic disease is present. During the test, empty the bladder every 60-120 minutes and measure USG and, if possible, urine osmolality. Assess body weight and hydration hourly. Measurement of serum osmolality periodically is ideal but not always available.

An endpoint to the test is reached when: USG is >1.030 in dogs or 1.035 in cats; the patient is clinically dehydrated, azotemic or appears ill; the serum osmolality is 320 mOsm/kg; or there is a loss of 5% of body weight. There is no specific time limit to this test, and in patients with mild pu/pd, an MWDT can take longer than 12 hours. If the endpoint has not been reached when the clinic is closing, the patient can be transferred to an overnight facility for continuation of the MWDT, or the animal can be provided with a maintenance water amount (2.75 ml/kg per hour that the animal is unobserved). The next morning, the patient should be weighed, the USG measured, the water withdrawn and the test continued until an endpoint is reached.

If the patient has concentrated adequately at the endpoint, the diagnosis is psychogenic polydipsia. If there is inadequate concentration, the bladder is emptied, water is still withheld and aqueous ADH administered (0.55 U/kg IM with a maximum of 5 U per dog or cat). The bladder is then emptied every 30 minutes for 1-2 hours. Alternatively 10 to 20 µg of the sterile preparation of desmopressin acetate (DDAVP), a synthetic vasopressin analogue, can be given intravenously or 20 µg of DDAVP (approximately 4 drops of the 100 µg/ml intranasal preparation) can be administered into the conjunctival sac. Measurement of USG or urine osmolality should occur every 2 hours for 8 hours and then at 12 and 24 hours. The maximal response to intravenous desmopressin usually occurs 4 to 8 hours after administration, but it may take up to 24 hours. If adequate concentration occurs (i.e. USG > 1.018 or urine osmolality increases at least fivefold), the diagnosis is CDI. If urine still remains unconcentrated, the diagnosis is NDI.

CDI can be differentiated into partial, where ADH release is subnormal but still present, and complete where no ADH release occurs. In an MWDT, those with partial CDI show some concentrating ability in response to absolute water deprivation and then increase another 10-50% in response to administration of exogenous ADH. Those with complete CDI will not concentrate in response to dehydration but will when given exogenous ADH. CDI can be congenital, idiopathic or due to trauma or inflammation or a pituitary tumor. In a dog >6 years old, the most common cause of CDI, either partial or complete, is a pituitary tumor. Even if neurological signs are absent, diagnostic imaging is warranted.

An option to the MWDT when psychogenic polydipsia, CDI and primary NDI remain as the only possible differential diagnoses is to evaluate response to DDAVP therapy. In some clinics this has become the test of choice as compared to the MWDT for differentiating these three causes of pu/pd.

The patient’s 24-hour water intake for 2-3 days is measured allowing free-choice water. A urine sample is collected at a given time each day to check urine osmolality and USG. After these initial days, the patient is treated with DDAVP by administering the intranasal preparation (1-4 drops placed in conjunctival sac) or the oral tablets (0.1 mg) every 12 hours for 5-7 days. Water intake is monitored and a urine sample obtained on the 5th to 7th day at the same time of day as before treatment. A dramatic reduction in water intake and/or increase in urine concentration (i.e. >50%) provides strong evidence for CDI. Moderate response is consistent with partial CDI. A mild response is suggestive of psychogenic polydipsia. If no response is seen, NDI is present.

Case summary
An MWDT was performed and complete CDI diagnosed. A CT scan of the brain was normal. Therapy with DDAVP was initiated. After a few months, the medication costs were decided to be too much. The dog remained outside during the day when the owners were not at home. Plenty of fresh water was available at all times. She was brought inside at night and given a dose of DDAVP.

References available upon request.
Diabetic Conundrums: Difficult-to-Manage Cases
Ellen Behrend, VMD, PhD, DACVIM
Auburn University
Auburn, AL

Diabetes mellitus (DM) is the most challenging endocrine disease to treat. Good monitoring is essential to determining what to do. When all issues accounting for poor control have been exhausted, resistance should be considered. An orderly work-up will be needed.

Monitoring diabetic pets can be quite challenging in many ways. No technique is perfect. In one study, all blood glucose (BG) measurements, fructosamine and GHb were consistent with good glycemic control in 60% of dogs judged to have good clinical control or with poor control in only 39% of judged to have poor clinical control. Furthermore, monitoring can become a financial burden to owners. Although somewhat controversial and not perfect, I am an advocate of monitoring through performance of BG curves. Their disadvantages need to be recognized (and in part can be overcome by having owners conduct curves at home), but they are the only technique that not only confirms poor control but indicates how an insulin dose should be altered. Measurement of urine glucose and glycosylated proteins as well as assessment of clinical signs is also recommended to get as much information as possible for complete evaluation. In the following manuscript, I will address questions commonly asked regarding diabetic monitoring.

One question to ask, is what are we looking for in monitoring diabetics, or, in other words, what is the goal of therapy? At all costs, hypoglycemia should be avoided. On the flip side, how high can BG go? The goal of therapy is to get rid of the clinical signs in order to provide a good quality of life for the pets and clients. The strict control aimed for in human diabetics is not practical and may not be necessary in veterinary patients. Strict control in humans is required to avoid serious diabetic complications such as nephropathy, retinopathy, vasculopathy, etc. For whatever reason, these complications are not prevalent in veterinary populations. To get rid of clinical signs, BG needs to be below the renal threshold the majority of the time, i.e., < approximately 200 mg/dL in dogs and approximately 250-300 mg/dL in cats.

Performance of in-hospital BG curves has long been the gold standard for assessing diabetic control. To construct a curve, BG is measured in general every 2 hrs for one interval between injections, i.e., for 12 hrs if insulin is administered twice daily and for 24 hrs if insulin is given once daily. When BG is <150 mg/dL, the concentration should be measured hourly. A normal insulin/feeding schedule must be maintained as much as possible. If a patient does not eat the normal amount of the normal food at the usual time, the serial glucose curve should probably not be performed. The patient should be fed its standard diet at the usual time and the insulin given by the owner in the hospital so the owner’s injection technique can be assessed. Obtaining a fasting sample for measurement of BG prior to insulin injection can aid in appraisal of glycemic control, but this may not be possible if normal feeding time occurs before the hospital opens. Furthermore, feeding a dog or cat at home may ensure that the pet will eat. If the patient is fed at home, the insulin should then be given by the owner either at home or, especially if owner technique is questionable and needs to be assessed, in the hospital in front of a technician or veterinarian. Clearly, cooperation between client and veterinarian is necessary to maximize the information obtained with minimal disturbance to routine. When first trying to regulate a diabetic patient, assessment of the owner’s technique is crucial.

A curve should be performed the first day insulin is given. Glucose concentrations may be lower than expected after the first 24 to 48 hours of insulin therapy, especially in cats as stress hyperglycemia resolves. This first curve is done solely to ensure that hypoglycemia does not occur. If hypoglycemia is found, the insulin dose should be decreased 25% and another curve done the following day with the same goal in mind – to check for hypoglycemia. The insulin dose should not be increased based on the first day’s curve. A patient requires 5-7 days on a dose of insulin to equilibrate and reach maximal effect, so another glucose curve should be performed at that time. Based on assessment of the curve after equilibrium, the insulin dose can be increased or decreased as deemed necessary.

A serial BG curve should establish the time to peak insulin effect, duration of effect and degree of fluctuation in BG. The pattern of insulin effect should be used to determine dose, interval, and feeding schedule. Ideally, glucose concentrations should reach a nadir at 80 to 150 mg/dL. The highest glucose concentration should be close to 200 to 250 mg/dL in dogs or 300 mg/dL in cats. Changes in insulin dose can usually be made without affecting the duration of effect. The glucose differential is the difference between the nadir and the BG prior to the next dose, and can be a measurement of insulin effectiveness. If the curve is relatively flat, e.g., differential of 50-100 mg/dL, the insulin, with the exception of glargine where such curves are expected, may not be having a desired effect. My definition of duration is the number of hours that the BG is in the desired range.

The absolute BG must also be taken into consideration. If all BG are < 200 mg/dL, the insulin is very effective. However, if all BG are between 350-400 mg/dL, then the insulin is ineffective at that dose, stress hyperglycemia is present or you have caught a patient post-Somogyi (for a number of hours after a Somogyi phenomenon, insulin resistance will be present). In assessing a glucose curve, whether it is the first curve performed on a patient or the last of many, two basic questions need to be asked. First, has the
insulin succeeded in lowering BG? And, second, how long has the insulin lasted? By answering these questions, logical changes in dosing regimen, if necessary, can be made.

For all insulins but glargine, the first aim in regulating a diabetic is to achieve an acceptable nadir. (For insulin glargine, dose adjustment is made based on the pre-insulin BG concentration.) In general, if an acceptable nadir is not achieved, the insulin dosage should be adjusted depending on the size of the animal and the degree of hyperglycemia. Usually changes of approximately 10% are appropriate. Obtainment of an acceptable glucose nadir may not be possible in some animals, however, if insulin with a short duration of activity is used. In these patients, the BG is typically quite high in the morning since there has been inadequate control for most of the previous day. Even if an insulin injection is capable of lowering BG, it does not have a long enough effective period to lower BG into an acceptable range. In other words, a glucose curve in this situation shows a noticeable but brief decrease in BG after the insulin injection. Increasing dosing frequency from once to twice a day or changing to a longer lasting insulin type is indicated.

Hypoglycemia should always be avoided. No matter what other BG concentrations are during the day, if the value of the BG nadir is <80 mg/dL, a reduction in insulin dosage is indicated. Decrease the dose 25% if there are no signs of hypoglycemia and 50% if there are signs, and then do another curve to ensure hypoglycemia does not recur.

Once an acceptable nadir is accomplished, duration of action, roughly defined as the time from the insulin injection through the lowest glucose and until the BG exceeds 200 to 250 mg/dL, can be determined by a glucose curve. The total time of BG control also needs to be considered. For example, if the BG is not controlled for the first 6 hrs after insulin administration, control is inadequate. If the dose of insulin is inadequate and the target glucose nadir has not yet been achieved, the dose must be increased until the nadir is acceptable before duration of effect of the insulin can be determined.

The Somogyi phenomenon, also called hypoglycemia-induced hyperglycemia, refers to hypoglycemia followed by marked hyperglycemia. The phenomenon results from a normal physiological response when BG declines to less than 60 mg/dL in response to an insulin dose that is too high or when BG concentration decreases rapidly regardless of the nadir. In either case, a number of reflexes are triggered that act to increase BG. Counter-regulatory hormones such as epinephrine, cortisol, glucagon and growth hormone (GH) are secreted, and the resultant hyperglycemia usually occurs rapidly, thus preventing a hypoglycemic seizure. Insulin secretion does not occur in response to the rise in glucose, however, as would occur in normal dogs and cats, and diabetics become extremely hyperglycemic (400 to 800 mg/dL). If the Somogyi phenomenon is observed, the insulin dosage should be decreased so the nadir is > 80 mg/dL.; counter-regulatory hormones will no longer interfere with the action of the exogenous insulin and the true duration of effect will become apparent. If the duration of insulin action is truly < 8 hours, adequate therapy with that type of insulin requires injections more frequently than twice daily, which is impractical for most owners. A switch between different types of intermediate-acting insulin can also be beneficial. For example, a dog or cat may metabolize NPH insulin quickly, resulting in too short of an effect, but lente insulin may have a longer duration.

Admittedly, glucose curves are not perfect. Results of a serial glucose curve should always be interpreted in light of clinical signs. Glucose curves can be affected by deviation from normal routine. Curves in dogs and cats can vary from day to day.4,5 (One related important point is that due to the variation, predicting the timing of a diabetic’s nadir on the basis of previous serial glucose curves and obtaining a single sample at that time is unlikely to give a reliable result, i.e. spot checking does not provide helpful information.) Stress hyperglycemia can also falsely elevate results.

However, curves serve 2 very useful purposes that other techniques do not. First, they can clearly show clinically undetectable hypoglycemia. A phenomenon exists in human diabetics referred to as “hypoglycemic unawareness”. In this situation, the body does not respond to mild or even moderate hypoglycemia as in normal patients and clinical signs do not develop. However, when moderate to severe hypoglycemia occurs, profound clinical signs appear acutely without warning. Although unproven, I believe the same occurs in veterinary patients. A glucose curve will hopefully document mild hypoglycemia that can be fixed before a seizure occurs. Thus, periodic curves can be helpful even in a seemingly well-controlled patient. Secondly, and more importantly, other techniques and clinical signs can suggest that control is lacking, but multiple reasons for poor control including too low and too high a dose of insulin exist. The only way to know how to change the therapy to gain control is by performance of a curve.

A few aspects of glucometers should be considered. First, a glucometer should be easy to use. Glucometers that require minimal amounts of blood as well as those that “sip” the blood into the strip are desirable. Second, they need to be accurate. Two recent studies6,7 suggest the Abbot AlphaTRAK® is the most accurate meter for dogs and cats. Care must be taken to code the machine for sample source, i.e. whether the sample is from a dog or a cat. Although in general glucometers are commonly believed to underestimate BG concentration, the AlphaTRAK can either over- or underestimate BG in dogs7, while, in cats, it tends to underestimate low and normal BG and overestimate high BG concentrations.6 The inaccuracies, however, are of little clinical significance.

Measurement of urine glucose can be helpful for monitoring, especially cats where stress hyperglycemia prevents obtaining an accurate curve. First, urine glucose levels can be determined as needed to aid in assessment of glycemic control, especially when other data are conflicting. Consistently negative urine glucose readings may indicate that insulin dosages are either adequate or excessive. Remember, a negative urine glucose reading only means that in the period since the last urination, the BG was below the
renal threshold. So, for example, the BG could be 200 mg/dL or it could be 40! The only way to know is to measure BG. With consistently negative readings, a serial glucose curve can be performed to differentiate between adequate insulin therapy and use of excessive doses that could result in hypoglycemic shock. If BG measurement is not an option, the risk of hypoglycemia is higher. Uniformly high urine glucose readings coupled with unresolved clinical signs indicate that the insulin dose is inappropriate. Second, urine glucose concentrations can be determined regularly (at least weekly) to help in the assessment of ongoing control. Changes in urine glucose levels may alert the owner and clinician to loss of glycemic control and a need for reevaluation. Third, for cats receiving garge insulin, a protocol exists for altering insulin dose based on urine glucose measurements.

Another possible means for monitoring is measurement of glycosylated proteins, either glycosylated hemoglobin or fructosamine. Glycosylated hemoglobin (GHb) is formed by non-enzymatic, irreversible binding of glucose to hemoglobin. Fructosamine refers to glycosylated serum proteins, mainly albumin. Both GHb and fructosamine form at a rate proportional to the average BG present, so the higher the mean BG concentration over time, the greater their concentrations should be. The levels of glycosylated proteins are also affected by the half-life of the native protein. Thus, GHb reflects glycemic control over the previous 2-3 months, while fructosamine reflects that over the previous 3 weeks.

Both parameters correlate with BG and are typically not affected by stress. However, the value obtained from the laboratory must be interpreted in conjunction with all other data. Normal animals or well-controlled diabetics can have elevated concentrations of either GHb or fructosamine, and, conversely, uncontrolled diabetic animals can have normal levels of either. Fructosamine may be elevated in sick, hyperglycemic, but non-diabetic cats.

Given the overlap in GHb or fructosamine concentrations that can occur between well and poorly controlled diabetics, in general, I think one of the best uses of glycosylated proteins is to evaluate trends in glycemic control if measured at each recheck. Current recommendations are not to try to normalize serum concentrations of glycosylated proteins but to aim, in general, for a concentration slightly above normal. A fructosamine below normal indicates chronic hypoglycemia. Lastly, home monitoring of clinical signs has been advocated as a useful adjuvant tool in assessing glycemic control. Observation of clinical signs is crucial. If a patient is not polyphagic, polydipsic or polyuric and body weight is stable or increasing, diabetic control is likely good. Although owner observation of the presence or absence of clinical signs is very important, judgment of adequacy of control should not rely solely on owner reports.

Insulin resistance should be suspected in any pet in which marked hyperglycemia persists throughout the day despite insulin doses of more than 1.5 U/kg per injection or when large doses of insulin (i.e. >2.2 U/kg per injection) are needed to maintain adequate glycemic control. However, use of these doses does not mean that insulin resistance is present. The problem could lie with owner technique of insulin administration, patient management (e.g., exercise, diet), or insulin choice. Lack of response to high doses of one insulin type does not mean all insulins will be ineffective; for example, 20% of cats did not respond to high doses of ultralente insulin but could be effectively managed by twice-daily lente. In addition, longer-acting insulin (PZI) will be more slowly absorbed and less bioavailable than shorter-acting insulin; thus slightly more than 2.2 U/kg of long-acting insulin may be required.

Before a thorough and costly workup for insulin resistance is initiated, factors that mimic insulin resistance should be ruled out. The owner’s technique and insulin handling should always be evaluated first. Possible causes for an unsatisfactory response to insulin include inadequate mixing of insulin before withdrawal into the syringe; use of the incorrect syringe (e.g., using a U100 syringe with U40 insulin); misunderstanding of how to read the insulin syringe; problems with insulin injection technique; inactivation of insulin as a result of improper handling; and, if diluted insulin is being used, improper dilution. A bottle of insulin should be discarded after 2 to 3 months of use because activity may begin to decrease. If owner issues are suspected, a glucose curve should be performed after the owner administers insulin using a new, undiluted bottle and while being observed. Second, the owner should be questioned to ensure consistent and appropriate diet and exercise. If hyperglycemia is believed to be due to a postprandial surge from feeding a meal when the insulin’s effects are waning, timing of meals should be adjusted. Alternatively, addition of an oral hypoglycemic agent such as acarbose can be considered. Third, if no response is seen to one type of insulin, then another should be tried to see if it might be effective. Fourth, absorption of insulin can vary among subcutaneous sites, so another injection site should be used; the lateral thorax or abdomen is recommended. Lastly, a glucose curve should be performed to eliminate other possible mimics of insulin resistance, such as the Somogyi phenomenon and inadequate duration of insulin action.

Once true insulin resistance has been documented, a number of differential diagnoses should be considered. Insulin antibodies are a commonly discussed cause of insulin resistance. The clinical significance of anti-insulin antibodies (AIAs) remains unclear. Although antibodies may form against exogenous insulin, associated clinical insulin resistance appears rare. If AIAs are believed to be causing insulin resistance, the insulin source should be switched to a different one. Glycemic control should improve within 2 weeks of changing the species of insulin if AIAs are causing resistance.

Infection, ketoacidosis, and concurrent illness can cause insulin resistance. The urinary tract and oral cavities are common sites of infection; a urinalysis and urine culture, regardless of urinalysis findings, and complete oral examination should always be performed. Renal disease, hepatic insufficiency, cardiac insufficiency, pancreatitis, and starvation should be considered as possible causes of insulin resistance. Malnutrition can lead to insulin resistance and diminished insulin secretion. Obesity has been linked to glucose
intolerance and abnormal insulin secretion in cats and dogs, but its role in creating insulin resistance is unclear insofar as obese diabetic pets generally remain insulin responsive. Hyperthyroidism, hypothyroidism, and hyperadrenocorticism can cause insulin resistance through diverse mechanisms.

Certain drugs can cause insulin resistance, most notably progestogens and glucocorticoids. Although cats are resistant to development of many of the common adverse effects of glucocorticoids, such as polyuria and polydipsia, they may develop glucocorticoid-associated glucose intolerance readily. If possible, use of these medications should be slowly discontinued in diabetic patients. Otherwise, the patients may need to be treated as insulin-resistant. Neoplasia has been associated with insulin resistance in 5% to 10% of diabetic cats and dogs. Hyperlipidemia should be considered as a possible cause of insulin resistance.

When a cause for insulin resistance is sought, the easiest causes to rule out and the most likely should be eliminated first, proceeding through to the least likely. The following order, in general, has been recommended in cats: concurrent drugs, obesity, concurrent disease (including infection and ketoacidosis), hyperthyroidism, acromegaly, hyperadrenocorticism, and insulin antibodies. The order to use in dogs, in general, is as follows: concurrent drugs, diestrus/acromegaly, obesity, concurrent disease (including infection and ketoacidosis), hyperadrenocorticism, hypothyroidism, hyperlipidemia, and insulin antibodies. This order is not absolute. If strong evidence exists for a differential diagnosis lower in the order, that possibility should be ruled out first.

Management of insulin resistance requires correcting the underlying disorder, if possible. For causes such as a simple bacterial infection or concurrent administration of diabetogenic medications, eliminating the underlying problem can be relatively easy; other problems, such as acromegaly, may be more difficult to correct.

If the cause cannot be determined or eliminated, the following guidelines are suggested: (1) Administer insulin at least twice daily. (2) Avoid long-acting insulins, unless regular insulin is added. Intermediate-acting insulins are more effective in overcoming insulin resistance and lowering blood glucose concentrations. (3) Consider using mixtures of short-acting and longer-acting insulins. (4) Administer insulin shortly before or at the time of feeding to help control postprandial hyperglycemia. Large insulin doses may be required, but it will be necessary to determine the actual dosage using serial blood glucose curves, as for any diabetic.

References available from author upon request
Diagnosing Canine Hypothyroidism: A Case-Based Approach
Ellen Behrend, VMD, PhD, DACVIM
Auburn University
Auburn, AL

Case 1
Signalment
3 yr old, CM, mixed breed dog.

History
Presented for annual exam. Low activity and obesity despite limited feedings only problems noted.

PE
Obese. Complete CBC, profile, urinalysis done.

Lab data
Abnormalities were: WBC 17.5 x 10^3/µL (6.0-17.0); Neutrophils: 14.6 x 10^3/µL (3.0-11.5); Lymphs 0.7 x 10^3/µL (1.0-4.8); Monos 1.7 x 10^3/µL (0.2-1.4)

When trying to diagnose any disease, it is wise to remember that common things occur commonly; in other words, if common aspects of hypothyroidism are not present in a patient, then hypothyroidism is less likely to be present. Most affected dogs are middle aged to older. The age range is 6 months to 15 years, with a mean of 7 years. There is no gender predisposition. Likely many breeds are predisposed, but the most commonly affected breeds are Doberman pinchers and golden retrievers. Beagles and Borzois can have heritable thyroiditis.

Testing should be performed only if clinical signs are present, the most common of which are obesity/weight gain, lethargy/weakness and skin changes; alopecia and seborrhea are the most common dermatological abnormalities. Approximately 70% of hypothyroid dogs have a combination of skin and metabolic, e.g. weight gain, abnormalities.

With regard to reproductive function, no proof exists that male fertility or female heat cycles are affected. Conception rates might be affected. The only proven association is low birth weights and a higher incidence of periparturient mortality. Neurologic signs of hypothyroidism are rarely seen, but more commonly affect peripheral nerves than central. Cranial nerves are most likely the most commonly affected. Laryngeal paralysis is not associated with hypothyroidism and megaesophagus very rarely is. Seizures and aggressive behavior are unlikely to be associated.

Findings on routine laboratory tests can provide support for hypothyroidism. A mild, non-regenerative anemia is seen in 30-40% of hypothyroid dogs. Hyperlipidemia, cholesterol, triglycerides or both, is seen in ≥ 75% of hypothyroid dogs.

The approach to a dog with no known non-thyroidal illness (e.g. renal disease, neurological disease, neoplasia, etc.) vs. a dog with non-thyroidal illness (NTI) is a bit different. In dogs with no known non-thyroidal illness, the diagnosis is more straightforward. Starting with measurement of total T₄ alone is reasonable and economical. If total T₄ is normal, it is highly unlikely that the dog is hypothyroid.¹⁻⁴ Since non-thyroidal factors such as drugs and NTI affect T₄, if the T₄ is below normal, the dog may or may not be hypothyroid;¹⁻³ further testing is required.

Case summary
Serum T₄ concentration = 28 nmol/L (reference range 20-50 nmol/L). Based on minimal clinical signs and normal serum T₄ concentration, diagnosis of hypothyroidism ruled out.

Case 2
Signalment
6 yr old, FS, miniature Poodle

History
Presented for decreased activity, obesity despite being on a weight-loss program, thinning hair coat, heat-seeking behavior.

PE
Obese; partial, bilaterally symmetrical alopecia. Complete CBC, profile, urinalysis done.

Lab data
Abnormalities were: RBC x 10^9/µL 5.0 (5.5-8.5); Hemoglobin 11.2 g/dL (12-18); PCV 33 % (37-55); Lymphs 0.5 x 10^3/µL (1.0-4.8); Cholesterol 470 mg/dL (130-370)

The clinical findings suggestive of hypothyroidism are much stronger than in Case 1. Starting with measurement of serum T₄ is still a good first choice, but be prepared to do further testing if the serum T₄ concentration is below normal.

Free T₄ (fT₄) is the portion of total T₄ not bound to protein, representing 0.1% of total T₄. The fT₄ concentration is affected less by non-thyroidal factors. Accordingly, fT₄ is a more sensitive and more specific test for diagnosis of hypothyroidism as compared to total T₄.¹ However, it is not as good a stand-alone test as once believed (see below). It can be the initial test for the diagnosis of hypothyroidism or can be used in dogs with a low total T₄ concentrations.

224
Free T₄ should always be measured by the equilibrium dialysis method. Other techniques for measuring fT₄ are not reliable and provide no additional diagnostic value over measurement of total T₄.⁵ Equilibrium dialysis is also the only RIA for measuring fT₄ that is unaffected by the presence of autoantibodies.⁶

Primary thyroidal failure is believed to be the cause of canine hypothyroidism in 99% of cases.⁷ Accordingly, negative feedback of thyroid hormones on the pituitary would be lost and TSH should increase. However, an elevated serum TSH occurs in only 63-85% of hypothyroid dogs.¹ ³ ⁴ ⁸ ¹⁰ In other words, if measurement of canine TSH were used alone for diagnosis of hypothyroidism, up to 1/3 of cases would be missed! Conversely, TSH can be elevated in approximately 10% of euthyroid dogs with NTI.¹ ³ ⁹ ¹¹ ¹² Therefore, measurement of TSH is best used not as a sole test but in conjunction with T₄ or, ideally, fT₄. Use of a combination will aid in identifying false-positive and false-negative results seen with assessment of TSH alone.

Measurement of baseline serum T₃ is of little value in differentiating hypothyroid from normal dogs. There is no apparent difference in serum T₃ concentrations between these groups.¹ ² ⁵

Case summary

Serum T₄ concentration was 13 nmol/L (borderline range: 12-19; reference range 20-50 nmol/L). Measurement of serum fT₄ concentration (by equilibrium dialysis) and serum TSH concentration were requested. The serum fT₄ concentration was 8 pmol/L (reference range 15-45 pmol/L, 10-14 pmol/L borderline) and serum TSH concentration was 0.25 ng/ml (normal <0.5 ng/ml).

The interpretation of the case is now a clinical dilemma. The question is whether this is a hypothyroid dog with a normal TSH or a euthyroid sick dog who’s TSH has remained normal while the fT₄ is falsely lowered. The danger of falsely diagnosing a dog with hypothyroidism are threefold: 1. If clinical signs are incorrectly attributed to hypothyroidism, the true diagnosis will be delayed or never sought. 2. Thyroxine is a catabolic hormone. Administering a catabolic hormone to an ill patient may be detrimental. 3. The patient will needlessly be treated with thyroid hormone for the rest of its life. On the other hand, the danger of not treating hypothyroidism is that the clinical signs will progress. However, in a case such as this one, the clinical signs are relatively mild and benign progression is typically insidious, i.e. not treating for a month will most likely not be detrimental in the long-term.

At this point there are 2 choices: 1. Retest in 4-8 weeks. 2. Start trial therapy. If choosing option 2, make sure that you have objective measures of efficacy determined beforehand, e.g. normalization of serum cholesterol concentration and return to normal weight. Hair regrowth is not a good endpoint to use; the haircoat of euthyroid dogs can improve in response to thyroid supplementation. Be prepared to stop administering thyroxine if the clinical signs do not improve given adequate post-pill levels and time. (You must measure post-pill levels to determine if the trial is successful or not.)

Case 3

Signalment
8 yr old, CM, Labrador retriever.

History
Presented for lethargy, weight gain and obesity despite a poor appetite, bilaterally symmetrical alopecia (non-pruritic) that has been progressive over the past year, heat-seeking behavior.

PE
Obese; partial, bilaterally symmetrical alopecia. Complete CBC, profile, urinalysis done.

Lab data
Abnormalities were: RBC x 10⁹/µL 5.0 (5.5-8.5); Hemoglobin 11.2 g/dL (12-18); PCV 33 % (37-55); Lymphs 0.5 x 10⁵/µL (1.0-4.8); Cholesterol 470 mg/dL (130-370)

In a case that seems to be “text book” for hypothyroidism, starting with measurement of serum T₄ concentration is reasonable. If no other abnormalities are found other than those that can be explained by hypothyroidism and the serum T₄ concentration is very low, a presumptive diagnosis of hypothyroidism can be made. It would be ideal to measure fT₄ by dialysis for confirmation, but it may be unnecessary. Measurement of serum TSH concentration is not worth the money in this situation. Given that the sensitivity of measuring serum fT₄ concentration is much higher than that of serum TSH concentration, in a case such as this, if serum fT₄ concentration were low but serum TSH concentration was normal, I would believe the serum fT₄ concentration and start treatment for hypothyroidism.

Case summary
Serum T₄ concentration was measured and was non-detectable. Due to financial considerations, fT₄ concentration was not measured. Therapy with L-thyroxine was instituted. Post-pill testing was done to ensure adequate serum T₄ concentration was achieved. Within 3-4 months clinical signs had resolved, further proving the diagnosis.

Case 4

Signalment
8 yr old, CM, English bulldog.
History
Originally presented to his primary veterinarian for a geriatric screen and then was referred for evaluation of an incidental finding of proteinuria. On a urinalysis, a 2+ proteinuria was noted with a specific gravity of 1.014. A urine protein/creatinine ratio (UPC) was determined and was 5.8 (normal <0.5). The dog had always received regular veterinary care. He lived in Alabama with no travel history. Vaccines were up-to-date, and he was receiving Interceptor for heartworm prevention. He was an indoor/outdoor dog.

The owners reported no problems. The dog’s activity had decreased slowly over the past year and was attributed to aging. His appetite was normal.

Physical examination
He was obese and had moderate to severe dental tartar and gingivitis. All else was unremarkable.

Lab data
Abnormalities (CBC, profile and UA): WBC 17.5 x 10^3/µL (6.0-17.0); Segs: 14.6 x 10^3/µL (3.0-11.5); Lymphs 0.7 x 10^3/µL (1.0-4.8); Monos 1.7 x 10^3/µL (0.2-1.4); Albumin 2.2 g/dL (2.7-4.5); 4+ proteinuria in urine with 1.021 specific gravity; urine protein/creatinine ratio = 7.5 (normal <0.5); Blood pressure: normal

Due to the magnitude of the UPC, a tentative diagnosis of immune-complex glomerulonephritis (ICGN) was made. ICGN can be idiopathic or secondary to chronic immune stimulation. As dental disease could be a source of antigens, a dental procedure was performed. One month later, the UPC was essentially unchanged at 7.2; BP remained normal.

Further diagnostics were initiated to find possible underlying disease processes for ICGN. Three-view chest radiographs were obtained to rule out neoplasia (primary or metastatic) as well as other pulmonic diseases, and they were within normal limits. Abdominal ultrasound was normal. An occult heartworm test was negative. Serology for *Ehrlichia canis*, *Bartonella* and Lyme’s disease was negative. PCR for *Bartonella spp.* and *Ehrlichia spp.* was negative. Urine culture yielded no growth.

At re-evaluation approximately 4 wks later, after all test results had been obtained, the UPC was 8.6, BP and cholesterol were moderately elevated (190 mm Hg and 412 mg/dl, respectively). In order to determine the pathology underlying the proteinuria (e.g. glomerulonephritis vs. amyloidosis) and whether the disease process was reversible, a renal biopsy was performed; histopathological diagnosis was glomerulonephritis. Enalapril was prescribed (0.5 mg/kg daily) to decrease proteinuria and blood pressure.

On subsequent rechecks the dog was doing well. Systolic BP was 140-150 mm Hg and the UPC was approximately 4.3. However, persistent hypercholesterolemia, obesity and poor hair regrowth after abdominal ultrasound were noted, and a diagnosis of hypothyroidism was considered.

Given the complexity of this case, I would start with measurement of serum total T₄, fT₄, and TSH concentrations. The effect of NTI on testing for hypothyroidism is quite significant. In one study, 223 dogs with normal thyroidal function but with NTI were divided into those with mild, moderate and severe disease. Mildly ill dogs were considered to have clinical signs of disease but could be treated as outpatients, moderately ill dogs were sick enough to generally require hospitalization and more aggressive treatment and severely ill dogs required intensive care and advanced treatment. Interesting results were obtained.¹²

<table>
<thead>
<tr>
<th>Disease severity</th>
<th>% abnormal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total T₄</td>
</tr>
<tr>
<td>All dogs</td>
<td>31</td>
</tr>
<tr>
<td>Mild disease</td>
<td>8</td>
</tr>
<tr>
<td>Moderate disease</td>
<td>28</td>
</tr>
<tr>
<td>Severe disease</td>
<td>60</td>
</tr>
</tbody>
</table>

Of 69 dogs with low T₄, 45% had a low fT₄ whereas only 8.7% also had a high TSH. Only 1.8% of sick dogs had a low T₄ and fT₄ in combination with a high TSH.¹² Similar results have been obtained from other studies.⁹,¹¹

Possibly, in order affect thyroid hormones, a NTI must cause systemic problems. For example, moderate to severe arthritis had no effect on thyroid testing.¹³ However, transient systemic illness can have prolonged effects on thyroid testing. Therefore, in sick dogs, the first choice for diagnosis of hypothyroidism is a TSH, fT₄ and T₄ combination, 2nd is a combination of TSH and fT₄ and third a combination of TSH and T₄. If the results are conflicting (some parameters suggest hypothyroidism while others do not), the ideal would be to resolve the NTI, if possible, and then retest.

If resolution of the other disease is not possible, diagnosis of hypothyroidism poses a clinical dilemma as in Case 2. The clinician must decide how high their index of suspicion is for hypothyroidism, e.g. what clinical signs are present that could be attributed to hypothyroidism alone and not to the other disease. The same drawbacks to treating or not treating exist as before but not treating could have more devastating consequences if some of the severe clinical signs are caused by the hypothyroidism, e.g. neuropathy. It may be best to treat the dog for hypothyroidism while still looking for other possible etiologies of the clinical signs.

Case summary
A T₄, fT₄ and TSH concentrations were measured. Serum T₄ was 13 nmol/L (normal 20-55 nmol/L; borderline 12-19 nmol/L), fT₄ was 11 pmol/L (normal 15-45 pmol/L, borderline 10-14 pmol/L) and the TSH was 0.04 ng/ml (normal <0.5 ng/ml). Due to the effect
that NTI can have on thyroid function testing, the dog was judged to be most likely euthyroid based on a normal TSH and minimal clinical signs. A recheck was recommended in 4-6 wks.

The dog improved on treatment. Blood pressure remained normal, the UPC stabilized at approximately 3.2 and cholesterol remained very mildly elevated (380-400 mg/dl). Two months after stabilization, $T_4$ was still below normal (16 nmol/L), but the $fT_4$ (18 pmol/L) and TSH (0.02 ng/ml) were within normal. Hypothyroidism was ruled out.

**Case 5**

**Signalment**

9 yr old, CM, Cavalier Spaniel.

**History**

Presented for geriatric examination. Doing well at home.

**PE**

Normal. Complete geriatric profile done.

**Lab data**

All within normal limits except ALP = 254 IU/L (normal 10-95) and $T_4$ = 12 nmol/L (normal 20-50).

What to do now? I believe in geriatric screening in some scenarios: thyroid testing in dogs is not one of them. One thing to consider with random testing (i.e. not testing based on the presence of clinical signs), what is the predictive value of a test? Sensitivity and specificity look at a test from the viewpoint of the patient. Sensitivity is the chance that an animal with the disease will test positive and specificity is the chance that an animal that doesn't have the disease will test negative. Sensitivity and specificity are NOT affected by the prevalence of the disease in a population tested. Positive predictive value (PPV) tells you how likely it is that an individual with a positive test result actually has the disease. Negative predictive value (NPV) tells you the likelihood that an animal with a negative test result does not have the disease. The PPV and NPV are greatly affected by prevalence of disease. If you randomly test for a disease in a population, the PPV goes way down.

In addition, $T_4$ is not that easy to interpret and depends on so many things including age. There is an age effect that no laboratory takes into consideration in their reference intervals.

**Case summary**

I would not recommend treating this dog without clinical signs, regardless of the $T_4$ measurement.

**Case 6**

**Signalment**

4 yr old, FI, Dobie.

**History**

Presented for breeding examination. Doing well at home.

**PE**

Normal.

**Lab data**

All within normal limits except ALP = 254 IU/L (normal 10-95) and $T_4$ = 82 nmol/L (normal 20-50).

Except in the evaluation of breeding dogs, measurement of thyroid auto-antibodies does not add much to evaluation of dogs for possible hypothyroidism. If a hypothyroid dog has auto-antibodies then it can be determined that the underlying etiology is lymphocytic thyroiditis as compared to idiopathic hypothyroidism. However, management of the hypothyroidism does not differ.

In general, the clinical and prognostic significance of autoantibodies is unknown. If autoantibodies are suspected, measure $fT_4$ for the best assessment of function. If the $fT_4$ concentration is normal, thyroid function is normal at that time but the patient should be re-evaluated periodically (e.g. q. 3 mths) for development of hypothyroidism. If $fT_4$ is low, the dog is likely hypothyroid. One study followed 234 dogs with normal $T_4$ and TSH levels and elevated anti-thyroglobulin antibodies (TGAA) for 1 year. Only 19% developed clinical signs of hypothyroidism or consistent laboratory values. Another 57% remained TGAA positive without signs or laboratory evidence of hypothyroidism, 8% went from positive to borderline results and 15% became TGAA negative. The final outcome of all the dogs is unknown (i.e. how many would become hypothyroid if followed for more than one year), but it can be said that not all dogs with autoantibodies will become hypothyroid, as at least 15% do not.

References available from author upon request.
I Found an Adrenal Tumor I Wasn’t Expecting. Now What?
Ellen Behrend, VMD, PhD, DACVIM
Auburn University
Auburn, AL

Ultrasonography has become a routine diagnostic tool for evaluation of the abdominal cavity. One consequence is the unexpected finding of a seemingly incidental adrenal mass. It should be remembered that an adrenal mass is not necessarily a primary adrenal tumor (AT), and not all AT are cortisol-secreting. In one study, 27% of canine and 60% of feline AT were metastatic lesions. A primary AT can be benign or malignant and may or may not be functional, i.e. secreting a hormone; myelolipomas or lipomas can occur in the adrenal cortex. Functional masses can arise from the cortex and secrete steroid hormones or arise from the medulla, i.e. a pheochromocytoma. Of primary AT, approximately 75% are adenocortical with the remainder of neuroendocrine origin. Non-tumorous possibilities for masses also exist, including nodular hyperplasia, cyst, abscess, hematoma, and granuloma.

Incidentaloma
An incidental adrenal mass (IAGM), i.e. an “incidentaloma”, is defined as a focal enlargement of the adrenal gland in patients without prior evidence of adrenal gland disease. An AT should be suspected when there is loss of the typical shape of an adrenal gland regardless of size, asymmetry in shape and size between the affected and contralateral adrenal glands is present, or the mass has infiltrated the phrenicoadominal vein, vena cava, or surrounding soft tissues. The incidence of IAGM is estimated at 4% in dogs overall, but with a higher incidence in older and larger dogs. Only 17% of dogs with IAGM were < 9 years of age and the median weight of dogs with an IAGM was 21 kg. Incidence of adrenal incidentalomas in cats is unknown.

As the first step, abdominal ultrasound should always be repeated to ensure the mass is a consistent finding. Once an IAGM is confirmed, a number of differentials, as discussed above, need to be considered. Many factors determine the aggressiveness of the diagnostic and therapeutic approach, including the severity of concurrent problems, the original reason for performing abdominal ultrasound, patient age, the likelihood the mass is hormonally active and/or malignant, the size and invasiveness of the mass, and the client’s desires.

The history, physical examination, and results of routine blood and urine tests should be assessed for evidence of hypercortisolism, hyperaldosteronism, elevated sex hormone concentrations or of a pheochromocytoma. Appropriate tests should be performed as indicated to confirm the diagnosis.

The chance of an IAGM being malignant may be between 14 and 30%. Unfortunately, it can be difficult to determine whether an IAGM is neoplastic and malignant or benign without histopathology. Although cytology has 90-100% accuracy for differentiating cortical from medullary origin, it is not reliable for distinguishing benign from malignant. Imaging may be helpful but must be interpreted carefully. Characteristics that do not help differentiate adrenal adenoma and carcinoma are mineralization or ultrasonographic echogenicity. Both adenomas and carcinomas can contain mineral densities or appear as a mass cranial to the kidney. While diffuse, ill-defined mineralization usually is associated with adrenal neoplasia, discrete, well-margined mineralization develops in normal animals and may be a dystrophic change. On the other hand, possible metastases may be identified by thoracic radiography. Certain ultrasonographic findings are highly suggestive of malignancy. Suspect metastases to abdominal organs, especially the liver, can be visualized and confirmed by ultrasound-guided biopsy. If the maximum diameter of the AT is >2 cm, chance of malignancy and growth may be high. Evidence of invasion into surrounding tissues and/or the vena cava is suggestive of a carcinoma, however, it can be missed. Presence of tortuous vessels and heterogeneity of contrast enhancement as judged by contrast-enhanced ultrasonography may also be markers of malignancy.

If the IAGM is suspected to be malignant, adrenalectomy is the preferred treatment, but it may not be indicated if the mass is small, hormonally inactive, not infiltrating surrounding structures and believed likely to be benign. If no suggestion of malignancy is found, clinical signs or findings on physical examination and routine blood and urine tests do not support a functional AT and the tumor is <2 cm in diameter, a conservative approach should be adopted. Monthly monitoring with ultrasound to determine the rate of growth of the mass and changes in the appearance of the adrenal gland is recommended. Growth of IAGM is unpredictable. Of 7 dogs with an IAGM, 3 lesions were not found when ultrasound was performed again >4 months later. No growth occurred after >6 months in 2 dogs. In 2 dogs with initially larger tumors, growth occurred. In one, the mass grew from 1.6 to 2.5-cm diameter and invaded the vena cava within 10 months; in the other, the mass grew from 2.5 to 3.1-cm diameter within 8 months. In 9 dogs with non-cortisol-secreting AT followed for 12 months, no change was seen in 7. The two tumors that did grow were originally 2.0 and 2.5 cm in length.

If the IAGM has not increased in size after 3 months, the time interval between ultrasound evaluations can be increased. However, if the IAGM is enlarging, changing in appearance, or compressing or infiltrating surrounding blood vessels or soft tissues, or if clinical signs affiliated with excess hormone secretion develop, adrenalectomy may be warranted. For non-cortisol-secreting AT, median
survival without surgery in 14 dogs was 29.8 ± 8.9 months (range 1.0 - 96.0 months). Larger tumor size was associated with shorter survival.6

**Hyperadrenocorticism**

Given the vast amounts written on hyperadrenocorticism (HAC), it will not be considered in depth here and the reader is referred elsewhere.9 For (HAC), the classic clinical signs in dogs are polyuria/polydipsia, polyphagia, panting and a pot-belly appearance. The tumor itself can cause issues, such as rear limb edema due to vena caval invasion, but these are rare. On routine laboratory testing, the vast majority have an elevated ALP activity; hypertension and proteinuria are also quite common. If HAC is suspected, a low-dose dexamethasone suppression test is the screening test of choice. The sensitivity of the ACTH stimulation test for diagnosing HAC secondary to an adrenal tumor is approximately 60%.

**Hyperaldosteronism**

Primary hyperaldosteronism (PHA) due to an AT, i.e. aldosteronomas, are being increasingly recognized in cats. Given the rarity in dogs, the discussion will focus on what is known in cats. However, information on clinical signs and diagnosis likely apply to dogs. Feline tumoral PHA is usually caused by a unilateral adrenocortical adenoma or carcinoma, although bilateral adrenal adenomas have been identified.10 Malignant tumors are more common than benign.11 No breed predisposition for feline aldosteronoma is apparent. Median age at diagnosis is approximately 13 years and most cats are >10 years. No gender predisposition has been noted.12 As aldosterone is responsible for increasing potassium excretion and blood pressure, clinical signs of hyperaldosteronism relate mainly to hypokalemia or hypertension. The most common clinical sign in affected cats is persistent, progressive weakness, i.e. “hypokalemic polymyopathy”11, which typically occurs when serum potassium concentrations is <3 mg/dL. Cervical ventroflexion, hindlimb weakness (sometimes plantigrade stance), difficulty jumping, listlessness, and ataxia are the most common owner complaints. Episodic signs or an acute onset can be reported.13 Respiratory failure secondary to weakness of the respiratory muscles can occur rarely. Owners may note acute blindness and/or a sudden change in eye color due to hypertension, usually due to intraocular hemorrhage or retinal detachments. On occasion, hypertension may cause neurological signs such as seizures, ataxia and behavioral changes.12 Tumors secreting both mineralocorticoids and glucocorticoids occur uncommonly, so clinical signs of and clinicopathologic changes consistent with glucocorticoid excess may also be present.

The single abnormality typical for PHA on routine laboratory testing is hypokalemia. Although hypernatremia can occur, it is uncommon. Creatine kinase (CK) is usually elevated due to the myopathy, but the degree is variable. Metabolic alkalosis is common. An aldosteronoma should be strongly considered in a cat with unexplained hypertension, especially if it is refractive to therapy. Approximately 85% of affected cats are persistently hypertensive.14 Radiology is often not helpful, but a large tumor may be visible. Adrenal calcification is present in approximately 33% of older, healthy cats, and should not be over-interpreted. Pulmonary metastases are uncommon. In all reported cases of aldosteronoma in cats, an AT has been identified by ultrasound; however, in a few cats with bilateral AT, only one tumor was visualized.10,15 The contralateral adrenal gland needs to be evaluated; a decreased size suggests the AT is secreting a hormone with glucocorticoid or progestogen activity16 and bilateral masses may occur.10 Signs of malignancy should be sought (see above). However, ultrasound has not correctly identified vascular invasion in a high proportion of cats with aldosteronoma.15,17 If a mass in the area of the adrenal gland is identified, cytology can be helpful in determining origin.18 While presence of an AT in a cat with persistent hypokalemia and/or hypertension is highly suspicious for aldosteronoma, confirmation of the diagnosis relies on demonstration of an elevated basal aldosterone concentration. The assay is relatively easily available, and no special sample handling is required. To date, the highest aldosterone concentrations reported have occurred with AT. However, as suspicion for PHA is becoming stronger due to an increasing prevalence, testing will likely occur earlier in the course of disease; when aldosterone concentrations likely can be in the upper end of the reference range. Furthermore, the ranges of aldosterone concentrations reported for primary and secondary hyperaldosteronism overlap to a large extent. (Secondary hyperaldosteronism is the result of a condition, e.g. heart failure or chronic kidney disease, which stimulates the renin-angiotensin-aldosterone system.) Distinguishing primary and secondary hyperaldosteronism can be quite difficult. Concentrations > 1000 pmol/L have been reported with secondary PHA, especially in cats with chronic renal failure. The ideal would be to measure plasma renin activity (PRA). Unfortunately, a PRA assay is not commercially available in the US.

Desoxycorticosterone-secreting tumors have been reported rarely.19,20 Clinical findings are the same as with primary hyperaldosteronism but aldosterone concentrations are low. As no desoxycorticosterone assay is commercially available, a diagnosis would be presumptive based on the constellation of diagnostic test results.

**Pheochromocytoma**

Pheochromocytomas are uncommon in dogs and rare in cats. They occur in middle-aged to older patients with no known sex or breed predisposition. For pheochromocytomas, the most common clinical signs are weakness, lethargy, tachypnea or panting and collapse. The severity of clinical signs may correlate with the size of the tumor. They often occur intermittently due to episodic catecholamine
secretion. They may, however, also present as acute events, e.g. associated with tumor rupture. Other clinical signs and physical examinations include anorexia, weight loss, cardiac arrhythmias, tachycardia, polyuria/polydipsia, vomiting and abdominal pain.

Diagnosis of a pheochromocytoma can be a challenge. No consistent changes in the CBC, serum biochemistry panel and urinalysis exist which support the suspicion of a pheochromocytoma. Hypertension is present in more than 50% of dogs with a pheochromocytoma. As it can be episodic, repeat blood pressure measurements should be performed. The higher the systolic blood pressure the more likely a pheochromocytoma is present, e.g. systolic blood pressures > 300 mm Hg have so far only been seen in dogs with pheochromocytoma. A retinal examination may also provide proof of the presence of chronic hypertension. No definitive, validated biochemical test for diagnosis of a pheochromocytoma exists in veterinary medicine. Research into measurement of urinary metanephrine concentrations is promising.

Sex hormone-Secreting tumors
Adrenocortical tumors can synthesize and secrete sex hormones. A small number of cats and dogs with sex hormone-secreting AT have been described. The cats ranged in age from 7-15 years. A 14-year-old, female spayed domestic shorthair cat with bilateral adrenal enlargement and excessive estradiol and testosterone production has been reported.

Excess production of a progestin, e.g. progesterone or 17-hydroxy-progesterone, will cause signs typical of cortisol excess, such as a poor haircoat, dermal atrophy and cutaneous fragility. Diabetes was present in 3 of 4 cats with a progesterone-secreting tumor, and was poorly regulated in 2. Excess androgen production in cats can cause a change in the urine odor, urine spraying behavior, aggression and development of penile spines. Hyperestrogenemia may cause cyclic estrus behavior and vulvar enlargement. No dogs with clinical signs of hyperestrogenemia or hyperandrogenemia due to an AT have been reported. Tumor type was known in 5 cats, and only one was an adenoma.16,21-25

Suspicion of a sex-hormone secreting tumor will arise with clinical signs. No result of a routine test, e.g. complete blood count or serum biochemistry profile, will aid in the diagnosis. One of the main indications for sex hormone measurement is the finding of cortisol concentrations, including basal, below the reference range in a dog or cat tested for hyperadrenocorticism with an ACTH stimulation test or low-dose dexamethasone suppression test. If administration of exogenous glucocorticoids of any form or of medications that alter cortisol synthesis (e.g. ketoconazole) are ruled out, a sex hormone-secreting AT may be present. Finding of an AT on ultrasound further increases suspicion. Signs of malignancy should be sought and thoracic radiographs taken to assess for metastatic disease. Another indication would be the presence of sex hormone-associated changes and behaviors, e.g. urine spraying, mounting, vulvar enlargement, etc.

To document sex hormone elevations, an ACTH stimulation test should be performed as for typical hyperadrenocorticism. However, rather than cortisol, sex hormones are measured in samples drawn before and one hour after ACTH administration. In dogs at least, sex hormone concentrations should be interpreted cautiously. For estradiol, a wide range of variability exists within and between dogs; random, basal estradiol concentrations in individual dogs often exceed the reference range. In 6 dogs with a pheochromocytoma or a non-functional AT, androstenedione, progesterone, 17OHP, testosterone and/or estradiol concentrations were elevated.26

References available upon request.
Due to the high incidence of hyperadrenocorticism (HAC) and relatively non-specific clinical signs, older dogs are commonly screened for HAC. Due to the imprecision of diagnostic tests, HAC can be a difficult diagnosis to make. Clinicians are faced with the situation where their clinical impressions are that patients have HAC, but the tests do not confirm the diagnosis and no alternative diagnosis is identified. Recently, in order to explain such circumstances, syndrome termed occult HAC has been postulated. The 2012 American College of Veterinary Internal Medicine Small Animal Consensus Panel on the diagnosis of HAC defined the syndrome of atypical or occult HAC as “A syndrome in which a dog appears to have HAC based on history, physical examination and clinicopathologic findings, but the LDDST, UCCR and ACTH stimulation test fall into currently accepted reference ranges” 1. As the ACVIM Consensus Panel preferred the term “occult” over atypical, that is the name used here.

Occult HAC is supposedly caused by diversion of the normal adrenocortical pathways for cortisol synthesis into overproduction of sex hormones instead. The syndrome is diagnosed by performance of an ACTH stimulation test with measurement of serum sex hormone concentrations pre- and post-ACTH. However, conclusive evidence for the existence of occult HAC as a sex hormone-mediated condition is lacking. The Consensus Panel stated that sex hormones are not believed to be the cause of occult HAC. 1 Only 14 cases in the veterinary literature meet the definition.2,5 No specific phenotype for occult HAC is apparent. Although sudden acquired retinal degeneration syndrome6 and hyperphosphatasemia in Scottish Terriers7 have been linked with occult HAC, causative evidence is lacking.

**Evidence for and against the existence of occult HAC as a sex hormone-mediated disease**

In evaluating adrenal hormone secretion, whether basal or ACTH-stimulated concentrations were measured in any study must be taken into account. For the diagnosis of standard HAC, determination of basal cortisol concentration is not reliable and never used by itself. No evidence exists that measurement of basal serum sex hormone concentrations are any more trustworthy for diagnosis of adrenal dysfunction; thus, the following discussion focuses on ACTH-stimulated concentrations.

Adrenal sex hormone and cortisol precursor secretion as a cause of bilaterally symmetrical alopecia - Alopecia X is a condition most commonly affecting breeds such as Poodles and plush-coated dogs, e.g. Pomeranians, Chow Chows, Samoyeds and Keeshonds. It occurs in young adult dogs regardless of sex or neuter status. Clinical signs include loss of guard hairs, progressing to alopecia of the neck, tail, caudodorsum, perineum, caudal thighs and ultimately trunk. In addition, the skin may become intensely hyperpigmented.8 With Alopecia X, no systemic signs are noted. Whether Alopecia X is a separate entity from occult HAC or represents dogs with occult HAC that only have cutaneous manifestations, as can occur with standard HAC9 is unknown.

**Evidence in favor**

Sex hormones can cause endocrine alopecia. Castration-responsive alopecia is recognized. Hyperestrogenism as well as hyperprogesteronism associated with Sertoli cell tumors, for example, can lead to bilaterally symmetrical alopecia. Estrogen administration for treatment of urinary incontinence has led to bilaterally symmetrical alopecia and histopathological changes consistent with endocrine alopecia.

The first report of Alopecia X described 7 Pomeranians with bilaterally symmetrical alopecia and hyperpigmentation.10 Classic HAC was ruled out on the basis of normal ACTH stimulation test and LDDST results. Progesterone, 17-hydroxy-progesterone (17OHP), dehydroepiandrosterone sulfate (DHEAS), androstenedione, testosterone and estradiol were measured pre- and post-ACTH in the affected dogs, 12 unaffected Pomeranians and 19 non-Pomeranian control dogs. Only ACTH-stimulated 17OHP concentrations differed between affected and unaffected Pomeranians, but ACTH-stimulated progesterone and DHEAS concentrations were significantly higher in both groups of Pomeranians compared to controls. Given the constellation of abnormalities in affected and unaffected dogs, the alopecia was hypothesized to be due to a partial deficiency of 21-hydroxylase, an enzyme needed for cortisol synthesis.

In humans with 21-hydroxylase deficiency, cortisol is not synthesized and its precursors, most notably 17OHP and androgens, accumulate. Because affected Pomeranians had normal cortisol concentrations, the enzyme deficiency was assumed to be partial.10 Family members of human patients have sex hormone elevations to a lesser magnitude and no clinical signs, thus explaining the findings (i.e. increased progesterone and DHEAS levels) in the unaffected Pomeranians (many of the affected and unaffected Pomeranians in the study were related). Subsequently, 3 Alaskan Malamutes with Alopecia X were reported to have ACTH-stimulated 17OHP concentrations above the reference range that were significantly higher than those in 3 normal Alaskan Malamutes.11
Evidence against
Of 6 sex hormones assessed by Schmeitzel et al in the 7 Pomeranians, only ACTH-stimulated serum 17OHP concentration was significantly different between affected and unaffected dogs. However, when affected males and females were assessed separately, the males did not have elevated serum 17OHP concentrations. In 276 dogs with Alopecia X, including 63 Pomeranians, only 73% had at least one basal or post-ACTH sex hormone concentration above the reference range, i.e. 27% had no elevations. However, despite the preponderance of elevations in sex hormone concentrations, no consistent sex hormone abnormalities were identified. Of the ACTH-stimulated hormone concentrations, progesterone elevation was the most common abnormality, but it was found in only 36% of patients. Thus, it was concluded that Alopecia X should be referred to as alopecia associated with follicular arrest rather than an adrenal hormone imbalance. 12

Candidate genes in which mutations could cause the abnormalities, including 21-hydroxylase and enzymes in the cortisol synthesis pathway, have been cloned. No mutations affecting the primary structure of the enzyme or gene expression have been identified.

17-hydroxy-progesterone, other sex hormones, and cortisol precursors as causes of occult HAC

Evidence in favor
Initially, a study of 24 dogs with clinical and routine laboratory findings suggestive of HAC was reported. Eleven dogs with typical HAC with elevated cortisol responses to ACTH were assigned to Group 1. Of 13 dogs with normal ACTH stimulation test results, 6 had LDDST results consistent with HAC (Group 2A), 4 had negative LDDST results (Group 2B) and 3 had low plasma cortisol concentrations throughout testing so the LDDST was not interpretable (Group 2C). Despite the variation in serum cortisol concentrations on the tests for standard HAC, all 24 dogs had elevated ACTH-stimulated 17OHP concentrations. As ACTH-stimulated serum 17OHP concentration was elevated in dogs with both classic and occult HAC, it was concluded to be a marker of adrenal dysfunction.2

Numerous other studies have documented sex hormone concentration elevations in dogs with various forms of hypercortisolemia, either PDH or AT. Some studies were small, but elevations in DHEAS, testosterone, androstenedione, estradiol, progesterone, 17OHP, 21-deoxycortisol, 11-deoxycortisol and corticosterone have been found in 40-100%. 1,3,13-16

In cases in which cortisol and sex hormones are both elevated, which hormone(s) is causing clinical signs of HAC is difficult or impossible to determine. However, sporadic reports exist of dogs with sex hormone-secreting AT and low serum cortisol concentrations but in which clinical signs of HAC were present, ostensibly due to the sex hormones. Two dogs with AT had clinical signs of HAC despite markedly suppressed ACTH-stimulated serum cortisol concentrations; one tumor secreted progesterone, 17OHP, testosterone and DHEAS while the other secreted androstenedione, estradiol, progesterone and 17OHP.4 In a report of 8 dogs with AT and signs of HAC, 3 had suppressed ACTH-stimulated serum cortisol concentrations and 1 had elevated 17OHP concentrations; no other sex hormones were measured in any dog nor in the other 2 with subnormal cortisol concentrations.5

Evidence against
It is difficult to understand how sex hormones cause clinical signs of HAC. The sex hormone most mentioned as a cause of occult HAC is progesterone. However, little is known about the effects of elevated serum concentrations. Chronic progesterone excesses are not unique. In estrus and diestrus, serum progesterone concentration is elevated for 60-90 days and is higher than in dogs with HAC, yet no clinical signs of HAC develop.17 Massive elevation in serum 17OHP occur in humans with 21-hydroxylase deficiency, i.e., concentrations ranging from 3,000-40,000 ng/dl (reference range 20-600); however, clinically affected patients show signs either of aldosterone deficiency or androgen excess such as virilization, signs not reported in dogs with occult HAC. Lastly, a “cryptic” syndrome of 21-hydroxylase deficiency exists in which affected people lack 21-hydroxylase and have hormonal abnormalities but no clinical signs. Similarly, in dogs with Alopecia X, serum 17OHP concentrations can be quite elevated, similar to what is seen with dogs with purported occult HAC, yet none of the classical systemic clinical signs such as polyuria/polydipsia, polyphagia, pot belly and panting are reported.

Two mechanisms have been proposed for progesterone’s ability to cause signs of HAC: binding glucocorticoid receptors or displacing cortisol from its binding protein, elevating serum free cortisol concentrations. Examination of Pomeranians with Alopecia X, however, refutes the likelihood of either occurring. If elevated serum 17OHP concentration is sufficient to cause clinical signs due to glucocorticoid actions of 17OHP, endogenous ACTH (eACTH) concentration should be suppressed due to negative feedback effects of glucocorticoids on the pituitary. Indeed, for dogs with proven sex hormone-secreting AT and signs of HAC despite hypocortisolemia, eACTH concentrations can be low. However, Pomeranians with elevated serum 17OHP concentrations had higher eACTH concentrations than healthy dogs.10

How AT could have a shift in hormone synthesis activity can be understood easily. Tumor cells are not normal and can dedifferentiate, losing the ability to synthesize enzymes in the hormone synthesis pathways. In cases of pituitary-dependent occult HAC, how or why normal adrenocortical tissue should have altered steroid synthesis is unexplained.
Sex hormone panel testing

Evidence in favor
Measurement of serum sex hormone concentrations has been advocated as a means of diagnosing occult HAC. Use of a panel of hormones has been stated to increase sensitivity and specificity of the test over measurement of a single hormone alone. Elevations in concentrations of any hormone can be common, with estradiol elevations noted in approximately 40% of panels submitted to one reference laboratory.\(^1\)

Evidence against
Dogs with non-adrenal illness (NAI), e.g. a dog with diabetes mellitus, might not have the same ACTH response as healthy dogs because of adaptation of adrenocortical function to the stresses of chronic illness. Many stressed and sick dogs have increased cortisol concentrations and an exaggerated ACTH response, but do not have HAC.\(^1\) In one study, post-ACTH serum cortisol and 17OHP concentrations were significantly correlated both in dogs with neoplasia and those suspected of having HAC, suggesting that as adrenal function is increased either by adrenal disease or non-specifically by NAI, production of all hormones increases proportionately.\(^1\)

For estradiol, much variability exists within and between dogs; random, basal estradiol concentrations in individual dogs often exceed the reference range.\(^2\) With regard to 17OHP, the specificity of measurement is 59-70%, i.e. the chance of a false positive result is 30-41%.\(^3,4\) The specificity of progesterone measurement is 55%.\(^5\) In 6 dogs with a pheochromocytoma or a non-functional AT, androstenedione, progesterone, 17OHP, testosterone and/or estradiol concentrations were elevated.\(^6\) Therefore, dogs without adrenal disease can have elevated sex hormone, and sex hormones may be more likely to be falsely elevated by NAI as compared to cortisol.

Response to treatment

Evidence in favor
In dogs with either Alopecia X or purported occult HAC, treatment with agents that affect pituitary or adrenal function can resolve clinical signs. Melatonin controls seasonal reproductive and hair growth cycles and alters sex hormone concentrations in intact dogs. In 29 dogs with Alopecia X given melatonin; 15 had partial hair re-growth.\(^7\) In 3 Malamutes with Alopecia X, trilostane administration (3.0-3.6 mg/kg daily per os) resulted in complete hair re-growth within 6 months.\(^8\) Of 16 Pomeranians and 8 miniature poodles with Alopecia X, 14 Pomeranians and all poodles had hair re-growth in response to trilostane; the mean dose that caused hair re-growth was 11.8 mg/kg/day (range 5-23.5) in Pomeranians and 9 mg/kg/day (range 6.1-15.0) in poodles.\(^9\) Nine dogs with occult HAC treated with trilostane or mitotane all had clinical improvement. Decreased ACTH-stimulated cortisol and/or 17OHP concentrations were documented in 4.\(^1\) Lastly, in 1 dog with occult HAC, clinical signs resolved with mitotane therapy.\(^2\)

Evidence against
The response to mitotane, melatonin or trilostane, is neither uniform nor predictable. In 15 Pomeranians with Alopecia X treated with melatonin (mean 1.3 mg/kg per os BID; range 1.0-1.7) for 3 months, only 6 had mild to moderate hair regrowth.\(^2\) In the study evaluating 29 dogs diagnosed with Alopecia X treated with melatonin or mitotane, partial or complete hair re-growth was seen in only 62% overall. On mitotane, 4 of 6 dogs had partial to complete hair re-growth and 2 had none.\(^2\) More importantly, serum sex hormone concentrations did not change significantly in response to treatment nor correlate with whether response was seen. In dogs with partial or complete hair re-growth, 17OHP, androstenedione and progesterone were still elevated in 36%, 21% and 64%, respectively. In 16 Pomeranians and 8 miniature poodles with Alopecia X\(^2\) and 2 dog with occult HAC that responded to trilostane therapy, 17OHP concentrations were significantly elevated by therapy. Thus, hair coat and other clinical signs improve despite further increases in concentrations of the sex hormones purportedly underlying the clinical signs.

Indications for diagnostic testing
The author recognizes that cases that fulfill the criteria for occult HAC exist. However, sex hormones may simply be a marker of occult HAC, not the cause of it. At the current time, the recommended test is an ACTH stimulation test using the same protocol as with a standard test and measurement of cortisol, but the baseline and post-ACTH samples are used for measurement of sex hormones. Unfortunately, whether the protocol is optimal has not been evaluated.

Testing for occult HAC should not be undertaken if clinical indication for testing for classic HAC does not exist.\(^1\) If the clinical picture fits, the primary indication for measuring adrenal sex hormones is when a dog is screened for HAC with an ACTH stimulation test or LDDST and all cortisol concentrations, including basal, are below the reference range. If administration of exogenous glucocorticoids of any form, or administration of medications that alter cortisol synthesis (e.g. ketoconazole) are ruled out, a sex hormone-secreting AT may be present. Secretion of progesterone and 17OHP or other sex hormone or cortisol precursor may suppress pituitary ACTH secretion and cause atrophy of normal adrenocortical tissue. The ultrasonographic finding of an AT in such patients would further support the diagnosis, but the lack of one does not rule it out.

If clinical signs are mild, waiting and retesting for classic HAC when progression is noted may be the best course of action. If clinical signs are moderate to severe, abdominal ultrasound should be performed. If the adrenal glands are normal, the differential
diagnoses for the patient should be revisited. If bilateral adrenomegaly is present, pituitary imaging should be considered to identify a pituitary tumor causing early HAC. Lastly, food-stimulated HAC should be considered, as in these patients fasting cortisol concentration may be low.¹

A few explanations exist for the existence of such cases.¹ First, the reference ranges and cut-off values for the LDDST need to be reestablished. The ACVIM Consensus Panel believed the cut-offs should be lower than they currently are; a decreased cut-off would result in some dogs with occult HAC actually having typical HAC. Dogs with mild or early HAC that are “normal” on tests using current cut-off values may not be with revised (lower) values. Second, variable cortisol sensitivity exists in humans and may occur in dogs. Dogs with high sensitivity may show clinical signs of HAC at cortisol concentrations considered “normal” for the general population. Accordingly, the appropriate name for the syndrome may be “suspected HAC”. Third, dogs that meet the definition for occult HAC may have rare forms such as food-dependent HAC. Other explanations may also exist.

**Treatment**
The treatment of occult HAC has not been widely studied, but it would depend on the form of the disease. If caused by an adrenal tumor, adrenalectomy would be preferred. If a tumor is not the etiology, melatonin, trilostane, and mitotane have all had some success (see above). The efficacy of trilostane would depend on which hormone is in excess. As it is the author’s opinion that the true mediator of occult HAC is unknown but may relate to adrenal function, mitotane may be preferred, as concentrations of all sex hormones and cortisol intermediates would be suppressed. Whether the protocol for using either drug for treating occult HAC should be different than when treating hypercortisolemia has never been evaluated.
Treating Diabetes Mellitus: What Should I Use?
Ellen Behrend, VMD, PhD, DACVIM
Auburn University
Auburn, AL

Therapy of any disease is ideally aimed toward the underlying abnormality. In Type I DM, a lack of insulin exists, so treatment provides an exogenous source. Type I diabetics do not have the metabolic abnormalities present in Type II DM that are addressed by oral hypoglycemics. Consequently, administration of oral hypoglycemics to Type I diabetics is inappropriate, with the exception of acarbose. For Type II DM, oral hypoglycemic agents can be used initially, but as Type II DM progresses, exogenous insulin injections will be required. Dogs are mainly Type I diabetics, so oral hypoglycemics have not been used widely in them. Cats are believed to be mainly Type II, at least initially. In any case, patients with advanced Type II DM and glucose toxicity, a population likely to represent the majority of diabetic cats, will have totally lost insulin secretory ability. Accordingly, some diabetic cats will respond to oral hypoglycemic agents but most will require insulin therapy.

For cats, the best case scenario is to have the DM resolve. How likely this is in general is unclear, possibly approximately 50-60%. In one study, remission occurred after a median treatment time of 48 days (range 8-216). Unfortunately, remission is not permanent; in approximately 30% of cats in one study, insulin therapy had to be resumed after a median of 114 d (range 30-3,370). In 55 diabetic cats whose owners followed a highly intensive monitoring and blood glucose (BG) regulation (BG maintained between 50-100 mg/dL) protocol using insulin glargine and a low carb diet, cats that had received glucocorticoid treatment within 6 months prior to diagnosis of DM, that required a lower maximum insulin dose, and or that were intensively managed using glargine within 6 months of diagnosis were more likely to achieve remission, while cats with a peripheral neuropathy present at diagnosis (such as difficulty climbing stairs or a plantigrade stance) were less likely to do so. Other factors examined that were not predictors of entering remission were age at diagnosis, gender, obesity, evidence of diabetic ketoacidosis at diagnosis, development of azotemia during therapy, concurrent hyperthyroidism, and frequency of asymptomatic hypoglycemia. The presence of DKA does not mean that remission is impossible.

Diet

In order for DM to resolve, as good control of BG concentration is needed as quickly as possible. Diet plays an important role. The recommendation for diabetic cats is a high protein, high fat diet, e.g. Purina DM or Hill’s M/d. Following a moderate or high carb meal, cats have prolonged postprandial hyperglycemia. Cats already on insulin placed on a high protein, high fat, low carb diet had their DM resolve or experienced a marked reduction in insulin dose. In general, the canned version of DM or M/d is preferred as that is the lowest in carbs. While veterinary low carb, high protein prescription diets such as Purina DM or Hill’s M/d are the first choice dietary recommendation in most cats with DM, a carefully selected over-the-counter high protein, low carb diet can provide the same degree of effective glycemic control as prescription diets when financial constraints are present or when a cat will not readily eat the prescription diet. Many canned over-the-counter diets are relatively low in carb content (<5.0 g/100kcal), but information must be obtained from the manufacturer on specific brands and flavors to ensure the goal nutrient composition is being met. Most dry over-the-counter diets are higher in carb content. Thus, if a prescription dry veterinary low carb, high protein diet is not an option, it may, unfortunately, be more difficult to identify a good quality dry food with low carb content.

Caution should be used with these diets in cats with renal disease due to the high protein content. Whether it is more important to feed a diabetic diet or a renal diet in such cases is not known. If a high protein diet is not a possibility, feeding a more standard diet and administering acarbose may achieve the same goal. Insoluble fiber, the type present in commercial feline high fiber diets, can improve glycemic control in diabetic cats if a high protein diet is not feasible.

Inclusion of dietary fiber for treatment of diabetic dogs is still recommended. However, a recent study showed that diets with high fiber and moderate starch were not advantageous for dogs with stabilized DM compared to a moderate fiber/low starch diet. Although anecdotaly I have heard of cats that appear to be early diabetics and that have their DM resolve with dietary management alone, I do not recommend this. The longer a cat has uncontrolled DM, the less likely the DM will resolve. Insulin therapy is your best chance of getting control of the BG quickly!

Timing of feeding, especially as it relates to insulin administration, is important. In order to mimic physiological insulin release, insulin should ideally be given with each meal. The absorption of nutrients and development of postprandial hyperglycemia depends on numerous factors, but, ideally, calories should be ingested when insulin is still present in the circulation. Classically, the recommendation has been to feed patients BID to spread out caloric intake and insulin is most often given BID. In a patient receiving insulin BID, giving the meals before insulin additionally serves the purpose of ensuring a patient is eating. If inadequate calories are consumed, the insulin dose should be halved.
Some dogs and (especially) cats as well as households are not amenable to a BID feeding schedule. Judging an individual animal’s intake in a multi-animal household, however, can be difficult and may necessitate periodic isolation. Owners need be very strongly advised about the possibility of hypoglycemia as administration of a full dose of insulin in the face of inadequate caloric intake is more likely using this method.

**Insulin**

The choice of insulins is dwindling. At the current time, the insulins commonly used for maintenance in dogs or cats in the U.S. are NPH, PZIVet, Vetsulin, glargine and detemir. I prefer to start insulin BID; the majority of dogs and cats require BID therapy for good control and it may increase the chance of remission in cats.

Vetsulin can be used successfully in dogs, and at the current time is my first choice. In the majority of dogs, BID therapy will be needed. Similarly NPH can be used BID. Human recombinant NPH may have a shorter duration of action than the animal source NPH previously available. Anecdotally, the different brands NPH do not seem equivalent. It is my clinical impression that I have had greater success with Humulin, and that Novolin N has too short a duration of action in many dogs. With Vetsulin and NPH, I typically start at a dose of 0.5 U/kg BID. However, this is a higher starting dose than others use. Although some authors recommend a starting dose of 0.25 U/kg BID for dogs, others recommend using 0.5 U/kg if the BG is >360 mg/dL and 0.25 U/kg if <360 mg/dL.

Glargine (Lantus®) and detemir (Levemir®) are produced by recombinant DNA technology. Glargine’s chemical structure is altered slightly from native human insulin. It comes as a clear aqueous solution in 100 U strength with a very acidic pH (pH=4). When glargine is injected subcutaneously into a more neutral pH, the insulin forms micro-precipitates with a relatively constant absorption into the systemic circulation. The micro-precipitate formation and slow absorption are dependent on the pH of the glargine, so glargine cannot be mixed with other insulins or diluted. In detemir, the insulin molecule is modified via addition of a fatty acid side chain which facilitates reversible binding to plasma proteins, particularly albumin, from where it is released slowly into plasma. It also self-associates at the injection site which helps prolong absorption and duration of action.

Results with glargine in diabetic dogs have been inconsistent. In one study, 10 diabetic dogs were controlled with glargine and a high fiber diet at a mean of 38 days. In comparison, in 12 diabetic dogs, 58%, 33% and 8% attained good, moderate and poor glycemic control, respectively by week 24 of the study; thus, glargine was judged to be less successful than other insulins in diabetic dogs.

Finally, detemir can be used with success in dogs. It is VERY important to note that detemir is particularly potent in dogs, so the recommended starting dose is 0.1 U/kg BID. In one study of 10 dogs, all dogs improved subjectively. However, 6 episodes of clinical hypoglycemia occurred in 4 dogs. On the basis of clinical signs and blood glucose concentration curves, efficacy of insulin detemir at the end of the study was considered good in 5 dogs, moderate in 3, and poor in 2.

Human recombinant PZI (PZIVet) has variable efficacy in dogs. It is my last choice of insulin to use in dogs. The name brand product can be tried at a starting dose of 0.5 U/kg BID. However, a prolonged duration of action can result in hypoglycemia.

Compounded PZI products are unreliable; in one study, only 1 of 12 compounded products met all USP specifications in all vials tested. In cats, my first choice is glargine insulin. Vetsulin can also be used and may induce remission. Although no difference was seen in control or remission in diabetic cats when Lente was administered BID and glargine was administered once daily, when Lente, PZI or glargine were administered BID to 8 cats each, all 8 on glargine went into remission as compared to 3 of 8 on PZI and 2 of 8 on Lente. Thus, I recommend glargine BID for treatment of newly-diagnosed diabetic cats. Long-term diabetic cats have been switched to and treated with glargine as well with good success, but the diabetes has not resolved. One study found detemir to be similar to glargine in diabetic cats, offering no advantage. Lastly, PZIVet can be used with good success in cats.

Note: although glargine is my 1st choice insulin in a newly diagnosed cat or a cat not well regulated on another insulin, if a cat has been a long-term diabetic and is well regulated, I would not switch to glargine. In long-term diabetics, obtaining diabetic remission with glargine is much less likely, and if the cat is controlled, I would not “mess with success”.

**Recommendations** are to start cats on glargine or detemir BID at 0.5 U/kg if BG is >360 mg/dL or 0.25 U/kg if BG is <360 mg/dL. For the first 3 days, 12-hr BG curves should be performed (i.e. the curve should be performed for the interval between the a.m. and p.m. dose). The purpose of the BG curve is to detect hypoglycemia, if present, and lower the dose of glargine as needed. The insulin dose should not be increased for the first week no matter what the curves look like! After the first 3 days, the cat should be sent home and then return for a curve 7 days later. Subsequent BG curves should be performed 1, 2 and 4 wks later and then as required.

For the first 3 days, 12-hr BG curves should be performed (i.e. the curve should be performed for the interval between the a.m. and p.m. dose). The purpose of the BG curve is to detect hypoglycemia, if present, and lower the dose of glargine as needed. The insulin dose should not be increased for the first week no matter what the curves look like! After the first 3 days, the cat should be sent home and then return for a curve 7 days later. Subsequent BG curves should be performed 1, 2 and 4 wks later and then as required.

For the first 3 days, 12-hr BG curves should be performed (i.e. the curve should be performed for the interval between the a.m. and p.m. dose). The purpose of the BG curve is to detect hypoglycemia, if present, and lower the dose of glargine as needed. The insulin dose should not be increased for the first week no matter what the curves look like! After the first 3 days, the cat should be sent home and then return for a curve 7 days later. Subsequent BG curves should be performed 1, 2 and 4 wks later and then as required.

For the first 3 days, 12-hr BG curves should be performed (i.e. the curve should be performed for the interval between the a.m. and p.m. dose). The purpose of the BG curve is to detect hypoglycemia, if present, and lower the dose of glargine as needed. The insulin dose should not be increased for the first week no matter what the curves look like! After the first 3 days, the cat should be sent home and then return for a curve 7 days later. Subsequent BG curves should be performed 1, 2 and 4 wks later and then as required.

For the first 3 days, 12-hr BG curves should be performed (i.e. the curve should be performed for the interval between the a.m. and p.m. dose). The purpose of the BG curve is to detect hypoglycemia, if present, and lower the dose of glargine as needed. The insulin dose should not be increased for the first week no matter what the curves look like! After the first 3 days, the cat should be sent home and then return for a curve 7 days later. Subsequent BG curves should be performed 1, 2 and 4 wks later and then as required.
Administration of glargine should not be discontinued within 2 weeks of starting treatment regardless of the curve – decrease the dose if needed, but do not stop the insulin.

To determine if a cat is in remission, insulin administration should be continued until the cat is receiving 1 U BID. Then, if the pre-insulin BG is <180 mg/dL, go to once-daily administration. If the next day, the pre-insulin BG is still <180, do not administer insulin and do a complete curve. If the pre-insulin BG is >180 mg/dL when receiving once-daily insulin, go back to BID. An attempt to wean the cat can again be made in a couple weeks.

If performance of a curve is impossible, start glargine at 2 U/cat SQ BID and have the owner monitor urine glucose concentration or water intake. A cat well-regulated on glargine should have trace glucosuria at most and urine glucose should be negative the majority of the time. If after 2 weeks of receiving glargine, urine glucose is > trace, the dose should be increased 1 U/cat/wk until urine glucose is negative or water intake is <20 ml/kg/24h if eating canned food and <70 ml/kg/24h if eating dry food. At this point, keep the cat on the same dose for 2 wks then decrease the dose by 1 U/cat/wk until urine glucose is positive or the insulin has been discontinued.

The site of insulin injection is an important aspect. An appropriate location must be chosen, as absorption of insulin from various sites in the body differs. In dogs and cats, the dorsal neck or scruff has commonly been used as a site for injection, but this site may not be ideal due to low blood flow and increased fibrosis caused by repeated injections. A better option may be to administer the insulin at sites along the lateral abdomen and thorax. The chosen area should be rotated daily in order to prevent fibrosis at an injection site.

Insulin syringes, as compared to other types, are recommended due to the small needle size, but a needle prick can always be an unpleasant sensation. A good practice is to make the injections part of a good experience. For diabetics that are meal fed and are very into their food, inject them as they are eating. For others, you can give the injections when doing a pleasurable activity.

For any patient that needs a small amount of insulin, 0.3 ml syringes should be used for accurate dosing. These are referred to as “low-dose” syringes. The scale on the syringe is easier to read for small doses. Although this seems like a minor detail, believe me, giving insulin can be nerve wracking! The syringes are not that easy to read and a small error can have big consequences when you are only giving 2U to begin with!

The future: incretins?
In the last 5 years, much interest has focused on use of incretins as adjunctive therapy for DM. Incretins are hormones released from the gastrointestinal tract. The two incretins are GIP and GLP-1. In the past GIP stood for “gastric inhibitory peptide” but the name has been changed to “glucose-dependent insulinotropic polypeptide”; GLP-1 stands for glucagon-like peptide-1. Their secretion is stimulated by the presence of glucose, fatty acids, amino acids and fiber in the gastrointestinal tract. Their main action is to stimulate insulin secretion from pancreatic beta cells. In addition, GLP-1 can decrease glucagon secretion, stimulate beta-cell differentiation, delay gastric emptying and induce satiety, actions all beneficial for diabetics.

Mimetics of GLP-1 are available for administration, for example exenatide (trade name Byetta) and liraglutide (trade name Victoza). In addition, GLP-1 is metabolized by the enzyme, dipeptidyl peptidase-4 (DPP-4). Inhibitors of DPP-4 are also available commercially, e.g. sitagliptin (trade name Januvia) and vildagliptin (trade name Galvus).

As in humans, exenatide potentiates insulin secretion in healthy cats. Sitagliptin also has beneficial effects on glucose metabolism in healthy cats. As one pilot study evaluated an extended release (ER) form of exenatide in newly diagnosed diabetic cats. All cats were treated with insulin glargine BID and a low carbohydrate diet. In addition, cats were treated either with weekly injections of exenatide ER (Bydureon) or with a placebo. Cats on exenatide ER achieved remission or good metabolic control in 40% or 89%, respectively, as compared to 20% and 58%, respectively, in the controls. The exenatide ER was judged to be safe. Thus, exenatide ER has promise for improving diabetic control in cats and deserves further investigation. Similarly, liraglutide may have benefit in dogs.

References available upon request from author.
Trilostane vs. Mitotane: Which Should I Use?
Ellen Behrend, VMD, PhD, DACVIM
Auburn University
Auburn, AL

To treat or not to treat
An “urban legend” exists that survival is the same whether or not a dog with HAC is treated. Honestly, that has never been evaluated to my knowledge. It may be true for some dogs, but I do not think all. It also is a quality of life issue for both owner and dog.

I believe that not all dogs with positive tests for HAC need to be treated, however, and that decision should be made on a case-by-case basis. In deciding when to treat, I look at the dog, quality of life, owner and clinical signs. None of the drugs are cheap and neither mitotane nor trilostane are benign, so treatment is not to be taken lightly. If the only clinical sign truly is something like elevated ALP, I don’t treat. If the issue is only cosmetic (poor hair), I also don’t usually treat. If a dog is mildly pu/pd and an owner can live with it, I don’t treat. But if a dog is getting the owner up in the middle of the night all the time the be let out, I do treat. I do go back and review with the owner questions that might relate to clinical signs, e.g. has the dog stopped jumping on furniture (a sign of possible muscle weakness). I also look for evidence of clinical signs the owner might not note, e.g. look at urine s.g. to see if there is evidence of pu/pd. I also look for proteinuria (do a UPC) and hypertension - either or both of these are present in the majority of HAC dogs and both can damage the body. So if either or both is present, I'm more aggressive about treating. Having said all that, sometimes there are clinical signs an owner doesn’t notice or has attributed to old age until the HAC is treated - e.g. not playing, and when the HAC is treated activity increases.

How to use trilostane
A synthetic steroid analogue that inhibits the adrenal enzyme 3β-hydroxysteroid dehydrogenase, trilostane suppresses production of progesterone and its end-products including cortisol and aldosterone. Additional enzymes may also be affected.1 Trilostane (Vetoryl®) is FDA-approved for treatment of canine hyperadrenocorticism (HAC). Below is a discussion of latest information and outstanding questions.

The package insert in the U.S. has a starting dose of 2.2-6.7 mg/kg daily. Smaller dogs may need higher doses.2 A current anecdotal recommendation, the one used by the author, is to start at 2 mg/kg daily, divided if possible. Regardless of where therapy begins, dosage adjustments will be required during the course of treatment in most dogs. In general, larger dogs, e.g. >25 kg body weight, need lower doses on a per kilogram basis to control clinical signs.2

Despite recommendations in the package insert for once-daily dosing, trilostane may begin to lose effectiveness at 8-10 hrs post-pill.3-5 Trilostane has been administered twice-daily with good efficacy.5,8 Whether once- or twice-daily administration is better is unclear (see below). One paper reported using TID dosing.8

Trilostane absorption from the GI is increased by food. Thus, to be consistent, a patient should always be either fasted or fed when the trilostane is administered. Giving the pill with food may help to decrease the dose required for disease control, but this has not been evaluated. Compounded forms of trilostane are not recommended.9

The ideal cortisol concentrations for a dog on trilostane are approximately 30-150 nmol/L pre- and post-ACTH. A post-ACTH cortisol concentration up to 250 nmol/L is acceptable if the clinical signs are controlled. The initial recheck should be approximately 10-14 days after starting therapy. However, even if control is still inadequate, the dose should not be increased until the 30-day recheck. The basal and ACTH-stimulated cortisol concentrations usually continue to decrease until the 4-wk recheck even if the dog remains on the same dose. If cortisol concentrations are below ideal at any time, the trilostane dose should be lowered.

The ideal timing of post-pill sampling needs to be elucidated. Post-ACTH cortisol varies with the interval between dosing and testing.3 The package insert recommends a 4-6 hr interval. Some recommend initiating an ACTH stimulation test at 2-4 hours post-pill.10 However, insufficient data exist in the literature to determine the optimal time. For BID therapy, although one study recommended starting the test 8-12 hrs post-pill,7 such timing has not been critically evaluated. This author uses the manufacturer’s recommendations. It is important to keep the interval the same for an individual patient, e.g. if the first ACTH stimulation test to monitor trilostane therapy for a patient is started at 5 hrs post-pill, all the ones to follow should start at 5 hrs post-pill.11

Studies have evaluated alternative means of monitoring - either the urinary cortisol:creatinine ratio or measurement of baseline cortisol alone. Neither is sufficient; the only means of monitoring is ACTH stimulation testing.5,12,13

Trilostane is highly effective in suppressing cortisol secretion and controlling clinical signs in the majority of patients.5,7,14-17 As with mitotane, many clinical signs of HAC typically quickly resolve with disease control, but certain ones, e.g. dermatological abnormalities, can take up to 3 months. Other abnormalities such as calcinosis cutis or pseudomyotonia may not fully resolve. A small proportion of dogs with PDH are not well controlled with trilostane.14,16,17
Special consideration should be given to twice-daily dosing in dogs in which breaks in control of the HAC could be detrimental, e.g. dogs with concurrent diabetes mellitus or with pulmonary thromboembolism secondary to HAC. To this author, a concern with using trilostane, especially if once daily, is that the duration of control of cortisol secretion varies between dogs and is not easily determined. Although clinical signs may be in remission, we do not know how much control of cortisol secretion is needed to improve or prevent the serious complications of HAC. Adequate control of HAC with mitotane significantly decreases blood pressure and proteinuria. Control of hypertension and proteinuria may not be as good in dogs on trilostane, especially if dosed once daily. In a small retrospective study of 8 diabetic dogs, insulin requirements and fructosamine concentrations were not consistently reduced during trilostane treatment for HAC.

Reported adverse effects of trilostane for the most part are relatively mild, including lethargy and vomiting, but fatality has occurred. Although some studies found relatively low incidence of side effects, one non-peer-reviewed report states mild, self-limiting side effects such as diarrhea, vomiting and lethargy occur in 63% of treated dogs. Compared to mitotane, trilostane has less effects on suppression of aldosterone concentrations regardless of level of control of PDH.

As with mitotane therapy, excess adrenal gland suppression can occur and warrants discontinuing trilostane temporarily and lowering of the dose. Although, in theory, the effects of trilostane as an enzyme inhibitor should be rapidly reversible (e.g. within a couple days), suppression can last weeks to years. With oversuppression, recommendations from many sources are to discontinue the medication for a few days and then begin again. I prefer to perform an ACTH stimulation test to document return of function. One dog developed hypocortisolism after only 3 trilostane doses, and it lasted for at least one year!

Adrenal necrosis can occur secondary to trilostane administration. The hypoadrenocorticism reported after complete adrenocortical necrosis in one dog lasted for at least 3 months, but likely would be permanent. How often acute iatrogenic hypoadrenocorticism occurs with trilostane is unknown, but is likely more common than originally believed. In one study, 4 of 6 dogs with PDH and 1 of 1 with AT treated with trilostane had some degree of adrenal necrosis at necropsy. In 2 dogs, the damage was severe enough to potentially cause hypoadrenocorticism. Both dogs had received mitotane therapy before trilostane but had been on trilostane for 15 and 22 months, so the contribution of each drug is unclear. Adrenal rupture, possibly secondary to adrenal necrosis, may have occurred (Vetoryl® package insert).

**Final recommendations**

Given all the information, my current recommendations for using trilostane are:

1. Start as close to the bottom end of the dosing interval as possible: 2 mg/kg daily or 1 mg/kg BID. I prefer BID in general to get as much control as possible throughout the day. Definitely start BID in diabetics and in others in which elevated cortisol concentrations during the day may be detrimental, e.g. high risk for pulmonary thromboembolism.
2. Make sure the patient is always fed when the pill is given to increase drug absorption.
3. Be cautious with dose increases!
4. Do the ACTH stimulation test 4-6 hrs post-pill. Keep the timing and feeding consistent with every test.
5. If cortisol concentrations are too low, perform an ACTH stimulation test before reinitiating trilostane therapy. Suppression can be prolonged!

**When to use mitotane vs. Trilostane**

Trilostane and mitotane can be compared in multiple ways to guide a decision as to which to use.

**Efficacy for pituitary-dependent hyperadrenocorticism (PDH)** - As stated above, overall, trilostane appears to be highly effective in suppressing cortisol secretion and controlling clinical signs in the majority of patients. In 184 dogs with PDH treated with mitotane for a mean of 2 years, the response was judged as excellent in 83%, fair in 16% and poor in 0.6%. Survival with trilostane therapy is at least as good as with mitotane. In one study, median survival on trilostane given SID was 662 days (8-1971 d) while survival on mitotane was 708 days (33-1399 d). In dogs with PDH given trilostane BID, median survival was 930 days.

**Efficacy for adrenal tumors** - Surgical removal of cortisol-secreting adrenal tumors is recommended treatment, but surgery is sometimes neither possible nor desired. Trilostane has been used to treat dogs with AT. However, not enough information is available to ascertain whether the treatment protocol or efficacy varies if treating PDH versus AT. One dog with an AT did receive a maximum trilostane dose of 17.2 mg/kg, which is higher than typical for PDH.

Mitotane and trilostane have been compared in 37 dogs with AT. The aim of both drugs was control of cortisol secretion as for PDH, not ablation of the AT as some recommend. Median survival was not significantly different between the drugs (277 d overall). The only factor that affected survival was presence of metastases. In 11 dogs with AT treated with trilostane BID, median survival was 14 mths (range 3.5-55.0). Of 32 dogs with an AT treated with mitotane with the goal of tumor ablation, 66%, 28% and 6% were judged by their owners to have a good to excellent, fair response and poor response, respectively. Mean survival time was approximately 16 months with a reported range of 20 days to 5.1 yrs.
In dogs with AT, mitotane could theoretically be preferred as it is truly chemotherapeutic in this instance, killing primary neoplastic cells and, perhaps, metastatic ones as well. Trilostane controls tumoral secretion, not growth. In fact, in dogs treated with trilostane, adrenal gland size increases.\textsuperscript{25,33} If the goal is to prepare a patient for adrenalectomy, trilostane may be of choice.

**Efficacy for control of serious complications of hyperadrenocorticism** - To reiterate, one of my concerns with using trilostane, especially if once daily, is that the duration of control of cortisol secretion varies between dogs and is not easily determined. When serious complications of HAC are present or the patient is diabetic, twice-daily therapy should be considered. See above for more information.

**Adverse effects** - Trilostane has more adverse effects than originally believed (see above). Adverse effects of mitotane are generally gastrointestinal or neurological. One or more adverse effects occur in approximately 25\% of dogs with PDH during loading and include weakness, vomiting, anorexia, diarrhea and/or ataxia.\textsuperscript{26} Approximately 33\% of dogs on maintenance mitotane therapy for PDH develop adverse effects, typically shortly after initiation of the maintenance dosage or during relapse when daily therapy is reinstalled. Adverse effects occur in approximately 60\% of dogs with AT treated with mitotane.

Approximately 33\% of dogs will have a serum cortisol concentration less than ideal (e.g. post-ACTH cortisol concentration <30 nmol/L) after induction with mitotane for PDH. In most dogs, serum cortisol concentrations will rise into the ideal range within 2 to 6 wks, but up to 18 mths may be needed.\textsuperscript{26} Complete mineralocorticoid and glucocorticoid deficiency is seen in approximately 6\% of dogs anywhere from 1 mth to years after initiation of maintenance therapy and is usually permanent.\textsuperscript{26} Both drugs have greater effects on aldosterone than previously believed. Hypoaldosteronism is more serious than cortisol deficiency. Compared to mitotane, triostane has less effects on aldosterone concentrations but hypoaldosteronism can occur regardless of level of control of PDH.\textsuperscript{34}

**Contraindications** - The triostane package insert states that primary hepatic disease and renal insufficiency are contraindications. In Plumb's *Veterinary Drug Handbook*, it states that dogs with preexisting renal or hepatic disease should receive mitotane with caution and with more intense monitoring. A single case report of mitotane-induced hepatotoxicity exists.\textsuperscript{35} Hyperbilirubinemia has been documented in 3 dogs receiving triostane for PDH, but whether the triostane was the cause was not established. The true risk of using either drug in the presence of liver or renal issues remains unknown. Similarly, whether one drug is a better choice has not been established.

**Ease** - During the maintenance phase, mitotane is typically given 2-3 times per week. While some owners enjoy not having to give pills daily, others find it hard to remember to give the pill if it is not given every day.

Induction with mitotane seems to be scarier than initiation of triostane therapy. Recommendations for mitotane induction by some authors include intense monitoring – personally calling the owners every day starting day 3. The impression exists that it can be easier to use triostane if the owners are not very observant or hard to reach by phone or if the dog does not have obvious polyphagia. I am not sure the comfort level with triostane is deserved; cortisol decreases with both drugs over approximately equal time spans.

**Final recommendations**

Clearly, which drug to use is not a clear-cut decision. I suggest the following:

1. Talk to the owner describing both drugs, protocols, etc. so they make an informed decision.
2. If the dog has an AT and surgery is not an option, consider mitotane as first-line therapy.
3. If the dog has an AT and therapy is to be initiated to prepare for adrenalectomy, consider triostane.
4. If the dog is a diabetic or has a serious complication of HAC, consider mitotane as first-line therapy.

Note: to convert cortisol in nmol/L to µg/dl, divide the concentration in nmol/L by 27.6.

References available upon request.
Update on Canine Hypoadrenocorticism
Ellen Behrend, VMD, PhD, DACVIM
Auburn University
Auburn, AL

Recent work on canine hypoadrenocorticism has focused on trying to identify patients using more simple tests in which a diagnosis of hypoadrenocorticism should be pursued. Treatment can be expensive, but strategies are available to help with cost.

Point #1: Genetic basis has been proven in certain breeds
Certain breeds, i.e. Nova Scotia Duck Tolling retrievers (“Tollers”), Portuguese water dogs, standard poodles and bearded collies, can have a genetic component to development of hypoadrenocorticism. Knowledge of a genetic basis is important for breeders. In Standard poodles, the mode of inheritance is autosomal recessive. In Bearded collies, it is considered to be “highly heritable”.

Point #2: Addison’s disease is caused “the great pretender” for good reason
We are trained to look for hyponatremia and/or hyperkalemia to help determine if hypoadrenocorticism should be a differential diagnosis (DDX). However, atypical Addisonians have normal sodium and potassium concentrations. The presence of certain findings should make you consider whether diagnostic testing for hypoadrenocorticism should be undertaken even if sodium and potassium are normal. Hypoadrenocorticism can cause chronic GI bleeding, fresh or melena, or profuse hemorrhagic diarrhea in a crisis. If hemorrhagic gastroenteritis (HGE) is a DDX, so should Addison’s. In a dog with megaesophagus, always test for hypoadrenocorticism. Addison’s is one of the few fixable types of megaesophagus. Hypoalbuminemia for no identifiable cause (e.g. protein-losing enteropathy or nephropathy) and hypoglycemia should also prompt consideration of Addison’s. Last, Addison’s can look exactly like acute renal failure – azotemia, hyponatremia and/or hyperkalemia and inappropriately concentrated urine.

Point #3: Use of baseline cortisol for diagnosis
The only way to confirm a diagnosis of hypoadrenocorticism remains the ACTH stimulation test. However, dogs with basal cortisol concentrations >55 nmol/L (2 μg/dl) that are not receiving corticosteroids, mitotane or ketoconazole are highly unlikely to have hypoadrenocorticism; likely, the same applies to dogs receiving progestins or trilostane. On the other hand, if a basal cortisol concentration is <55 nmol/L, an ACTH stimulation test must be done to fully rule hypoadrenocorticism in or out.1,2 A cut-off of <55 nmol/L (2 μg/dl) has a sensitivity and specificity of detecting hypoadrenocorticism of 100% and 63.3%, respectively.2 A baseline will not differentiate between iatrogenic and spontaneous disease; a good history is needed to determine which is present.

Point #4: Use of sodium:potassium (Na:K) ratio for diagnosis
The Na:K ratio is evaluated often when diagnosing hypoadrenocorticism.3,5 Unfortunately it is not very specific.4 Although the lower the ratio, the higher the chance of hypoadrenocorticism1-3, of 162 dogs with a ratio <27 in one study, only 17% were Addisonians14 Thus, a low ratio should raise your suspicion for Addison’s but cannot confirm it, and the lower the ratio, the higher the suspicion should be.

Point #5: Differentiating between primary and secondary Addison’s disease
The most common form of hypoadrenocorticism is primary adrenal failure. Glucocorticoids (i.e. cortisol) alone or both glucocorticoids and mineralocorticoids (i.e. aldosterone) may be deficient with primary adrenal failure, depending on which adrenal cortical zones have been affected. Thus, primary Addison’s disease can be typical or atypical. Secondary hypoadrenocorticism is due to pituitary failure to secrete ACTH. Since ACTH has minimal effects on aldosterone secretion, ACTH deficiency causes isolated glucocorticoid insufficiency. In other words, secondary Addison’s is always atypical. It can be idiopathic or due to head trauma or neoplasia.6,7

Distinguishing primary from secondary disease in dogs with spontaneous, isolated glucocorticoid deficiency can be helpful. To differentiate primary from secondary hypoadrenocorticism, plasma endogenous ACTH (eACTH) concentration can be measured. If the disease is primary, aldosterone deficiency is likely to occur in the future, and serum electrolyte concentrations should be monitored regularly; if hypoadrenocorticism is secondary, mineralocorticoid secretion will remain normal. In primary disease, negative feedback on the pituitary is lost and eACTH concentrations will be greatly increased; secondary hypoadrenocorticism, in comparison, is by definition a lack of eACTH.

Point #6: Administration of 0.9% NaCl to a patient in crisis
For treatment of an Addisonian crisis, fluid therapy is paramount and the primary priority. Rapid correction of hyponatremia has now been recognized to lead to central nervous system dysfunction.8,9 During chronic hyponatremia, the brain adapts to prevent cerebral edema. With rapid correction of serum sodium concentration, osmotic shifts and cerebral dehydration occur, with a possible resultant pontine myelinosi and neurological signs such as disorientation, dysphagia, weakness and quadraparesis. Thus, although balanced
solutions such as Normosol-R or Lactated Ringer’s solution contain potassium, they may be the fluid of choice, with the latter possibly being the best as the sodium is the lowest. Hypertonic saline administration is contraindicated.

For treatment of an Addisonian crisis, shock doses of fluids should be given initially and then rehydration corrected over 6-24 hours depending on patient stability. Subsequently, fluid therapy should be adjusted to increase serum sodium concentration at a rate of 0.5 mEq/L/h. Frequent measurement of serum sodium concentration is important to ensure the rate of correction of hyponatremia is appropriate. Fluid type and rate can be adjusted accordingly. If hypoglycemia is present, dextrose should be added to the fluids to make a 5% solution. Response to initial therapy of hypoadrenocorticism should occur within 1-2 hours in patients suffering from hypoadrenocorticism.

**Point #7: When and how to use prednisone**

All animals beginning maintenance therapy for spontaneous hypoadrenocorticism should receive prednisone or prednisolone at a “physiological” dose (0.22 mg/kg once daily or divided BID). If a patient is receiving fludrocortisone, once a dose that maintains serum electrolyte concentrations within the reference range has been determined, the glucocorticoid can be tapered to alternate days and then discontinued to see if continued glucocorticoid therapy will be required. If the dog is lethargic, dull or unwilling to exercise or play or if clinical signs of hypocortisolism such as weakness, anorexia, vomiting and diarrhea are apparent, glucocorticoids should be reinstituted at the lowest dosage that keeps the patient free of clinical signs. In 178 dogs receiving glucocorticoid therapy long term for Addison’s, the median daily dose required was 0.2 mg/kg (range 0.02-0.7); for 5 dogs with secondary disease receiving only prednisone, the median required dose was 0.25 mg/kg (range 0.11-0.33 mg/kg).

Fludrocortisone has both glucocorticoid and mineralocorticoid activity, while DOCP has only mineralocorticoid properties. Thus, approximately 50% of dogs receiving fludrocortisone may not require concomitant glucocorticoid administration. Although some dogs on DOCP have not received glucocorticoid therapy, I do not recommend this as the patient will always be glucocorticoid deficient.

As cortisol is one of the major stress hormones, Addisonians cannot respond appropriately to stress. Stress can vary with a patient, e.g. boarding may be very stressful for some dogs but not for others, and is loosely defined, e.g. boarding, car travel, being hospitalized, etc. are all “stress”. During times of stress, glucocorticoids should be administered at 2-10 times the physiologic dose, depending on the level of the stress.

In non-Addisonian patients receiving chronic glucocorticoid therapy, every-other-day administration is recommended in order to minimize resultant adrenal atrophy. As patients with spontaneous hypoadrenocorticism already have significant adrenocortical destruction or atrophy, atrophy secondary to glucocorticoids is not a concern. Therefore, if a patient with spontaneous hypoadrenocorticism is deemed to need physiological glucocorticoid replacement therapy, the medication should be given daily to make sure the patient is never glucocorticoid deficient.

**Point #8: Mineralocorticoid replacement therapy**

Maintenance therapy for hypoadrenocorticism begins when vomiting, diarrhea, weakness, and depression have resolved. Mineralocorticoid replacement is needed only for patients that are aldosterone deficient and is available in oral or depot preparations. The initial recommended dose of fludrocortisone in dogs is 0.01-0.02 mg/kg per os daily. Dosage adjustments, if necessary, are made based on serum electrolyte concentrations. Ideally, sodium and potassium should be within reference ranges. Sodium and potassium should be monitored every 1-2 weeks after initiating therapy until a patient is stable. The daily dosage is adjusted by 0.05-0.1 mg increments. Once electrolyte concentrations have stabilized, a patient should be re-evaluated monthly for the first 3-6 months and every 3-6 months thereafter, as long as no clinical signs are apparent. In the author’s experience, however, fludrocortisone fails to normalize sodium in a proportion of patients no matter how high the dose.

In dogs, the final fludrocortisone dose varies greatly between patients; in one study, the median final dose was 0.023 mg/kg/day (range 0.008-0.75 mg/kg/day). Required doses often increase over the initial 6-18 months of therapy, possibly as a result of ongoing destruction of the adrenal cortex or changes in drug absorption and/or metabolism.

Overall, fludrocortisone therapy is clinically effective. In 33 dogs, the response to treatment was considered good to excellent in 78.8%, fair in 9.1% and poor in 12.1%. The most common side effects are polyuria and polydipsia, but polyphagia, hair loss and weight gain may be seen. Most of the adverse effects occur when prednisone and fludrocortisone are administered concurrently and resolve when glucocorticoid therapy is discontinued, but polyuria and polydipsia can be seen with fludrocortisone alone. Although fasting hypercholesterolemia and hypertriglyceridemia have been noted with fludrocortisone administration, the significance of these changes remains unknown.

Recently, a new FDA-approved form of desoxycorticosterone pivalate (DOCP) became available (Zycortal; Dechra). Percorten (Elanco) has been an FDA-approved veterinary product for years. For either preparation, the starting dose is 2.2 mg/kg q 25 d. Although Percorten is labeled to give IM, the SQ route can be and typically is used. Zycortal is labeled for SQ use. Although not all dogs need that high a dose, starting at 2.2 mg/kg is safe.
In order to decrease cost, I try to lower the dose. Many dogs do not need the full label dose. The package insert for Zycortal gives instructions for a single dose adjustment while Percorten does not. With DOCP, I start with a 28-day interval and a dose of 2.2 mg/kg. Electrolytes should be measured on days 14 and 28, and if within the reference range on day 28, the DOCP dose can be decreased 10%. The same procedure can be repeated monthly until a dose is found that no longer maintains serum sodium and potassium concentrations in the reference range for the full 28 days, and then the lowest DOCP dose that lasted 28 days can be used.

An alternative is to administer 2.2 mg/kg DOCP and lengthen the interval by 3 days with each injection until the interval is too long, i.e. sodium and potassium concentrations are no longer normal when the injection is due, and then use the longest interval during which serum electrolyte concentrations were in the reference range. However, it is probably harder for owners to remember the injections on a long interval, and I prefer lowering the dose and maintaining a 28-day interval instead.

A small percentage of dogs, however, require either injections more frequently than every 25 days or more than 2.2 mg/kg to keep the interval 25 days or longer. If the patient is hyponatremic and/or hyperkalemic day 14, the next dose should be increased by 10%. If the electrolytes are normal day 14 but abnormal day 28, the interval between injections should be decreased by 2 days or the dose increased 10%. In dogs that require DOCP more frequently than every 28 days, clinical signs of Addison's disease may recur before the recheck on day 28. If return of the hypoadrenal state is suspected, the dog should be seen immediately and serum electrolytes measured. If hyponatremia and hyperkalemia are documented, the DOCP injection can be given at that time. If the dosing interval is shortened, the timing of monitoring should be changed accordingly for the next treatment period. Two rechecks should be performed during each dosing interval until good control of the Addison’s disease on the last day of the dosing interval is demonstrated.

DOCP is a highly efficacious treatment for hypoadrenocorticism with minimal side effects. Adverse effects reported include depression, polyuria, polydipsia, anorexia, skin and coat changes, diarrhea, vomiting, weakness, weight loss, incontinence, and pain on injection, but all are uncommon. Some of the adverse effects, e.g. polyuria/polydipsia, are more likely due to concurrent glucocorticoid administration than to DOCP itself. Treatment failures occur rarely.

Any recheck, whether monitoring fludrocortisone or DOCP therapy, should include a full physical exam, complete history and determination of BUN concentration as well as measurement of electrolytes. If at any recheck the serum electrolyte concentrations are within the reference range but problems, sometimes quite vague exist, such as anorexia, vomiting, diarrhea or unwillingness to play, glucocorticoid deficiency is the likely cause; the prednisone dose should be adjusted accordingly. An elevated BUN concentration can be a sign of dehydration due to insufficient therapy.

Advantages and disadvantages exist with the use of either fludrocortisone or DOCP. I prefer using DOCP. For fludrocortisone, the major advantage is the ease of diagnosing and adjusting an incorrect dosage as daily administration is easily altered. Daily therapy also constantly reminds owners that their pet is afflicted with a life-threatening disease and needs constant therapy and monitoring. Lastly, the medication is readily available at most pharmacies. However, fludrocortisone can be quite expensive despite the availability of a generic product, especially if higher doses are required; some patients may not be adequately controlled and side effects may occur, even when used without concomitant glucocorticoid therapy. If expense, existence of side effects or lack of efficacy necessitate discontinuation of fludrocortisone, DOCP becomes the only choice. For DOCP, advantages include a low incidence of adverse effects, less common treatment failures than with fludrocortisone and need for infrequent administration. A subcutaneous injection can be given by owners if trained properly, but great care should be taken in selection of owners for this task. Missing an injection or giving one inappropriately and not realizing the mistake could be fatal for the patient. Apparent failures may be due to owner difficulty with providing injections; improper technique should always be ruled out. If a patient truly does not respond to DOCP, fludrocortisone therapy should be instituted.

References available upon request from the author.