Endocrinology

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This course will consist of some formal lectures and case-based presentations covering the most commonly diagnosed endocrine disorders. After an initial presentation on principles of diagnosing endocrine disease, the course will focus on the interpretation of tests for thyroid and adrenal gland dysfunction. The role of endocrine diseases in common presenting problems will be highlighted and there will be a focus on newer therapeutic regimens for hyperadrenocorticism and feline diabetes mellitus.
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Introduction on principles of interpreting endocrine results

Problems of interpretation
- Diagnosis of disorder based on abnormal endocrine results
- Dismissing a disorder because endocrine results are not abnormal
- Confusion, frustration, irritation

Reasons for the difficulties
- Multiple/variable clinical signs
  - Non-specific
  - Few pathognomonic
  - Iatrogenic versus natural
- Hormone analyses
  - There is no perfect test
  - Imperfections differ
  - Most are relatively expensive
  - Many must be assayed by commercial laboratories
  - Assay methodology may be important

Principles of interpretation
- Know the frequency with which the disorder occurs
  - Data on incidence increasing
  - Defined by
    - Your population
    - Breed type
    - Preventive measures/longevity/finances
    - Geographical location etc.

Dogs: 10% of all medical illness
- Common
  - diabetes mellitus
  - hyperadrenocorticism
  - hypothyroidism
  - hypoadrenocorticism
- Uncommon - rare
  - diabetes insipidus
  - insulinoma
  - parathyroid disease
  - hyperthyroidism
  - acromegaly
  - dwarfism
Cats: prevalence > 0.5 %
- Common
  - diabetes mellitus (1916)
  - Hyperthyroidism (1979)
- Uncommon – rare
  - hyperaldosteronism
  - acromegaly
  - parathyroid disease
  - hyperadrenocorticism
  - hypoadrenocorticism
  - phaeochromocytoma
  - hypothyroidism
  - dwarfism
  - diabetes insipidus
  - insulinoma

Endocrine diseases are important
- In their own right as distinct clinical entities
- Often a differential of common presenting complaints
  - If common may need to be ruled in/out as investigation proceeds
  - If less common or rare, other diseases should be ruled in/out first
- Multiple endocrine disorders together
  - Polyglandular autoimmune disease
  - Multiple endocrine neoplasia (MEN syndromes)

Principles of interpretation
- Understand the limitations of hormone measurements
  - Low = underactivity
  - High = overactivity
- Basal hormones
- Concurrent analyses
- Dynamic function tests

Basal hormone analyses
- Some have well defined reference ranges
  - Low or high values abnormal
- Some cannot be reliably interpreted
  - Overlap of normal/abnormal range
- Effect of age/sex/nutrition/breed
- Circadian rhythms/hormone fluctuations
- Effect of other illnesses
- Effect of drug therapy
Concurrent analyses
- Hormone concentration dependent on another factor
- Cannot be interpreted in isolation
- Only possible to interpret when measured concurrently

Dynamic function tests
- Rely on stimulation/suppression with multiple analyses over time
  - Suppression for overproduction
  - Stimulation for underproduction
- May be confirmatory
- May be useful in distinguishing abnormality
- Many factors affect test results
- Variety of protocols

Principles of interpretation
- Appraise your laboratory
- Methodology
- Validation
- Sample artefacts and handling
- Type of interpretation

Methodology
- Radioimmunoassay (RIA)
- Immunoradiometric (IRMA) assay
- Non-isotopic
- ELISA
- Chemiluminescent

Radioimmunoassay
- Antibodies specific to hormone
- Radio-labelled hormone
- Competitive binding
- Measurement of minute circulating concentrations
- Extremely specific for hormones under test
- ELISA/Chemiluminescent
- Must be correlated to RIA
  - Expensive
  - Non-isotopic
  - Routine commercial automated use

Type of sample
- Serum/plasma
- Care with plasma with RIA
- Some hormones require specific anticoagulants

- Tube type
  - Glass
  - Plastic/siliconized

Special considerations
- Proteolysis
  - Degradation after sample obtained
  - Proteolytic enzyme inhibitors (aprotinin)
  - Freezing
- Haemolysis/lipaemia
  - Non RIA methods
- Interfering substances
  - Antibodies generated during disease
  - Hormones administered as treatment

Principles of interpretation
- Acknowledge the importance of test performance
  - Sensitivity
  - Specificity
  - Positive predictive value
  - Negative predictive value

Principles of interpretation
- Implement a policy to increase prevalence
  - Test likely cases
  - Optimise the circumstances avoiding confounding factors

Select
- Correct signalment for disease
  - Species/age/sex/breed
- Appropriate historical/clinical features
- Supportive routine clinicopathological abnormalities
  - Haematology
  - Biochemistry
  - Urinalysis
  - And other routine diagnostic tests e.g. dynamic imaging

Select
- Appropriate hormone analyses
- Methodology
- Species specific
- Validation
- Reference intervals
• Type of sample
• Protocol for dynamic function testing

Avoid
• Those with abnormalities attributable to another disease
• Those on treatment
• Those with another endocrine disorder until stable
• Principles of interpretation

Remember the reason for performing the test
• What question were you asking

Principles of interpretation
• Sometimes diagnosing endocrine disease is a ‘guess’
  o But it should be a ‘best guess’

Principles of interpretation
• Never forget your patient
• The animal tells you what test to select and how to interpret
• The laboratory provide you with numbers
Testing for thyroid disease

As for most endocrine disorders, diagnosing thyroid disease relies on appropriate historical and clinical features and demonstration of supportive clinicopathological changes prior to undertaking specific hormonal investigations.

Feline hyperthyroidism

A variety of haematological and biochemical changes are reported for hyperthyroidism. However, most are of limited diagnostic value with the exception of elevations in the activities of the liver enzymes. The degree of their elevation is correlated with the degree of thyroid hormone excess and hyperthyroidism is generally regarded as the most common cause of liver enzyme abnormalities in the older cat.

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>% of cases</th>
<th>Cause and significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild erythrocytosis, macrocytosis</td>
<td>40-50</td>
<td>Thyroid hormone-mediated beta-adrenergic stimulation of erythroid bone marrow, increased production of erythropoietin. Not clinically significant.</td>
</tr>
<tr>
<td>Leucocytosis, neutrophilia lymphopenia, eosinopenia</td>
<td>20</td>
<td>Stress leucogram common in sick cats.</td>
</tr>
<tr>
<td>Elevated ALT, AST, ALP, LDH</td>
<td>90</td>
<td>Hepatic hypoxia, congestion, lipidosis, direct toxic effects of thyroid hormones on liver, increased bone metabolism (ALP). Most frequent finding in hyperthyroid cats, parallels increase in thyroid hormones.</td>
</tr>
<tr>
<td>Azotaemia</td>
<td>20-30</td>
<td>Decreased renal perfusion due to hyperthyroidism-induced reduced cardiac output, increased protein catabolism (urea). Careful evaluation necessary given protective effect on renal function.</td>
</tr>
<tr>
<td>Hyperphosphataemia</td>
<td>35-45</td>
<td>Altered bone metabolism so often elevated without azotaemia.</td>
</tr>
<tr>
<td>Mild hyperglycaemia</td>
<td>5</td>
<td>Stress, thyroid-hormone induced insulin resistance. Not clinically significant.</td>
</tr>
</tbody>
</table>

Routine clinicopathological abnormalities associated with hyperthyroidism
**Thyroid function tests**

The diagnosis of hyperthyroidism is confirmed by the demonstration of increased thyroidal radioisotope uptake or circulating concentrations of the thyroid hormones.

**Total thyroxine:** Its measurement is extremely reliable in identifying cats with hyperthyroidism. It is elevated in over 90% of hyperthyroid cats and is never elevated in euthyroid animals (100% specific). Approximately 10% of hyperthyroid cats have values within the reference range as a result of thyroid hormone fluctuation or the suppressive effects of concurrent non-thyroidal illness (NTI). Total T₄ fluctuation or suppression is of limited significance if total T₄ elevation is marked, but in mildly affected animals a marginally elevated total T₄ can descend into the reference range. As non-thyroidal illness has a suppressive effect on total T₄ concentrations in euthyroid cats, concurrent hyperthyroidism should always be suspected in severely ill cats with total T₄ concentrations in the mid to high end of the reference range. If concurrent non-thyroidal illness is not present and a mid to high reference range total T₄ value is obtained in an animal with suspected hyperthyroidism, further diagnostic tests should be considered or a T₄ measurement should be repeated some weeks later.

**Free thyroxine concentration:** Basal free T₄ measurement is a more sensitive diagnostic test for hyperthyroidism and over 98% of affected animals have elevated values. However, free T₄ concentrations must be measured by the more expensive methods of equilibrium dialysis or ultrafiltration. More importantly however is the fact that free T₄ concentrations are elevated in up to between 6 and 20% of euthyroid cats with NTI. As a consequence it is not recommended as a first line diagnostic test for hyperthyroidism. If a total T₄ concentration is within the mid to high reference range and there remains a high index of suspicion for hyperthyroidism, free T₄ should be measured in the same sample. A high value will confirm hyperthyroidism. By contrast in euthyroid cats with non-thyroidal illness and high free T₄ concentration, total T₄ values are usually suppressed to the lower half of the reference range.

**Canine thyrotropin:** In human patients, measurement of circulating TSH concentrations provides a reliable indication of thyroid status in most cases. A species specific assay is not yet available for cats. However, many researchers have attempted to use the canine assay, although controversy surrounds its ability to measure feline TSH appropriately. A major
problem with the assay is its poor sensitivity and inability to distinguish normal from suppressed values. In almost all studies thus far completed, hyperthyroid cats have values at or below the limit of detection of the assay. However, many healthy cats and those with NTI may have similar values. Interpretation of TSH measurement is more reliable if a mid or high end reference range value is found as this eliminates a diagnosis of hyperthyroidism.

**Other diagnostic tests:** In the majority of hyperthyroid cats, identification of any concurrent non-thyroidal illness and measurement of total T₄ concentration either alone or in combination with free T₄ obviates the need for any further diagnostic testing. In the past, various other diagnostic tests such as thyroidal radioactive iodine or technetium uptake or evaluating the thyroid gland response to either T₃ suppression or TRH or TSH stimulation have been recommended but they are rarely used today.

<table>
<thead>
<tr>
<th>Case</th>
<th>Total T₄ (nmol/L)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical signs of hyperthyroidism</td>
<td>&gt; 60</td>
<td>Hyperthyroidism confirmed</td>
</tr>
<tr>
<td></td>
<td>30 – 60</td>
<td>Early/mild hyperthyroidism. Assess free T₄ or retest in 3 – 6 weeks</td>
</tr>
<tr>
<td>Non-thyroidal illness present</td>
<td>&lt; 30</td>
<td>Euthyroidism likely</td>
</tr>
<tr>
<td></td>
<td>30 – 60</td>
<td>Hyperthyroidism likely particularly if concurrent illness severe</td>
</tr>
</tbody>
</table>

**Guidelines for interpreting total T₄ concentrations in diagnosing feline hyperthyroidism**
*(Based on a reference range of 15 – 60 nmol/L)*

**Canine hypothyroidism**
Various routine clinicopathological abnormalities are known to occur in hypothyroidism. None are specific for hypothyroidism although the magnitude of the hypercholesterolaemia tends to be greater in hypothyroidism than in other diseases. The major role of these tests is to provide supportive evidence of hypothyroidism and screen for the presence of non-thyroidal illness.

**Thyroid function tests**
Because of the myriad non-specific clinical signs associated with hypothyroidism, accurate confirmation using further diagnostic tests is required. Unfortunately, of the diagnostic tests available, none are wholly accurate. The thyroid suppressive effect of non-thyroidal illness and various drugs is a major reason for confounding results. As a consequence, a diagnosis of hypothyroidism should be based on appropriate clinical signs and routine clinicopathological abnormalities together with results of thyroid function tests. Non-thyroidal illness should be ruled out as far as possible and drugs known to have an effect withdrawn for several weeks prior to testing. Interpretation must also take into account the underlying cause of the hypothyroidism.

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>% of cases</th>
<th>Pathophysiology</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mild anaemia (normochromic and normocytic)</strong></td>
<td>30 – 50</td>
<td>Reduced need for oxygen carrying capacity</td>
</tr>
<tr>
<td><strong>Hypercholesterolaemia</strong></td>
<td>70 – 80</td>
<td>Reduced degradation</td>
</tr>
<tr>
<td><strong>Mildly increased creatinine kinase</strong></td>
<td>20</td>
<td>Decreased clearance, subclinical myopathy</td>
</tr>
</tbody>
</table>

**Routine clinicopathological abnormalities associated with canine hypothyroidism**

**Total thyroxine:** Circulating total T₄ concentration is invariably decreased in dogs with hypothyroidism. However, many non-thyroidal factors will also decrease total T₄. Fluctuations occur in healthy dogs with no diurnal pattern. Certain breeds have low values (greyhounds, Irish wolfhounds, salukis) and there is an inverse correlation between age and total T₄ concentration, with progressively lower values encountered in older dogs. In addition to these normal physiological effects, decreased total T₄ concentration is also a common feature in non-thyroidal illness and in dogs treated with various drugs (steroids, potentiated sulphonamides, anti-convulsants, thyroxine and certain NSAIDs). Therefore demonstration of a total T₄ concentration below the reference range does not confirm hypothyroidism. However its measurement remains a useful method of ruling out hypothyroidism as few clinically affected hypothyroid dogs have reference range values. Approximately 8 % of hypothyroid dogs have T₄ autoantibodies
that potentially result in falsely elevated total T₄ concentrations. Most of these animals are thyroglobulin autoantibody (TgAA) positive.

<table>
<thead>
<tr>
<th>Total T₄</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Advantages:</strong></td>
</tr>
<tr>
<td>Inexpensive and sensitive marker for hypothyroidism</td>
</tr>
<tr>
<td>Widely available and easily measured</td>
</tr>
<tr>
<td><strong>Disadvantages:</strong></td>
</tr>
<tr>
<td>Lower in elderly dogs and certain breeds</td>
</tr>
<tr>
<td>Decreased by most non-thyroidal illness</td>
</tr>
<tr>
<td>Subnormal at random times during the day</td>
</tr>
<tr>
<td>Decreased by steroids, barbiturates, NSAIDS, and sulphonamides</td>
</tr>
</tbody>
</table>

**Endogenous thyrotropin:** Decreased circulating thyroid hormone concentrations result in reduced negative feedback on the pituitary gland. Circulating cTSH concentration is therefore usually increased in primary hypothyroidism. However, approximately 20 - 30 % hypothyroid dogs have reference range cTSH values. The cause for this is still somewhat unclear but possible explanations include pituitary exhaustion, random fluctuation, the presence of various isoforms of cTSH some of which may not be measured with current assays, the presence of concurrent disease, central hypothyroidism and pituitary exhaustion. Although the specificity of cTSH measurement has been reported as relatively high, abnormally elevated values can occur in euthyroid dogs receiving sulphonamide therapy, during the recovery phase of non-thyroidal illness and in compensating hypothyroidism. As a result of this poor performance, measurement of cTSH alone has limited value in investigating hypothyroidism.

<table>
<thead>
<tr>
<th>Thyrotropin (cTSH)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Advantages:</strong></td>
</tr>
<tr>
<td>Helps differentiate primary hypothyroidism from other causes</td>
</tr>
<tr>
<td><strong>Disadvantages:</strong></td>
</tr>
<tr>
<td>Should not be measured alone</td>
</tr>
<tr>
<td>Increased by certain drugs and recovery from NTI</td>
</tr>
<tr>
<td>“Normal” in &gt; 20 % hypothyroid dogs</td>
</tr>
</tbody>
</table>

**Free thyroxine:** Free T₄ is the metabolically active fraction of T₄ and its measurement is widely acknowledged to more closely reflect tissue thyroidal status than total T₄ determination. Free hormone is less affected by non-thyroidal illness and various drug therapies than total T₄. However, recently, both glucocorticoids and barbiturate anticonvulsants have been shown to decrease free T₄ concentrations in dogs and certain breeds such as greyhounds have low values. Severe non-thyroidal illness is also known to decrease free T₄ concentrations.
**Free T₄**

<table>
<thead>
<tr>
<th>Advantages:</th>
<th>Disadvantages:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less affected by NTI and drug therapy than total T₄.</td>
<td>Must be measured by “dialysis” - more expensive than total T₄</td>
</tr>
<tr>
<td>Unaffected by T₄ autoantibodies</td>
<td>Can occasionally also be decreased in NTI or by certain drugs</td>
</tr>
<tr>
<td>Decreased values more specific for hypothyroidism than total T₄</td>
<td>Less robust during transport than total T₄</td>
</tr>
<tr>
<td></td>
<td>May be low-normal in early hypothyroidism</td>
</tr>
</tbody>
</table>

**Thyroglobulin autoantibodies:** TgAA are produced during the development of lymphocytic thyroiditis. Until 1997, the commercially available methods for TgAA estimation were based on human methods and were unreliable, with false positive results being a particular problem. However, a sensitive and more importantly specific, commercially available assay for canine TgAA is now available and can be used to confirm the presence of thyroid pathology. The principal limitation of TgAA measurement is that not all dogs with hypothyroidism have lymphocytic thyroiditis (it is found in approximately 50% of hypothyroid dogs) and it provides no detail on thyroid function. Therefore, whilst a positive TgAA result is strong evidence of thyroid disease, a negative result certainly does not rule it out. Epidemiological analysis of the prevalence of TgAA has shown a peak in dogs up to 4-6 years of age, which subsequently declines, presumably as the thyroid tissue becomes ablated and the antigenic stimulus decreases. In addition, it is of highest prevalence in breeds known to be predisposed to hypothyroidism. The ability to reliably measure TgAA has resulted in its use as a marker of thyroid disease in clinically healthy dogs. Since there is known to be a hereditary component to the development of thyroiditis, TgAA measurement is now used by dog breeders to identify predisposed animals prior to breeding, before clinical signs have developed.

**Combining basal analyses:** When different tests are used together, the diagnostic shortcomings of each test are minimised and the diagnostic capability for hypothyroidism is significantly increased. In combination, the gain from the high sensitivity of total T₄ and high specificity of cTSH is maximized and a low total T₄ and high cTSH provides us with the ability to confidently diagnose hypothyroidism in most cases. The main diagnostic difficulties associated with total T₄ and cTSH measurement arise when the total T₄ is subnormal but the cTSH value is within the reference range. In this situation, if the index of suspicion for hypothyroidism remains
high, free T₄ and TgAA may both be useful next steps. Free hormone analysis should help distinguish genuine hypothyroidism from other causes of decreased total T₄ and a positive antibody status confirms thyroid pathology.

In summary, combined total T₄ and cTSH measurement is a practical, economic and fairly reliable approach, especially if pre-evaluation has been performed and further diagnostic tests (TSH/TRH response tests) are only warranted in a minority of cases.

**Thyroglobulin Autoantibodies (TgAA)**

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reliable method for determination is now available</td>
<td>Provides no assessment of thyroid functional capacity</td>
</tr>
<tr>
<td>Positive result is extremely suggestive of thyroid pathology</td>
<td>Negative result does not rule out significant thyroid disease</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Normal total T₄</th>
<th>Low total T₄</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Normal cTSH</strong></td>
<td><strong>Non-thyroidal illness</strong></td>
</tr>
<tr>
<td><strong>Euthyroid</strong></td>
<td><strong>Drug therapy</strong></td>
</tr>
<tr>
<td>Old age/certain breeds</td>
<td>Hypothyroidism (20 – 30 % of cases)</td>
</tr>
<tr>
<td><strong>High cTSH</strong></td>
<td><strong>Recovery from illness</strong></td>
</tr>
<tr>
<td><strong>Withdrawal from drugs</strong></td>
<td><strong>Hypothyroidism</strong></td>
</tr>
<tr>
<td>Hypothyroidism with T₄ autoantibodies</td>
<td></td>
</tr>
<tr>
<td>Compensating hypothyroidism</td>
<td></td>
</tr>
</tbody>
</table>

Guidelines for interpreting total thyroxine (T4) and canine thyroid stimulating hormone (cTSH) concentrations. Those highlighted in bold are most likely within each category.
Testing for hyperadrenocorticism

Canine hyperadrenocorticism, although often easy to recognize clinically, can be challenging to diagnose. Many of the clinical features and clinicopathological abnormalities are shared by a variety of other disorders and of the numerous adrenal function tests recommended, no true gold standard exists. Each recommended test differs significantly with regard to diagnostic sensitivity, specificity and efficiency. Some are capable of differentiating the site of the lesion (pituitary dependent hyperadrenocorticism (PDH) versus adrenal tumour (AT)) while others may be useful in monitoring the response to therapy. Interpretation of test results in individual patients requires knowledge of what each test is assessing and what its characteristics are.

Routine clinicopathological abnormalities include mild erythrocytosis, a stress leucogram, dilute urine, increased liver enzymes (with a disproportionate increase in ALP), hypercholesterolaemia, hypertriglyceridaemia and increased bile acids. Although these abnormalities are not specific for hyperadrenocorticism, almost all cushingoid dogs have at least one abnormality. Care should be taken if other abnormalities are found as they may represent non-adrenal illness, which may influence the response to adrenal function tests.

Adrenocorticotropic hormone response test

The ACTH response test serves to demonstrate functional adrenal reserve following administration of a pharmacological dose of ACTH. It is generally used to screen for the presence of hyperadrenocorticism. It can distinguish between iatrogenic and spontaneous hyperadrenocorticism but does not reliably distinguish between PDH and functional AT. It is useful in the monitoring of adrenocorticolytic and trilostane therapy. Although cortisol is the main hormone measured, other precursors can also be assayed allowing investigation of sex hormone imbalance and non-cortisol producing tumours.

The ACTH response test is a simple and quick procedure easily performed in the practice environment. The standard protocol is measurement of circulating cortisol concentration before and 1-hour after a single intramuscular or intravenous injection of synthetic ACTH (tetracosactrin, cosyntropin) at 250 µg/dog, although doses as low as 1.0 µg/kg can be used.
Dogs with hyperadrenocorticism theoretically have an exaggerated response to ACTH. The absolute post-ACTH cortisol concentration is most frequently used to assess the response during an ACTH stimulation test. Although values above the reference range are frequently cited as abnormal, most clinicians use a value that significantly exceeds this range, often between 600 and 650 nmol/l. Approximately 80% of dogs with PDH have an exaggerated cortisol response to ACTH while only approximately 60% of dogs with AT have such results. Despite the low sensitivity of this test, an advantage is that it is highly specific (approximately 90%) and has a relatively high positive predictive value. The likelihood of an abnormal result in a non-cushingoid dog generally increases the more severely or chronically ill the animal is. Occasionally, dogs with AT have a subnormal cortisol response to exogenous ACTH.

In conclusion, an abnormal cortisol response in a dog with suspicious clinical and clinicopathological features is supportive of hyperadrenocorticism but provides no information on the site of the lesion. Although abnormal results can occur particularly in an animal known to have concurrent non-adrenal illness (e.g. unstable diabetes mellitus), a more common diagnostic dilemma is finding a reference range (or rarely subnormal) cortisol response in a highly suspicious case. Decreasing the post ACTH cortisol cut-off point (e.g. to approximately 500 nmol/l) for hyperadrenocorticism improves the test sensitivity with minimal effect on specificity and helps improve the diagnostic performance of this test. Alternatively, a more sensitive diagnostic test should be considered in these suspicious cases.

**Low-dose dexamethasone suppression test**

In healthy dogs, glucocorticoids exert negative feedback inhibition on ACTH secretion. A low-dose of dexamethasone (0.01 – 0.015 mg/kg) administered intravenously to healthy dogs, causes inhibition of ACTH secretion and reduced plasma cortisol concentrations within 2 to 3 hours lasting up to 8 hours. In hyperadrenocorticism, the 8-hour cortisol value is not sufficiently suppressed and remains above approximately 30 to 40 nmol/l. The LDDS test is considered extremely sensitive for hyperadrenocorticism. In approximately 95% of dogs with PDH and up to 100% of dogs with AT, cortisol suppression is inadequate. Many patterns are recognised from lack of suppression at both 3 and 8 hours, to suppression at 8 but not 3-4 hours (inverse), suppression at 3-4 hours but not at 8 hours, to values that increase throughout the course of the test. However, by far the greatest problem with the test is that false-positive results frequently occur in dogs with non-adrenal disease with a reported specificity as low as low as 40%. In general, the more severe the non-adrenal illness, the more likely that cortisol suppression will
be inadequate. On the other hand, the high negative predictive value of this test means that hyperadrenocorticism is unlikely if normal cortisol suppression occurs.

An additional value in performing a LDDS test is its ability to distinguish between PDH and AT in up to 60% of cases when circulating cortisol concentrations are measured at 3 or 4 and at 8 hours. Criteria that indicate a diagnosis of PDH include a decrease of circulating cortisol concentration to less than a laboratory reference value at 3 or 4 hours, less than 50% of the baseline value at 3 or 4 hours, or less than 50% of the baseline value at 8 hours. However, PDH cannot be ruled out if such suppression does not occur. The LDDS test cannot be used to evaluate response to therapy for hyperadrenocorticism.

**Urinary cortisol (corticoid):creatinine ratio**
The determination of the UCCR in urine samples taken in the morning can be used in the investigation of hyperadrenocorticism in dogs. It is the least stressful of all the diagnostic tests as owners can obtain samples in the home environment. It is also extremely sensitive with a reported range of 75 to 100%. However, it lacks specificity with values as low as 20% reported especially if the animal is stressed or concurrent moderate to severe non-adrenal illness is present. Overall, its high negative predictive value suggests that hyperadrenocorticism is unlikely if the UCCR is within the reference range but that further investigation for hyperadrenocorticism is warranted if it is elevated.

Extremely elevated UCCR values occur almost exclusively in PDH. Suppression to greater than 50% of baseline following oral administration of three doses of dexamethasone (0.1 mg/kg) is similarly consistent with PDH. Overall, it is considered an inappropriate test for accurate monitoring of adrenocorticolytic therapy.

**Measurement of 17α-hydroxyprogesterone and other cortisol precursors**
Within the adrenal gland, 17-α-hydroxylase catalyses the conversion of pregnenolone to 17α-hydroxyprogesterone (17-OHP). It is ACTH responsive and 17-OHP is further metabolised by 21-hydroxylase and 11-β-hydroxylase to produce 11-deoxycortisol and cortisol, respectively. Its measurement has proven useful in the investigation of dogs with AT that have a subnormal cortisol response to exogenous ACTH. In these individual (and rare cases), the adrenal gland presumably retains the ability to respond to ACTH but the cortisol production pathway is not intact.
Recent research has suggested that measurement of 17-OHP is also useful particularly in dogs with clinical and clinicopathological signs suggestive of hyperadrenocorticism that do not exhibit classical results using traditional tests, although this is unusual. However, because of the overlap in test results between healthy and sick dogs and those with hyperadrenocorticism, it cannot be advocated as a routine screening test for hyperadrenocorticism.

A variety of other sex hormones can potentially be measured during an ACTH response test but the interindividual variation in results limits their value in investigating hyperadrenocorticism.

**Plasma adrenocorticotropic hormone concentration**

Measurement of circulating ACTH concentration is an excellent test to discriminate between PDH and AT but cannot be used for diagnosis. Dogs with PDH release large amounts of ACTH but dogs with AT have reduced ACTH output. Inappropriately elevated plasma ACTH concentrations are consistent with PDH while low values are consistent with AT. Meticulous sample handling procedures (cold collection, immediate freezing) are necessary to avoid degradation and falsely low values. Aprotinin has a profound preservative effect on ACTH and it may be possible to submit unfrozen plasma samples to which aprotinin has been added.

**Diagnostic imaging**

Ultrasonography is a widely available useful imaging method for assessing hyperadrenocorticism. However, like endogenous ACTH measurement, it is most valuable in distinguishing PDH from functional AT. As a screening test it has limitations because of the overlap in adrenal gland size between healthy and sick dogs and those with PDH and because unilateral adrenal gland enlargement may represent incidental non-functioning adrenal tumours or those capable of producing other hormones. Co-existing PDH and AT and bilateral AT have been described rarely. In such cases, the results of the adrenal function tests and endogenous ACTH measurement are at variance with the ultrasonographic appearance of the adrenal glands.

**Conclusions**

Whilst hyperadrenocorticism is undoubtedly difficult to diagnosis, selecting appropriate cases significantly increases the diagnostic performance. It serves to minimise inappropriately diagnosing hyperadrenocorticism in dogs with non-adrenal illness and to have confidence to
consider more diagnostic tests in animals highly suspicious of the disorder but with one negative adrenal function test result.

If finances allow, the selection of a highly specific test with one of high sensitivity maximises diagnostic performance. In our clinic, the ACTH response test and LDDS test are recommended in all suspicious patients. The simultaneous measurement of 17-OHP during the ACTH response test is not considered routinely but is reserved for investigation of animals with suspicious clinical signs and a subnormal response to ACTH administration. Measurement of endogenous ACTH concentration and diagnostic imaging are most useful in distinguishing between PDH and AT when a diagnosis of hyperadrenocorticism has been confirmed.
The new regimes for diabetic cats

Traditionally, diabetes mellitus has been classified in dogs and cats based on clinical presentation and the need for routine (insulin, diet + oral hypoglycaemic agents) or more intensive (intravenous insulin, fluid and electrolyte therapy) therapies. However, the value of such a classification system is questionable because it fails to consider the significant pathophysiological differences between the various types of diabetes mellitus, and how addressing these may improve the prognosis for each individual animal. As a consequence there has been a move to attempt to apply the human classification system particularly to cats and to institute more aggressive and targeted therapy if it is possible to do so.

Diabetes mellitus in humans

In humans, diabetes mellitus is classified into type 1, type 2, other specific types and gestational diabetes). Although other sub-categories are recognised, type 1 disease tends to occur most commonly in young lean individuals who are totally dependent on insulin to prevent ketoacidosis and death (hence previously known as juvenile onset or insulin dependent). It results from autoimmune destruction of the β-cells of the pancreas. Autoantibodies to islet cells or their components are found in the majority (85 – 90 %) of patients. Environmental triggers are important but the disease has a strong genetic component. Although the progression can be variable, it is usually fairly rapid in younger individuals but may be slower in adults (often classified as latent autoimmune diabetes of adults (LADA)). Type 1 disease only accounts for 5 – 10 % of patients with diabetes mellitus.

By contrast, type 2 disease (previously known as adult onset and non-insulin dependent) is more common accounting for 90 – 95 % of patients. It is characterised by impaired insulin secretion and insulin resistance. It tends to occur in older patients who are obese and who do not exercise, are resistant to the development of ketosis and who can often be managed by weight control and oral hypoglycaemic agents alone. Pancreatic amyloid deposition is common. It is associated with a strong genetic predisposition although it is complex and poorly defined.

Other specific types of diabetes are less common but include some genetic disorders of insulin secretion or action, diseases of the pancreas (pancreatitis, carcinoma etc.), various endocrinopathies (growth hormone, cortisol, glucagon and catecholamine excess) or prolonged...
diabetogenic drug administration. Whether diabetes resolves depends on whether the primary disease process can be treated and if irreversible damage has yet occurred.

**Diabetes mellitus in cats**

Diabetes mellitus is one of the most common endocrinopathies affecting cats with an estimated prevalence of between 1 in 100 and 1 in 400 depending on the population being studied. Today, the prevalence is undoubtedly increasing, as it is in humans. In one study the prevalence of feline diabetes mellitus at veterinary teaching hospitals increased significantly from 8 cases per 10,000 in 1970 to 124 per 10,000 in 1999.

Undoubtedly cats tend to develop type 2 disease while on the other hand type 1 disease is rare. Similar to humans, major risk factors appear to be increasing age, obesity and physical inactivity. Most cats are in excess of 7 years at the time of diagnosis. Obesity is considered to increase the risk of diabetes 3 to 5 fold. Neutered cats have nearly twice the risk and male cats 1.5 times the risk of developing diabetes. There is a strong genetic predisposition with Burmese cats overrepresented in many countries. Histopathological examination of pancreatic tissue form affected cats shows that pancreatic amyloid deposition occurs. However there are significant differences between humans and cats. The majority is or ultimately becomes insulin dependent and many develop ketoacidosis. This may be related to delayed recognition/diagnosis, or because cats appear more susceptible to the effects of glucose toxicity in impairing insulin secretion or because many develop pancreatitis. As a consequence, treatment regimens differ between cats and humans. Dietary management and exercise modification are at least as important. However, certain oral hypoglycaemic agents are less efficacious in the face of glucose toxicity and may enhance the progression to insulin dependency by further exacerbating amylin deposition in the pancreas. Insulin therapy is therefore preferred as it is more likely to reduce hyperglycaemia and the effects of glucose toxicity and will significantly increase the rate of remission. Although estimates vary, up to 40 % of cats with type 2 disease are likely to go into remission if treated appropriately.

The factors (*putative) that contribute to impaired insulin secretion and insulin resistance characteristic of type 2 diabetes mellitus in cats are listed below. Many of these can be successfully addressed leading to remission. Other factors can contribute in any individual (e.g. glucorticoid induced insulin resistance) that may require specific additional treatment.
Impaired insulin secretion | Peripheral insulin resistance
---|---
Genetic | Genetic
Amyloid deposition | Obesity
Glucose toxicity | Physical inactivity
Lipid toxicity | Lipid/glucose toxicity
Pancreatitis* | 
Diet*

**Current treatment strategies**

Given the previous knowledge of factors affecting insulin secretion and insulin resistance, therapy should be aimed at

1. Reducing factors known to cause insulin resistance – obesity, physical inactivity, concurrent illnesses, drug therapies
2. Addressing factors that promote impaired insulin secretion - decrease amyloid deposition by providing insulin, decrease hyperglycaemia and hypertriglyceridaemia through the use of potent hypoglycaemic agents (e.g. insulin), provide an appropriate diet

A wide variety of insulin preparations are available for maintenance therapy and isophane (NPH), lente, ultralente, protamine zinc insulin (PZI) and glargine have all been used with varying success in diabetic cats. The type of insulin chosen is often dependent on local availability. NPH and lente insulins have an intermediate duration of action and require twice-daily dosing. Ultralente and PZI are longer acting insulins and can sometimes be effective when administered on a once-daily basis. The blood glucose response is often less predictable with longer acting insulins and in many cats they are better given twice daily. Glargine is a new long-acting insulin analogue that can be administered once or twice daily and has a concentration of 100U/mL. However, it is not licenced for veterinary use. Both bovine lente and porcine lente (Insuvet Lente and Caninsulin, Intervet Schering Plough) are licenced for cats and are frequently used in diabetic management. The species of origin of insulin has few implications in cats as opposed to dogs. Caninsulin may be preferred because it is 40 IU/mL and potentially more accurate when lower doses are used. Supply of Insuvet lente is no longer guaranteed.

For lente insulin preparations a safe starting dose is 0.25-0.5 IU/kg bodyweight, with a maximal dose of 2 IU per injection adjusting the dose based on the severity of the
hyperglycaemia. Stabilisation in the hospital is not strictly necessary but it may be prudent to evaluate the nadir blood glucose concentration (usually 4 to 6 hours after administration) after the first few injections to ensure hypoglycaemia has not occurred. Cats can then be discharged and asked to return for a repeat blood glucose concentration every three days with dose adjustments of 1 IU until stability is achieved. Most cats eventually stabilise on 2 to 5 IU per injection per cat.

The optimal proportion of dietary protein, carbohydrate, and fat for diabetic cats is still largely unknown. However, it does appear that diets with a higher protein and lower carbohydrate content are preferable and increase the frequency of diabetic remission. Obviously obese diabetic cats will benefit from an appropriate weight loss programme.

The most appropriate method for monitoring diabetic cats is controversial. One of the primary aims of therapy of diabetic cats is resolution of clinical signs and it is therefore important to regularly monitor water intake and body weight. Blood glucose curves are frequently recommended but are problematic if performed in the hospital because of the effects of stress on blood glucose concentrations in cats. Owners can be taught to obtain blood samples from their own cats and while decreasing the effects of stress, there can be widely variable responses in individual cats from day to day despite a consistent insulin and food regimen. The glycated protein, fructosamine is a useful indicator of glycaemic control in diabetic cats. There is an overlap in results between untreated diabetics, poorly-controlled diabetics, well-controlled diabetics, and normal cats. However, a fructosamine concentration that approaches the reference range may indicate diabetic remission.
Distinguishing causes of hypercalcaemia

Introduction
Although relatively uncommon, hypercalcaemia is diagnosed with increasing frequency in practice because of the ease with which both total and ionised calcium can now be measured. When recognised, the clinician is often faced with the dilemma of separating the clinical signs induced by the hypercalcaemia itself versus those caused by the underlying disorder. A second dilemma is instituting treatment for hypercalcaemia to minimise potential complications whilst avoiding those that could adversely affect the diagnostic work-up. Fortunately, clinically significant hypercalcaemia has a relatively well defined set of differential diagnoses and a wide array of diagnostic tests are now available that offer an opportunity to confirm a diagnosis with greater ease than previously. In addition, therapies are now available capable of effectively managing the hypercalcaemia without interfering with any subsequent diagnostic tests.

Tests of calcium homeostasis
In evaluating calcium homeostasis both calcium and phosphate should be measured simultaneously. Total calcium is usually measured as part of a routine clinicopathological panel and consists of protein-bound (mainly albumin) calcium (40 %), ionised calcium (iCa)(50 %) and calcium that is complexed (10 %) with other anions such as phosphate, citrate, bicarbonate or lactate. The iCa fraction is considered to be biologically active and is the component that regulates PTH secretion. Serum phosphorus consists of inorganic phosphate, phospholipids and phosphate esters. An increase in either calcium or phosphate causes a reciprocal decrease in the other. Soft tissue calcification is most severe when the calcium phosphate product exceeds 5.0.

Total calcium concentrations tend to be higher in younger animals and are obviously influenced by circulating albumin concentrations. Measurement of ionised calcium gives a much clearer indication of actual calcium status since it is not influenced by the protein-bound or complexed fractions. Caution is advised with measurement of ionised calcium as it is influenced by pH (higher concentrations as pH decreases) and should be analysed relatively rapidly. Valid specific, two-site intact PTH immunoradiometric assays are now commercially available. Serum PTH concentrations should be evaluated relative to the total or preferably, ionised
calcium concentration. Serum or EDTA plasma can be used but since PTH is relatively labile it should be appropriately handled to prevent erroneously low results. Parathyroid hormone-related protein is associated with certain malignancies. Some laboratories now offer this assay but it should not be used as a replacement for thorough investigation for neoplasia.

Assays for vitamin D are becoming increasingly available but their usefulness in small animal medicine remains unclear unless vitamin D toxicosis requires confirmation.

**Effects of hypercalcaemia**

The clinical signs associated specifically with hypercalcaemia are often mild, insidious and non-specific and commonly relate to the renal, gastrointestinal or neuromuscular systems. More severe clinical signs are usually associated with the underlying disease, the development of renal failure or in some cases, severe hypercalcaemia.

- Gastrointestinal features include anorexia, vomiting, constipation, and, rarely, pancreatitis.
- Renal features include polyuria/polydipsia and occasionally signs related to recurrent urinary tract infections or calculi.
- Neuromuscular features include listlessness, weakness, muscle wastage, and rarely stiff gait, shivering, obtundation, coma.

Polyuria and polydipsia are common in dogs. Anorexia and lethargy predominate in cats. A cervical nodule may be palpable in cats with hyperparathyroidism.

**Causes of hypercalcaemia**

In dogs, hypercalcaemia is most often associated with malignancy, hypoadrenocorticism and renal disease with lower prevalences of hyperparathyroidism, and vitamin D toxicosis. In cats, neoplasia, renal failure and idiopathic hypercalcaemia appear to be most common. Other infrequent causes of hypercalcaemia include the diuretic phase of acute renal failure, a small percentage of cases of nutritional hyperparathyroidism, disseminated osteomyelitis, granulomatous disease and severe hypothermia.

Hypercalcaemia of Malignancy: Malignancy associated (paraneoplastic) hypercalcaemia is the most common cause of hypercalcaemia in dogs. Whilst the presence of neoplasia is often apparent on physical examination, isolated hypercalcaemia should always prompt thorough investigations for occult neoplasia. The hypercalcaemia may be intermittent but if severe can result in renal failure, encephalopathy, coma and death. Generally more clinical signs are
apparent in dogs with hypercalcaemia of malignancy because of the co-existence of the hypercalcaemia and neoplasia.

Hypercalcaemia may result from local factors that stimulate osteoclastic resorption (e.g. multiple myeloma), or tumour tissue, situated at a site distant from bone may produce PTHrP (e.g. lymphosarcoma, anal gland adenocarcinoma). Destruction of bone from metastatic lesions may also play a role in some tumours.

Hypoadrenocorticism: Approximately 20 % of dogs with hypoadrenocorticism have hypercalcaemia. The mechanism is obscure but may relate to hypocortisolaemia and reduced renal output. Ionised calcium concentrations may be normal or elevated. The hypercalcaemia is usually only mild to moderate and phosphate concentrations also tend to be increased.

Chronic Renal Failure: 10 to 20 % of dogs have mild to moderate hypercalcaemia although normal or low calcium is more common. Associated ionised calcium concentrations are either normal or low. Serum phosphate concentrations are elevated. Diagnostically these animals pose a challenge as further investigations are required to determine if they have chronic renal failure or renal failure induced by hypercalcaemia. Ionised calcium concentrations help differentiate the two.

Hyperparathyroidism: In dogs a single benign parathyroid gland adenoma is the most common cause of primary hyperparathyroidism. Parathyroid adenocarcinoma and parathyroid hyperplasia are less common. There is a familial predisposition in Keeshounds. It is rare in cats.

Idiopathic Hypercalcaemia of Cats: A hypercalcaemic syndrome of cats of unknown aetiology has emerged in recent years. Many cats have concurrent evidence of a lower urinary tract disorder.

Vitamin D Toxicosis: Vitamin D toxicity may result from overzealous dietary supplementation, overdosage of Vitamin D in the treatment of hypoparathyroidism or intoxication with cholecalciferol containing rodenticides and human topical psoriatic treatments. It is associated with moderate to severe hypercalcaemia with hyperphosphataemia and therefore diffuse soft tissue calcification.
Treatment
Surgical removal of the tumour is the optimum treatment for primary hyperparathyroidism. The dog/cat must be monitored for hypocalcaemia.
Symptomatic therapy for hypercalcaemia is indicated when dehydration, azotaemia, cardiac arrhythmia, severe neurological dysfunction or weakness exists or when the hypercalcaemia is severe (> 4 mmol/l). Several methods have been suggested to control acute or severe hypercalcaemia. Correction of fluid deficits, saline diuresis, and diuretic therapy with furosemide are the most commonly used methods. Glucocorticoid therapy should be avoided. Glucocorticoids are rapidly beneficial in malignancy associated hypercalcaemia and such a response helps to support a diagnosis. However, confirmation of occult neoplasia and its successful treatment becomes more difficult in dogs that have received glucocorticoids.

- Fluid therapy
Rehydration is an important step in treating hypercalcaemic dogs as dehydration worsens pre-existing hypercalcaemia. Correction of fluid deficits does not normalise serum calcium concentrations. Rehydration with mild volume expansion eliminates the effects of dehydration and promotes calciuresis. Normal saline given at two to three times maintenance over the dehydration deficit is usually effective. The patient should be monitored for signs of overhydration and potassium may require supplementation.
- Diuretic therapy
The use of furosemide together with saline diuresis ensures maximal renal excretion of calcium. Volume expansion must precede diuretic administration. One protocol suggests a 5 mg/kg IV bolus followed by a 5 mg/kg/hour infusion or 2-4 mg/kg every 8-12 hours.
- Bisphosphonates
Fluid therapy is usually successful and other treatments rarely necessary. However if more long-term control of hypercalcaemia is required (e.g. whilst awaiting other results) alternative therapies must be instituted. These include bisphosphonate infusions (pamidronate, clodronate), calcitonin, plicamycin, EDTA, bicarbonate and dialysis. Salmon calcitonin (Calsynar®) is administered subcutaneously at a dose of 4 – 8 iu/kg BID to TID but its effects are short-lived and multiple treatments are required. Sodium bicarbonate as a slow intravenous bolus (1 mmol/kg every 10 – 15 minutes for four treatments) has a minimal effect on circulating calcium concentration. Plicamycin (25 µg/kg slowly intravenously over 4 – 6 hours once/twice weekly) is a potent inhibitor of osteoclastic bone resorption but is associated with numerous
adverse reactions including thrombocytopenia and hepatic/renal failure. The bisphosphonates are osteoclastic inhibitors widely used in human medicine. At a dose of 1.3 (1.0 – 2.0) mg/kg in 150 ml 0.9 % saline infused intravenously over 3-4 hours (pamidronate, Aredia®) or 20 - 25 mg/kg intravenously in 500 ml saline over four hours (clodronate), calcium concentrations can be suppressed within 48 hours for up to several weeks.

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**Abnormalities of calcium homeostasis in certain disorders.**
Treating hyperadrenocorticism

Hypophysectomy
If a pituitary adenoma is suspected then ideally therapy should be directed towards removing the pituitary lesion. Hypophysectomy, however, although successful requires an experienced surgeon. In addition it carries the risk of temporary diabetes insipidus, permanent hypothyroidism and secondary hypoadrenocorticism.

Surgical adrenalectomy
There are some reports of satisfactory results with bilateral adrenalectomy for PDH but there are a number of major drawbacks. It requires submitting a sick, high risk patient to extensive surgery which is technically difficult and many will not survive the procedure. If the dog recovers it will require life-long replacement therapy for Addison’s disease. Unilateral adrenalectomy is obviously the treatment of choice for adrenal tumours particularly adenomas or small carcinomas that have not yet metastasised. Care must be exercised to ensure adequate glucoocorticoid replacement at least temporarily after surgery until the contralateral gland recovers.

Medical therapy
Trilostane (Vetoryl®, Dechra Veterinary Products) has an inhibitory effect on glucocorticoid synthesis within the adrenal gland through reversible blockage of the 3-beta hydroxysteroid dehydrogenase enzyme. It is licensed and authorised for the treatment of PDH and AT within Ireland. However given it is an enzyme inhibitor surgical removal remains the best treatment option for AT.
It requires daily therapy but the limited risk of severe adverse reactions and their easy treatment by simple drug withdrawal make it an attractive alternative to mitotane. It is available as 10, 30, 60 or 120 mg hard capsules. Hyperadrenocorticism is generally controlled using doses between 2-6 mg/day but because the capsules cannot be split, empirical dosing must be used e.g.
> 3 kg, < 10 kg – 30 mg once daily
10-20 kg, – 60 mg once daily
> 20 kg < 40 kg, – 120 mg once daily
> 40 kg, 120 – 240 mg once daily

It is usually recommended to start at the lowest dose possible, working upwards if required. Absorption is enhanced by administration in food. The drug has a half life measured within hours with a peak inhibitory effect 4 – 6 hours after administration. Cortisol production appears to be inhibited enough over 24 hours to achieve reasonable clinical control in most dogs but some will require twice daily dosing. Trilostane should be administered with food as this enhances absorption.

Evidence of clinical efficacy is slightly slower than with mitotane with some dogs taking up to three weeks for resolution of metabolic signs. Post ACTH cortisol concentrations should be suppressed to < 150 nmol/L but the ACTH response test must be completed 4 - 6 hours after drug administration. ACTH response tests are carried out after 10 days, 4 weeks, 12 weeks and every 3 – 6 months thereafter. However, if suppression is demonstrated but clinical signs persist, an ACTH response test 24 hours after drug administration may exemplify the need for twice daily dosing. It is recommended that the drug be temporarily stopped if there is complete cortisol suppression, recommencing therapy 7 – 30 days later (providing there is cortisol stimulation after ACTH administration) using a lower dose. However, experience suggests that this is unnecessary unless clinical signs of hypocortisolaemia develop.

Adverse reactions include

- Sudden death
- Hypocortisolaemia
- Nelsons phenomenon
- Addisons disease
- Complete irreversible adrenal necrosis and adrenal enlargement (megaplasia)

The product is contraindicated in dogs with pre-existing renal disease or primary hepatic disease. Sudden death has been particularly described in animals concurrently receiving ACE inhibitors. Potassium concentrations frequently increase over the course of therapy but many dogs do not exhibit adverse clinical effects.

Medical management using mitotane (o,p'-DDD, Lysodren, Bristol Laboratories) is simpler and was once the mainstay of treatment for PDH. o,p'-DDD is a chemical derived from the insecticide DDT and causes severe, progressive necrosis of the zona fasciculata and reticularis while tending to spare the zona glomerulosa.
Initiating therapy - loading dose: Therapy can commence at home once the owner is adequately forewarned as to potential side effects and forearmed with prednisolone (0.2 – 0.5 mg/kg once daily) once these effects are noted. The initial dose is 50 mg/kg administered once daily or divided twice daily. The drug should be administered either in or immediately following a meal as this enhances its absorption. Handling of the drug should be avoided.

The success of therapy is monitored by measuring the dogs water intake and stopping treatment once it reaches 60 ml/kg/day. Treatment is also stopped if the animal is unusually listless, becomes anorexic, begins vomiting or has diarrhoea. Owners should not be allowed continue treatment for longer than 9 days without returning to the veterinarian.

At the check-up, if treatment has stopped, an ACTH stimulation test is performed and o,p'-DDD withheld until this is evaluated. The goal of therapy is to achieve a response test indicative of hypoadrenocorticism. This occurs in most dogs between 5 and 10 days after commencing therapy when the post ACTH cortisol value will be < 100 nmol/l.

Some dogs require a longer course of loading therapy. This should only be continued after the 10 day check-up on the basis of ACTH stimulation tests, with repeated tests every 3 - 5 days thereafter. Almost all dogs respond by day 14.

Maintenance therapy: Once weekly therapy is instituted using 50 mg/kg. The animals should be checked using ACTH stimulation tests at 1 and 3 months and every 3 - 6 months thereafter. Dogs undergoing significant stress should be given additional glucocorticoids.

Hypoadrenocorticism is an uncommon but significant side effect. It usually occurs during maintenance therapy but only develops in 3 – 5 % of dogs. Lifelong mineralocorticoid therapy is required.

Neurological signs occurring during the initial stages of treatment due to a rapidly expanding pituitary tumour usually respond to prednisolone (often dubbed as Nelson’s phenomenon).

Failure of therapy: Various possible reasons

- Not receiving or absorbing drug (always administer with food containing a reasonable fat content)
- Not cushingoid (mitotane is less potent against healthy adrenal tissue)
- Concurrent administration of drugs such as phenobarbitone which induce the hepatic microsomal enzyme system, will accelerate the metabolism of mitotane
• Adrenal tumour (these respond less favourably to mitotane and require higher induction and maintenance doses for any effect e.g. cumulative induction doses of 5000 mg/kg and maintenance doses of 150 mg/kg/week)
• Resistant form of pituitary mediated Cushings disease (may require lengthy induction phase)

More recently, the use of a high dose of o,p'DDD to chemically ablate the adrenal glands (50 - 100 mg/kg daily for 25 days) has been recommended with concurrent lifelong mineralo- and glucocorticoid replacement therapy as in Addison’s disease. Unfortunately the initial mortality rate is quite high, relapses do occur, and daily medication with mineralocorticoids may prove as expensive in the long-term. In addition, withdrawal of mineralocorticoid therapy is life-threatening while occasionally missing weekly mitotane therapy is rarely of importance.