Adrenal Tumors:

Adrenal tumors in veterinary patients can be challenging both to diagnose and to treat. An additional conundrum for the clinician is deciding when to treat and when not to treat, especially when tumors are diagnosed incidentally. Perhaps most commonly, the diagnosis of an adrenal tumor occurs when the veterinary practitioner is presented with a dog exhibiting symptoms consistent with hyperadrenocorticism (HAC or Cushing’s Syndrome). The observed HAC findings are often the result of excessive cortisol production either from the over production of ACTH in the pituitary gland or autonomous adrenal gland production.

Approximately 80-85% of cases of HAC are a result of excessive secretion of ACTH from pituitary microadenomas; also known as pituitary dependent hyperadrenocorticism (PDH). This excessive ACTH secretion causes bilateral adrenal cortical hyperplasia and leads to cortisol excess. These cases generally respond well to medical treatment, and therefore, surgery is rarely indicated. The remaining 15-20% of HAC cases result from functional adrenocortical tumors. Functional adrenocortical tumors, as will be discussed in detail below, tend to be poorly responsive to medical management long term and are most amenable to surgical excision. As such, being able to differentiate these etiologies of HAC will determine the best treatment course to follow.

In the absence of HAC, adrenal tumors may be diagnosed incidentally, or based on other clinical signs such as those associated with excessive catecholamine release from adrenomedullary tumors (pheochromocytoma), or excessive androgen and steroid intermediate production associated with “atypical” adrenocortical tumors. Similar adrenocortical tumors associated with HAC, pheochromocytomas and atypical adrenocortical tumors are most amenable to surgery.

Because pituitary dependent HAC is treated in a very different way relative to adrenal cortical and medullary tumors, it is paramount for the clinician to understand the diagnostic steps and differentiating tests involved in the working up of suspected adrenal related diseases.

Diagnosing Adrenal Tumors: In patients presenting for clinical signs and laboratory findings consistent with Cushing’s disease, an abdominal ultrasound is often the most rewarding first diagnostic test to either rule in or out a functional adrenal tumor, PDH or non-adrenal associated disease processes. An increasingly common means of diagnosing adrenal neoplasia also occurs during abdominal ultrasound for clinical signs unrelated to potential adrenal disease.

Regardless of whether overt clinical signs attributable to adrenal related disease are present at the time of diagnosis, once an adrenal mass has been identified via imaging (abdominal ultrasound or less commonly radiography, CT, or MRI), it is important to perform basic adrenal testing and ideally consult with an internal medicine specialist prior to definitive treatment. This is important due to the fact that functional adrenal tumors, even in the absence of overt clinical signs at the time of diagnosis, can have systemic clinical implications in the intra- and postoperative setting. Empirical support for tumor type and functionality through adrenal specific tests can help predict potential adverse events allowing for preemptive perioperative planning and medical management to minimize surgery related complications. Even in cases where the underlying histogenesis is known, pre-treatment functional testing allows establishment of a baseline for subsequent testing and monitoring.

First and foremost, obtaining a thorough medical history and performing a complete physical exam often gives the clinician the most insight into the type of adrenal tumor that is present. For example, a dog presenting with recurrent skin infections, PU/PD/polyphagia and weight gain
supports the diagnosis of a cortisol secreting functional adrenal cortical tumor. In contrast, a dog with a history of intermittent episodes of collapse, periodic anxiety, with or without evidence of retinal hemorrhage or detachment would suggest a functional adrenal medullary tumor. Once history and physical exam findings are evaluated, ancillary diagnostic tests are performed to further support the preliminary diagnosis or to aid diagnosis in cases where clinical history and exam findings are equivocal.

Adrenal function tests include ACTH stimulation test, low and high dose dexamethasone suppression tests, endogenous plasma ACTH concentration, and urine cortisol:creatinine ratio.

The ACTH stimulation test, which measures the response of the adrenal glands to maximal ACTH stimulation, has an intermediate sensitivity and specificity of roughly 60% and 85%, respectively. This test has minimal utility in the diagnosis of Cushing's disease, but is useful in monitoring response to treatment (i.e. surgery or pre-surgery medical management) and to differentiate iatrogenic Cushing's disease from naturally occurring hyperadrenocortism.

The low dose dexamethasone suppression (LDDS) test is the current recommended test for supporting the diagnosis of HAC and further differentiation of PTH from a functional adrenal tumor. The LDDS test is performed by first obtaining a baseline serum sample followed by injecting 0.01mg/kg dexamethasone IV. Subsequent blood samples are then obtained at 4 and 8 hours post dexamethasone administration. Suppression of cortisol in response to administration of low dose dexamethasone rules out the presence of a cortisol-secreting adrenal tumor.

Measure of endogenous ACTH concentration in dogs with a functional adrenocortical tumor has little value in the diagnosis of HAC alone. However, when used in combination with tests such as the LDDS test, endogenous ACTH concentration can help differentiate PDH from a functional adrenal tumor. The expected ACTH concentration in dogs with a functional adrenal tumor is low due to negative feedback through the hypothalamic-pituitary-adrenal axis. A normal to elevated ACTH in the face of HAC is suggestive of PTH or possibly an incorrect diagnosis of HAC.

The urine cortisol:creatinine ratio (UCCR) is considered an alternative test that can be used for those patients who become excessively stressed in the hospital setting or if obtaining a blood sample from the patient is problematic. The UCCR test is performed on a free catch urine sample collected at home by the owner. This test is very sensitive but has a relatively poor specificity. Thus, a negative UCCR test is good at ruling out HAC, especially in patients who are not PU/PD or if they have a concentrated USG. But, because of the fact that the UCCR test has a low specificity, a positive test cannot exclude other causes of urine cortisol elevations, and is therefore not accurate at confirming HAC.

The above tests are used alone or in combination as discussed primarily to confirm the diagnosis of a functional adrenocortical tumor. If such tests do not support the diagnosis of HAC, then potential rule outs for the observed adrenal tumor include atypical Cushing’s disease, a pheochromocytoma, or a non-functional adrenal tumor. Atypical Cushing’s disease is defined as HAC caused by overproduction of adrenal steroids, typically androgens or steroid intermediates other than cortisol. In cases of atypical HAC, cortisol concentrations can be low or within normal reference ranges. For a suspected case of atypical HAC, the practitioner can utilize the University of Tennessee’s Endocrinology laboratory. Steroid hormone profiles are indicated in cases where other routine adrenal function tests fail to support “typical” (cortisol induced) HAC, yet the dog still exhibits signs of Cushing’s syndrome. Such steroid hormone profiles are performed in a similar fashion to the ACTH stimulation test—samples are obtained pre- and 1 hour post ACTH stimulation.

Importantly, human patients with atypical HAC show similar risk for perioperative thromboembolic complications despite having normal cortisol levels. A similar risk is likely the case for dogs with atypical HAC. Therefore, diagnosis and treatment for HAC (see below) is warranted for patients with atypical HAC in a similar fashion as those with the more typical hypercortisolemia.
Diagnosis of a pheochromocytoma is typically based on the presence of consistent physical exam and clinical history findings as discussed above in addition to ruling out HAC with functional adrenal testing. In human medicine, urine catecholamine and metabolite concentrations are used; however, these tests are rarely used in veterinary medicine due to the difficulty of sample handling (catecholamines and their intermediates have short half lives and are volatile), cost, and lack of validation (sensitivity and specificity) of such tests.

Finally, if patients are truly asymptomatic and fail to show evidence of HAC, “atypical Cushing’s disease”, or pheochromocytoma, then the diagnosis by exclusion is a non-functional adrenal tumor, also commonly referred to as an “incidentaloma”.

Normal Adrenal Gland Anatomy and Physiology: The adrenal glands are located in the retroperitoneal space closely associated with the vena cava and aorta at the level immediately cranial to the kidneys. The left adrenal gland is juxtaposed to the to the abdominal aorta medially and the left renal artery caudally at roughly the level of the transverse process of the 2nd lumbar vertebra. The right adrenal gland is situated more cranial to the left at the level of the 13th thoracic vertebra and adhered to the lateral aspect of the abdominal vena cava. Grossly, both adrenal glands are beige in appearance but are often obscured by the surrounding retroperitoneal fat and overlying phrenicoabdominal vein. If difficult to directly visualize due to the surrounding adipose tissue and phrenicoabdominal vein, the adrenal gland size and shape can easily be assessed by palpation. The normal adrenal parenchyma is firm and lobular, and thus easily differentiated from surrounding fat, vessels, and musculature.

The blood supply to each adrenal gland is complex, arising from numerous branches of the phrenicoabdominal, renal, and cranial abdominal arteries as well as directly from the abdominal aorta. After supplying each gland with a rich blood supply, blood leaves the left adrenal gland via a single adrenal vein into the left renal vein, while the right adrenal gland drains directly into the abdominal vena cava. The normal adrenal gland is composed of a highly vascular adrenal capsule, a cortical region, and a medulla. The cortical region, responsible for production of corticosteroids (mineralocorticoids, glucocorticoids, and androgens), is further divided into 3 functional layers. From superficial to deep, these layers include the zona glomerulosa, zona fasciculata, and zona reticularis. The zona glomerulosa is the primary source of mineralocorticoids (aldosterone) production necessary for salt and fluid regulation within the body. Release of aldosterone is primarily regulated by the renin-angiotensin system and blood potassium concentrations. When secreted, aldosterone promotes sodium, chloride and water reabsorption and potassium excretion. This latter property becomes importantly apparent in patients with aldosterone secreting tumors (“Conn’s syndrome”) where marked hypokalemia results causing sodium and fluid retention and potassium wasting. Cells within the zona glomerulosa are incapable of producing glucocorticoids and androgens due to the lack of 17α-hydroxylase, which is required for the conversion of cholesterol to cortisol and androgens, but not aldosterone.

The zona fasciculata and zona reticularis do contain 17α-hydroxylase, and therefore are capable of synthesizing cortisol and androgens under the direction ACTH and cortical androgen-stimulating hormone, respectively. The zona fasciculata makes up roughly 75% of the adrenal cortical mass and is the primary site of glucocorticoid production. A small amount of adrenal androgens are also produced in the zona fasciculata. The zona reticularis, the deep layer of the cortex, is the primary site of adrenal androgen secretion but is also responsible for the production of small amounts of estrogens and some glucocorticoids. Glucocorticoids are required for homeostasis of many biochemical processes including metabolism and inflammation. Cortisol mobilizes fatty acids from adipose tissue and amino acids from muscle and other body tissues and facilitates the conversion of these amino acids into glucose within the liver. Cortisol also contains marked anti-inflammatory properties through the inhibition of the arachadonic acid metabolism into inflammatory mediators, stabilizing of lysosomal membranes, decreasing
capillary permeability and inflammatory cell extravasation, and through inhibition of lymphocyte effector function.

Aldosterone and cortisol are regulated by independent mechanisms. For example, angiotensin II specifically induces hypertrophy of the zona glomerulosa and increases the output of aldosterone, but has no effect on cortisol secretion. Similarly, ACTH, which causes hypertrophy of the zona fasciculata and zona reticularis for the production of cortisol, has no effect on aldosterone secretion.

Deep to the adrenal cortex lies the adrenal medulla. The adrenal medulla, derived from neuroectoderm, is essentially a sympathetic ganglion responsible for the synthesis and secretion of catecholamines, primarily norepinephrine and to a lesser extent epinephrine. Norepinephrine and epinephrine act through adrenergic receptors throughout the body, most notably, $\alpha_1$, $\alpha_2$, $\beta_1$ and $\beta_2$ receptors. The dominant effect of these catecholamines is the very abundant $\alpha_1$ receptors on vascular smooth muscle resulting in peripheral vasoconstriction and increases in blood pressure via increased peripheral vascular resistance. The vasodilatory effect of norepinephrine and epinephrine through $\beta$ receptors is often superseded by the vasopressor effect of $\alpha_1$ receptors due to the sheer number of $\alpha_1$ receptors on vascular smooth muscle compared to $\beta$ receptors.

**Adrenal Tumor Classification and Pathophysiology:** As briefly mentioned above, adrenal tumors can arise from either the medulla or cortex. Adrenal cortical tumors can be defined as either benign (adenoma) or malignant (adenocarcinoma). The majority of adrenal cortical tumors are adenocarcinomas. Similarly, adrenal medullary tumors can also be classified as either benign or malignant. The majority of tumors of the adrenal medulla are considered benign in the sense they are unlikely to metastasize. Regardless of whether adrenal tumors are classified as histologically benign or malignant, any adrenal tumor has the potential to be problematic. Benign and malignant adrenal tumors alike can be locally aggressive/invasive and can have detrimental systemic effects through the secretion of active hormones.

Tumors involving the adrenal cortex are simply referred to as adrenal cortical adenoma or adrenal cortical adenocarcinoma. These tumors, regardless of their malignancy classification (adenoma versus adenocarcinoma) can synthesize and secrete various corticosteroids including their intermediates. The most common secretory product arising from adrenal cortical tumors is cortisol; with the resulting clinical signs being consistent with HAC also referred to as “typical” Cushing’s syndrome. Such clinical signs include PU/PD, hypertension through aldosterone-like effects, immune suppression as often manifested by UTI and pyoderma, muscle loss and redistribution of body fat stores, and dermatopathy. Additionally, HAC is associated with coagulopathies often resulting in exuberant clotting. The hypercoagulability secondary to Cushing’s syndrome is hypothesized to be the result of hyperactivation of vascular endothelial cells, increases in clotting factor activation, and a decrease in fibrinolysis. Anti-thrombin wasting through the kidneys is an additional mechanism that may contribute to the hypercoagulable state seen in Cushing’s syndrome.

In addition to cortisol secreting tumors, some tumors of the adrenal cortex produce and secrete primarily aldosterone, androgens, or various steroid intermediates in the absence of cortisol oversecretion. Tumors that produce androgens or various steroid intermediates results in a syndrome often referred to as “Atypical Cushing’s Syndrome”. In cases of atypical HAC, cortisol concentrations can be low or within normal reference ranges making the specific diagnosis of a functional adrenal tumor difficult based on traditional testing as discussed below. Importantly, even in the absence of cortisol over-production, patients with atypical Cushing’s disease often display overlapping clinical signs of “typical” Cushing’s disease and likely share the same perioperative risks such as hypercoagulation, delayed healing, etc. Functional tumors of the zona glomerulosa within the adrenal cortex produce excessive amounts of aldosterone. “Conn’s Syndrome” is the result of primary hyperaldosteronemia, and is characterized by sodium retention, relative hypotension/hypervolemia, and hypokalemia.
Clinical manifestations of hyperaldosteronemia are often related to hypokalemia. These signs include muscle weakness, ventroflexion of the neck, and constipation.

An important differential for an aldosterone secreting adrenal tumor is secondary hyperaldosteronemia which can result from chronic “low output states” such as low output heart failure. Secondary hyperaldosteronemia can also be caused by an “apparent mineralocorticoid excess (AME)” which can occur in patients deficient in 11β-hydroxysteroid dehydrogenase activity. This enzyme is responsible for inhibiting cortisol from binding and activating aldosterone receptors. Interestingly, ingestion of excessive amount of licorice, which contains the 11β-hydroxysteroid dehydrogenase inhibitor, glycyrrhetinic acid, can result in AME and clinical signs consistent with hyperaldosteronemia (hypertension, hypokalemia, and muscle weakness).

Tumors involving the adrenal medulla are referred to as pheochromocytomas, which belong to the neuroendocrine class of tumors. These tumors arise from the catecholamine producing chromaffin cells within the medulla and tend to be locally invasive but rarely metastasize. The primary catecholamine produced by these tumors is norepinephrine, but lesser amounts of epinephrine is also produced by these tumors. The clinical signs associated with pheochromocytoma, if functional, are often episodic and can mimic that of sympathetic nervous system stimulation—tachycardia, hypertension, retinal hemorrhage, etc., mainly through their stimulation of vascular receptors as discussed above. With that said, many dogs with pheochromocytoma lack overt clinical signs. In one retrospective study looking at dogs histopathologically diagnosed as having a pheochromocytoma, greater than 50 percent were asymptomatic for their lesions, and only 35 percent of these animals had signs consistent with overproduction of catecholamines.

**Treatment of Adrenal Tumors:** Unlike the treatment of PDH in which medical therapy is often successful, the treatment of choice for most adrenal tumors, especially functional adrenal tumors, is surgical removal. Small, incidentalomas occasionally warrant active surveillance, but subsequent surgery is indicated if the mass continues to grow, shows signs of invasion, or if clinical signs develop. With appropriate surgical management, assuming the patient survives the perioperative period, the majority of animals experience long-term disease free intervals and often cure. However, perioperative mortality associated with adrenalectomy can approach 25% if preoperative precautions and proper medical management are not employed in the perioperative setting.

Factors complicating surgical treatment of adrenal tumors include vascular invasion and tumor functionality. Earlier studies suggested that vascular invasion was not a negative prognostic factor; however, a more recent study did show that vascular invasion was in fact a negative prognostic factor for short-term survival. This more recent study also showed that patients with pheochromocytoma were at an increased risk for perioperative death compared to those patients being treated for adrenal cortical adenoma or adenocarcinoma. Additionally, tumor size has been directly correlated with malignant potential in people, and is likely the case in canine patients. For this reason, it is recommended that if caught early, very close monitory or pre-emptive surgery be performed prior to the tumor becoming invasive, highly functional, or excessively large. In humans, non-functional tumors <4cm are usually monitored rather than surgically excised. A similar approach in dogs is likely warranted, but the size cut-off is less well established. In general, in the dog, monitoring is recommended for non-functional lesions <2cm, surgery or monitoring is recommended for lesions 2-4cm, and surgery is recommended for tumors >4cm. Again, any tumor that is suspected to be functional or invasive, surgical excision is the primary recommendation.

If a functional adrenal cortical tumor has been diagnosed (either typical or atypical with regards to cortisol secretion), it is imperative to manage the HAC prior to surgery. The current treatment of choice for pre-operative management of HAC is with trilostane. Mitotane (Lysodren), which is cytotoxic to adrenal cortical tissue, has been shown to be less effective at alleviating Cushinoid signs and is associated with more side effects compared to trilostane. Trilostane is a competitive
inhibitor of 3-β-hydroxysteroid dehydrogenase, which is responsible for the conversion of pregnenolone to several intermediates and ultimately cortisol. Serum aldosterone concentrations are also decreased during trilostane therapy, however, and this effect is often inconsequential except in rare cases where iatrogenic hypoadrenocorticism can occur.

Trilostane is initiated at 1-2mg/kg q12h initially for 3-4 weeks before surgery in order to reverse many of the metabolic derangements associated with HAC. After 10-14 days of therapy, an ACTH stimulation test and serum electrolytes should be measured 4-6 hours after trilostane administration. The goal of therapy is to obtain a post ACTH stimulation cortisol between 2-5ug/dL in addition to clinical improvement (reduction in PU/PD and polyphagia), prior to performing surgery. Mitotane can be considered at an induction dose of 50mg/kg divided over 3 daily doses for 10-14 days, or until similar ACTH stimulation criteria and improvement in clinical signs as mentioned for trilostane is achieved.

Assuming improvement in clinical HAC is achieved with either trilostane or mitotane, the following day of surgery therapeutics are recommended. Coagulation profiles, blood type, and anti-thrombin activity should be assessed prior to surgery. At induction, dexamethasone is administered at 0.1mg/kg IV and heparinized fresh frozen plasma (35U/kg of heparin added to 10mL/kg of canine plasma) is administered as a CRI during surgery and following over 3-4 hours. Ideally, heparin dose should be adjusted accordingly such that aPTT is increased to 1.5x the aPTT baseline obtained prior to heparinized plasma transfusion. Following surgery, frequent walks or at a minimum repositioning should be performed every 1-2 hours to promote blood flow and to minimize clot formation. Dexamethasone is administered at 0.05mg/kg IV immediately post-op then every 8 hours until transition to oral prednisone at 0.25mg/kg every 12 hours can be performed. Prior to starting prednisone, ideally within 24 hours following surgery, a recheck ACTH stimulation is performed. Prednisone is then tapered over the subsequent 4-6 weeks as tolerated. Some references recommend continuation of heparin therapy for 2 weeks following surgery. However, due to risk associated with at home use of heparin and lack of strong evidence supporting extended use of heparin following adrenalectomy, this is not currently part of the recommendations utilized at Seattle Veterinary Specialists for removal of adrenal cortical tumors.

Perioperative treatment for suspected pheochromocytoma is quite different. Additionally, one of the greatest challenges to the surgical management of pheochromocytoma lies not in the hands of the surgeon, but rather the anesthetist. Patients suspected of having a pheochromocytoma are treated with an β-antagonist (phenoxybenzamine or prazosin) prior to surgery. A minimum of 2 weeks of phenoxybenzamine starting at 0.5mg/kg q12h then increased every 2-3 days to effect (signs of hypotension, lethargy, weakness, etc.) or to a maximum of 2.5 mg/kg q12h, whichever is achieved first. Alternatively, prazosin is administered at 0.5mg/kg PO BID. Based on the shorter half-life and time to effect of prazosin following adrenalectomy, this is not currently part of the recommendations utilized at Seattle Veterinary Specialists for removal of adrenal cortical tumors.

In a recent report retrospectively comparing dogs receiving phenoxybenzamine 2 weeks prior to pheochromocytoma excision had a significantly lower perioperative mortality rate (13%) compared to those dogs not receiving pre-operative β-blockade (48%). Intra-operative hypertension is controlled with administration of the short acting injectable β-antagonist phentolamine at 0.1mg/kg IV loading dose followed by 1-2ug/kg/min. If surges of intra-operative hypertension persist despite the addition of phentolamine, a direct vasodilator such as nitroprusside (0.1-0.8ug/kg/min) is considered. Treatment with β-blockers is less commonly indicated, and should never be used in the absence of co-administration with β-blockers. Administration of β-blockers alone can result in excessive hypertension by removal of the antagonistic β effects on vascular smooth muscle. In conjunction with β blockade, β-blockers can reduce the incidence of severe tachyarrhythmias. In most cases however, lidocaine 2-4mg/kg IV bolus followed by 50-100ug/kg/min CRI is preferred over β-blockers in the treatment of intra-operative ventricular tachyarrhythmias, polymorphic complexes or R-on-T phenomenon.
Fortunately, the majority cardiovascular abnormalities subside shortly after tumor removal, and therefore, in most cases IV catecholamine antagonists and anti-arythmics can be discontinued shortly after the procedure.

In cases where routine pre-operative diagnostic tests fail to differentiate an adrenal cortical tumor from a pheochromocytoma, a combination of the above perioperative medical strategies is employed with the exception of pre-operative trilostane or mitotane therapy. For example, prior to surgery, prazosin or phenoxybenzamine is administered for 2 weeks and a pre-operative coagulation profile, blood typing, and ACTH stimulation test is performed. Heparinized fresh frozen plasma is administered at 10mL/kg plasma and 35U/kg heparin is administered intraoperatively over 3-4 hours. Immediately prior to surgery, dexamethasone is administered at 0.5mg/kg IV, then every 8 hours until transition to oral prednisone can be made. A post-operative ACTH stimulation test is performed prior to transition to prednisone, then the prednisone is tapered as tolerated over the subsequent 4-6 weeks. Frequent walks and repositioning is performed every 1-2 hours.

Using these protocols, along with close intra and post-operative monitoring, the perioperative mortality for adrenalectomy is likely less than 10%.

**Prognosis and Adjuvant Therapies:**
As discussed above, the prognosis associated with adrenal tumors managed successfully with surgery is good to excellent. In cases where metastasis is present at the time of diagnosis or develops following surgical excision of the primary tumor, chemotherapy with or without trilostane OR mitotane is considered. In general, both adrenal cortical tumors and pheochromocytomas are inherently chemoresistant. No studies in dogs have objectively looked at efficacy of traditional cytotoxic chemotherapy such as doxorubicin in dogs. In people with metastatic adrenal tumors show less than a 30% objective tumor response even when multi-agent maximum tolerated chemotherapy dosing schedules are employed. Mitotane and trilostane have been used with some success for the management of metastatic functional adrenal cortical tumors but responses and remissions, if achieved, are often short lived. Combinations of cytotoxic chemotherapy with concurrent mitotane administration has resulted in the highest percentages (~50%) of responders in metastatic human adrenocortical carcinoma, but long term control remained poor. Based on the lack of effective adjuvant strategies, it should be clear that the goal of therapy is relatively early intervention prior to the development of metastatic or non-resectable tumors.