Dogs of the hunting breeds are commonly presented to the veterinarian for perceived exercise intolerance. Exercise intolerance can result from orthopedic, cardiovascular, respiratory, hematologic, metabolic/endocrine, neuromuscular, muscular and neurologic disorders.

**History**
A complete history investigating every body system is important. Details regarding the type, duration and intensity of exercise that results in exercise intolerance and a clinical description of the exercise intolerance itself should be collected.

**Physical examination**
Physical examination at rest may be diagnostic. Complete respiratory, cardiovascular, musculoskeletal and nervous system examinations should be performed as well as thorough abdominal palpation. When clinical examination and laboratory evaluation do not provide a diagnosis it may be necessary to exercise the dog in order to examine it while it is exercise intolerant.

**Orthopedic disorders**
Discomfort from abnormalities of the bones or joints causes reluctance to exercise. Young dogs suffering from panosteitis, hip dysplasia or osteochondrosis dessicans and mature dogs with ligamentous injuries or degenerative joint disease all show a reluctance to exercise. Immune mediated polyarthritis and tick-borne infectious polyarthritis cause a stiff, stilted gait and reluctance to exercise.

**Cauda equina syndrome**
Compression of the cauda equina by type II disk prolapse and soft tissue proliferation at the L7-S1 site causes rear limb lameness or weakness that worsens with exercise, and pain on palpation of the dorsal sacrum and dorsiflexion of the tail.

**Cardiovascular disorders**
Dogs in heart failure due to congenital anomalies, acquired valvular heart disease or cardiomyopathy will be unable to exercise due to poor perfusion and tissue hypoxia. Physical evidence of cardiac failure will typically be present.

Tachyarrhythmias and bradyarrhythmias reduce cardiac output resulting in weakness, syncope or sudden death. Auscultation, femoral pulse quality, thoracic radiographs, ECG and echocardiography may be normal at rest. Continuous ambulatory ECG or cardiac event recording can document a cardiac arrhythmia during collapse.

Dogs with pericardial effusion causing cardiac tamponade are often presented to the veterinarian for exercise intolerance. Tachycardia, weak pulses and muffled heart sounds are common.

**Respiratory disorders**
Inability to maintain tissue oxygenation results in weakness, exercise intolerance or collapse in dogs with severe respiratory disease. Auscultation and observation of the respiratory pattern at rest and during and following exercise can aid localization within the respiratory tract. Thoracic radiographs, heartworm testing, laryngoscopy, tracheal wash cytology and culture, bronchoscopy, thoracocentesis, and arterial blood gas analysis may be useful in diagnosis.

**Anemia**
Acute severe anemia from trauma, ruptured splenic hemangiosarcoma, bleeding intestinal lymphoma, gastric ulceration, anticoagulant rodenticide ingestion, thrombocytopenia or acute hemolysis typically results in acute collapse and profound weakness. Chronic severe anemia causing exercise intolerance is seen with low grade GI or urinary bleeding, chronic hemolysis or bone marrow disease. A CBC should be performed in all dogs with exercise intolerance.

**HYPOGLYCEMIA**
In adult dogs, hypoglycemia is most likely to be caused by insulin secreting neoplasms, other tumors, liver failure, hypothalamic-pituitary-adrenal axis dysfunction, or xylitol intoxication.
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Deficient muscular dystrophy in male Golden Retrievers and centronuclear myopathy in male and female Labrador retrievers. Diagnosis is by clinical features, muscle biopsy and genetic testing.

Atypical seizures
An episodic movement disorder that may be a partial focal motor seizure has been recognized in Labrador Retrievers. Exercise is a common trigger, prompting evaluation for exercise intolerance. May progress to generalized seizures.

Exercise induced collapse in labrador retrievers
An inherited syndrome of exercise induced collapse (EIC) is the most common cause of exercise induced weakness in otherwise healthy Labrador retrievers. Affected dogs are normal at rest, but strenuous exercise results in ataxia and rear limb weakness that sometimes progresses to collapse. Diagnosis is by eliminating other causes of exercise intolerance and demonstrating that the dog is homozygous for the causative dynamin1 mutation.

Diagnostic evaluation
Diagnostic evaluation of a hunting breed with exercise intolerance will be determined by historical features, physical findings at rest and initial laboratory results. When there are no abnormalities at rest, the clinician may need to observe exercise. It is important to systematically rule out metabolic, respiratory and cardiac causes of exercise intolerance as well as orthopedic, muscular, neuromuscular and neurologic disorders.

Muscular weakness that worsens with exercise or stress may be the only presenting complaint, especially in dogs that are only deficient in glucocorticoids, with normal mineralocorticoids (atypical Addison’s). Laboratory findings may include the absence of a stress leukon and (less commonly) hypoglycemia. Definitive diagnosis requires an ACTH stimulation test. Hunting breeds at high risk include Golden retrievers, Standard poodles, Portuguese water dogs and Nova Scotia Duck Tolling Retrievers.

Hypothyroidism
can be associated with obesity, lethargy and exercise intolerance caused by a decrease in metabolic rate. Severe chronic hypothyroidism can also cause a reversible peripheral neuropathy or impaired muscle energy metabolism. Laboratory testing of thyroid function is recommended in dogs with exercise intolerance.

Canine acquired myasthenia gravis
Acquired myasthenia gravis (MG) is an immune-mediated disorder in which autoantibodies are directed against acetylcholine receptors (ACHRs) of skeletal muscle. The characteristic clinical presentation is appendicular muscle weakness that worsens with exercise and improves with rest. Concurrent megaesophagus is common. Dogs with MG are usually severely exercise intolerant, developing weakness and collapse after only a few steps. Definitive diagnosis is made by demonstrating serum antibodies directed against ACHRs.

Polymyositis
Polymyositis (PM) causes weakness, reluctance to exercise, and sometimes muscle pain. Affected dogs have normal reflexes and proprioception and are neurologically normal. Diagnosis is based on clinical findings, elevated CK, EMG, and muscle biopsy. Attempts should be made to rule-out an infectious cause (Neospora, Toxoplasma). Polymyositis is most often seen as a primary immune mediated disorder but it can also occur as a paraneoplastic condition, or a complication of drug administration.

Congenital/inherited muscle disorders
Metabolic disorders of muscle can cause muscle weakness, pain, cramping and exercise intolerance. Metabolic screening is available through (http://research.vet.upenn.edu/penngen). Inherited myopathies described in retrievers include X-linked dystrophin deficient muscular dystrophy in male Golden Retrievers and centronuclear myopathy in male and female Labrador retrievers. Diagnosis is by clinical features, muscle biopsy and genetic testing.

Hypoadrenocorticism
Muscular weakness that worsens with exercise or stress may be the only presenting complaint, especially in dogs that are only deficient in glucocorticoids, with normal mineralocorticoids (atypical Addison’s). Laboratory findings may include the absence of a stress leukon and (less commonly) hypoglycemia. Definitive diagnosis requires an ACTH stimulation test. Hunting breeds at high risk include Golden retrievers, Standard poodles, Portuguese water dogs and Nova Scotia Duck Tolling Retrievers.
A syndrome of exercise intolerance and collapse (EIC, now known as dynamin-associated EIC; d-EIC) has been recognized in Labrador Retrievers.

Investigators from the Western College of Veterinary Medicine at the University of Saskatchewan (Taylor, Shmon), the College of Veterinary Medicine at the University of Minnesota (Patterson, Mickelson, Minor), and the Comparative Neuromuscular Laboratory at the School of Medicine - University of California (Shelton) have been researching this condition for more than 15 years.

Who gets it?
Dynamin-associated exercise intolerance and collapse (d-EIC) is a common inherited disorder in Labrador Retrievers. Black, yellow and chocolate Labradors of both sexes are affected. Signs first become apparent in young dogs - usually between 5 months and 3 years of age (average 14 months). Affected dogs exhibiting symptoms of collapse are usually described as extremely fit, muscular, prime athletic specimens with an excitable temperament and lots of drive.

Description of collapse
Dogs with d-EIC can tolerate mild to moderate exercise, but 5 to 20 minutes of strenuous exercise with excitement induces weakness and then collapse. Typically the rear limbs become weak and unable to support weight and dogs will continue to run while dragging their back legs. In some dogs the rear limb collapse progresses to forelimb weakness and occasionally to a total inability to move. Muscles of the rear limbs are flaccid and there is loss of the patellar reflex during collapse. Some dogs appear to have a loss of balance and may fall over, particularly as they recover from collapse. Most collapsed dogs are totally conscious and alert, still trying to run and retrieve but as many as 25% of affected dogs will appear stunned or disoriented during one or more episodes. Dogs are not painful or stiff during the collapse or upon recovery. A few dogs have died during or immediately after an episode of exercise-induced collapse.

Dogs worsen after exercise
An affected dog’s exercise should ALWAYS be stopped at the first hint of incoordination or wobbliness because the symptoms worsen for 3 to 5 minutes even after exercise has been terminated. A few affected dogs have died during collapse.

Veterinary Evaluation
Nervous system, cardiovascular and musculoskeletal examinations are unremarkable at rest in dogs with EIC as is routine blood analysis at rest and during an episode of collapse. These dogs do not experience heart rhythm abnormalities, low blood sugar, electrolyte disturbances or respiratory difficulty. Body temperature is remarkably elevated during collapse (average 41.7°C, many >42°C) but this finding is common in normal exercise-tolerant Labradors as well. Affected dogs hyperventilate and experience dramatic decreases in their blood carbon dioxide concentration and increases in blood pH similar to unaffected dogs. Patellar reflexes disappear during collapse and for a short period of time during recovery. Testing for myasthenia gravis is negative as is testing for hypothyroidism, hypoadrenocorticism and malignant hyperthermia.

Recovery from collapse
Most dogs recover quickly and are normal within 5 to 25 minutes with no residual pain, weakness or stiffness.

Factors contributing to collapse on a given day
Ambient Temperature. Hot weather does not seem to be necessary to induce collapse, but if the temperature is very warm, collapse is more likely.

Excitement. Collapse is most likely to occur when an affected dog is very excited or stressed.

Type of Exercise. Routine exercise like jogging or hiking is not very likely to induce an episode in dogs with d-EIC. Activities with continuous intense exercise, particularly if accompanied by a high level of excitement...
or anxiety most commonly cause collapse. Activities commonly implicated include pheasant hunting, repetitive "happy retrieves", repetition of difficult retrieves where the dog is receiving or anticipating electric collar correction, and excitedly running alongside an all terrain vehicle.

**Genetics**
In 2007 the genetic mutation responsible for susceptibility to d-EIC was identified. This is a mutation in the gene for dynamin-1 (DNM1), a protein expressed only in the brain and spinal cord where it plays a key role in repackaging synaptic vesicles containing neurotransmitters. DNM1 is not required during low level neurological stimulation, but when a heightened stimulus creates a heavy load on release of CNS neurotransmitters (as with intense exercise, a high level of excitement or perhaps increased body temperature), DNM1 is essential for sustained synaptic transmission in the brain and spinal cord. Dogs with 2 copies of the d-EIC mutation (EE) are susceptible to collapse in those conditions.

**Testing**
DNA testing for the genetic mutation causing d-EIC susceptibility can now be performed.
http://www.cvm.umn.edu/ndl/ourservices/canine neuromuscular/home.html

**How common is d-eic?**
Homozygosity for the DNM1 mutation (EE) is the most common reason for exercise/excitement induced collapse in apparently healthy Labrador Retrievers. Current data shows that 30% to 40% of Labradors are carriers (EN) and 3% to 14% of dogs are affected (EE) and susceptible to collapse. Interestingly, the prevalence of carriers is not different between field trial dogs and show dogs.

**What is the impact of the mutation?**
Most (>83%) affected Labradors (EE) experience at least one episode of collapse by the time they are 4 years of age. Most competitive dogs are unable to continue training and competing at a high level. If trigger activities can be avoided, dogs with d-EIC live normal lives. A few EE dogs never exhibit collapse, perhaps because they do not engage in the required strenuous activity with extreme excitement as required to produce collapse. DNA testing is the only way to know for certain whether a dog has dEIC.

**Treatment**
The best treatment consists of avoiding known trigger activities and activities that involve intensive exercise in conjunction with extreme excitement especially in hot weather. A few d-EIC affected male dogs have experienced improvement after neutering - with an improved ability to tolerate intensive exercise without collapse. Phenobarbital treatment has resulted in similar improvement in some dogs. This improvement may be a result of a decrease in the general excitement level of the dog.

**IMMUNE MEDIATED POLYARTHRITIS IN DOGS**
Susan M. Taylor, DVM, Diplomate ACVIM (Small Animal Internal Medicine)
Professor of Small Animal Medicine
Western College of Veterinary Medicine, University of Saskatchewan
Canada
sue.taylor@usask.ca

Canine inflammatory joint disease can be classified based on its etiology (infectious vs. non-infectious) and radiographic/histologic appearance (erosive vs. nonerosive). Immune mediated, non-infectious, non-erosive polyarthritis (IMPA) is most common and thought to be the result of immune-complex deposition within the joints.

**Clinical manifestations**
Dogs with IMPA are occasionally presented to the veterinarian with a classical history of stiffness, lameness, a “walking on eggshells” gait, reluctance to exercise, fever and swollen joints. It is important to realize, however, that joint effusion and joint pain are only detected in 30% to 70% of dogs with polyarthritis. Some dogs merely exhibit vague non-localizing signs such as depression, anorexia or fever with or without inflammatory hematologic or biochemical parameters. Some dogs with polyarthritis are presented for neck or spinal pain because of polyarthritis affecting the vertebral facetal joints or because of concurrent immune mediated meningitis.
Diagnostic evaluation
Diagnosis of inflammatory joint disease can only be made through cytologic examination of synovial fluid.

Synovial fluid collection
Collection of synovial fluid is a safe, simple procedure that should be routine in every veterinary hospital.

Joints to tap
When evaluating for immune mediated disease, the small distal joints (carpi and hocks) are most commonly affected.

Technique
(1) Clip and prep the area, (2) Flex and extend the joint, palpating the joint space, (3) With the needle attached to the syringe, enter the space, (4) Apply gentle suction (5) When joint fluid appears, release suction, (6) Withdraw the needle from the skin, (7) Disconnect the needle from the syringe, place air in the syringe, reconnect and expel the synovial fluid from the needle onto a glass slide (8) Smear the fluid and air dry before staining.


Analysis
Normal joint fluid is clear and colorless and viscous. Estimates of cell numbers are made from a stained direct smear (normal 100 to 3000 cells/ul; corresponding to less than 3 cells per high dry field). In normal joint fluid, mononuclear cells predominate. An increased mononuclear cell count is seen in joints that have been traumatized or undergone degenerative change. Neutrophils should not be present.

Neutrophils indicate inflammation. In dogs with IMPA and dogs with tick-borne infectious polyarthritis and joints with low grade septic arthritis the synovial fluid will be less viscous than normal and will contain normal appearing neutrophils. Any inflammatory joint fluid should be submitted for aerobic and anaerobic and Mycoplasma culture. Chances of obtaining a positive culture can be enhanced by inoculating synovial fluid into broth enrichment media and incubating for 24 hours prior to routine culture.

Septic arthritis is usually monoarticular in adult dogs. It is usually caused by direct inoculation of the joint through trauma (bites), surgery, or penetrating foreign bodies (quills, grass awns). Cytology may reveal toxic neutrophils with intracellular bacteria. 50% are culture positive.

Tick borne infectious polyarthritis should be considered in endemic regions – realizing that it is not as common as primary immune mediated disease. Polyarthritis is a feature of Borreliosis, Anaplasmosis, Bartonellosis and RMSF. Often there are other systemic abnormalities such as thrombocytopenia or vasculitis. Serology and PCR may be useful in diagnosis. When in doubt, a doxycycline therapeutic trial can be performed. A rapid and sustained response is expected with infectious polyarthritis.

Non-erosive, non-infectious IMPA is much more common than infectious polyarthritis. It can occur as an idiopathic syndrome, as a feature of systemic lupus erythematosus (SLE), or secondary to prolonged antigenic stimulation (reactive polyarthritis) caused by chronic infection, neoplasia, drugs or vaccines.

Once infectious causes have been eliminated in a dog with polyarthritis, it is important to:

1) Look for an underlying cause of reactive polyarthritis. Obtain a thorough history regarding systemic symptoms or recent drug administration. Perform a careful physical examination and consider tests to look for evidence of chronic infection or neoplasia. Endocarditis, diskospondylitis, foreign body abscess, prostatitis, pneumonia and a variety of cancers have been implicated.

2) Look for SLE. Polyarthritis it the most common manifestation of SLE in dogs. Diagnosis of SLE requires two clinical syndromes (e.g. polyarthritis, glomerulonephritis, uveitis, dermatitis, thrombocytopenia, etc.) and a positive antinuclear antibody (ANA) test.

Idiopathic impa
IMPA with no detectable underlying cause is the most common form of polyarthritis diagnosed in dogs. This condition is most common in middle-aged dogs of the sporting and medium and large breeds. Diagnosis is made based on synovial fluid analysis, failure to identify an infectious cause for the polyarthritis and, lack of evidence to support a diagnosis of SLE or reactive polyarthritis.
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PRELIMINARY INVESTIGATIONS OF AN EXERCISE INTOLERANCE SYNDROME IN BORDER COLLIES

Susan M. Taylor, DVM, Diplomate ACVIM (Small Animal Internal Medicine)
Professor of Small Animal Medicine
Western College of Veterinary Medicine, University of Saskatchewan
Canada
sue.taylor@usask.ca

Investigators from the Western College of Veterinary Medicine at the University of Saskatchewan (Taylor, Shmon, Su), the College of Veterinary Medicine at the University of Minnesota (Minor, Patterson, Mickelson), and the Comparative Neuromuscular Laboratory at the School of Medicine, University of California (Shelton) are investigating an exercise intolerance disorder in Border collies we call Border collie collapse (BCC).

Exercise intolerance in border collies
A syndrome of exercise intolerance and collapse has long been recognized in Border collies throughout North America, Europe and Australia. This disorder, which we call Border collie collapse (BCC) appears to be most common in dogs used for working stock, but has also been seen in dogs trained for agility or fly-ball competitions and pet dogs repeatedly retrieving a tennis ball. The collapse in BCC affected dogs has been variably attributed to or called malignant hyperthermia, heat intolerance, heat stroke, exercise-induced hyperthermia, canine stress syndrome, “the wobbles”, and exercise-induced collapse. A presumptive diagnosis of BCC can only be made by eliminating all other causes of exercise intolerance and weakness.

During the last 15 years, as our research team has been researching the syndrome of dynamin-associated exercise induced collapse (d-EIC) in Labrador retrievers, we have been contacted by numerous owners and veterinarians about individual Border collies with an exercise intolerance/collapse syndrome resembling d-EIC. Once the genetic cause for the Labrador condition was established (a dynamin 1 mutation) our team also received DNA samples from collapsing Border collies for testing. All of the dogs tested were negative for...
the dynamin 1 mutation and they were also negative for the RYR1 mutation that has been associated with malignant hyperthermia in dogs. Owners of affected dogs commonly reported that littermates, half-sibs, and offspring of affected dogs were affected, suggesting that BCC may have a heritable basis.

We recently initiated a comprehensive study of BCC. The objectives of this research are to (1) describe the clinical and laboratory features of BCC-related collapse so that it can be recognized by dog owners and veterinarians, (2) to thoroughly evaluate affected dogs to try to establish an efficient means of diagnosis and to gain some insight into the cause of collapse (3) to determine the mode of inheritance and the genetic basis for BCC and (4) to develop a DNA test for the condition. To accomplish these goals we are collecting and evaluating questionnaires completed by owners of affected dogs, we are evaluating dogs with BCC before, during and after participation in a strenuous exercise protocol (retrieving a ball or herding sheep), and we are collecting pedigrees and DNA from affected dogs.

Preliminary results

At rest
Border collies affected by BCC are normal at rest. They are in good body condition, well muscled, and have normal neurologic and orthopedic evaluations. Baseline laboratory evaluation (CBC, Biochemistry profile, arterial blood gas, thyroxine, cortisol) has not revealed any reason for exercise intolerance. Thoracic auscultation, thoracic radiographs, electrocardiograms (ECGs) and echocardiography have all been unremarkable.

Clinical features of BCC
Normal Border collies and Border collies with BCC are being evaluated using one of two strenuous exercise protocols. Exercise is halted at 10 minutes or earlier if there are signs of gait or mentation abnormalities.

Ball chasing dogs. Dogs are evaluated before and after participating in a videotaped 10 minute strenuous exercise protocol where they repeatedly retrieve a tennis ball thrown 40 to 50 meters inside a climate controlled facility.

Sheep herding dogs. Dogs are evaluated before and after participating in a videotaped 10 minute strenuous exercise protocol where they perform a series of continuous short outruns and fetches of three sheep in an outdoor pen.

All of the BCC affected dogs evaluated have exhibited abnormalities in the 15 minutes following exercise. Abnormalities observed have included disorientation, dull mentation, swaying, falling to the side, exaggerated lifting of limbs each step, choppy gait, delayed limb protraction, scuffing of rear and/or forelegs, and crossing legs when turning. All dogs returned to normal by 30 minutes.

Physiologic and laboratory features
Rectal temperature, pulse and respiration, patellar reflexes, ECG, and laboratory evaluations were performed in normal dogs and dogs with BCC immediately after exercise and sequentially for up to 120 minutes after exercise. The study is ongoing, so results reported are preliminary.

Normal and affected dogs experienced alterations in rectal temperature, hematologic, biochemical, blood gas and acid base parameters similar to those previously described in Labrador retrievers and other breeds. All dogs were hyperthermic (mean >42C), and all dogs hyperventilated (mean PaCO2 <10mmHg) after exercise. Plasma lactate and pyruvate concentrations increased significantly after exercise. There have been no significant differences in temperature, pulse, respiration, or any laboratory parameter at any time point between normal and affected dogs. No arrhythmias were detected.

Preliminary conclusions
BCC appears to be an episodic nervous system disorder that can be triggered by exercise. Common causes of exercise intolerance have been eliminated, but the cause of collapse in BCC has not been determined and no clinical or biochemical marker to aid diagnosis has yet been established.

How can you help
If you know of a Border collie that may be affected by BCC please contact us regarding having the dog participate in our study. Questionnaires can be filled out online, and there are opportunities for DNA submission and participation in the clinical phase of the study as well. For more information go to the website: http://www.cvm.umn.edu/vbs/faculty/Mickelson/lab/home.html
Click on Border Collie Collapse

Proceedings of the European Veterinary Conference - Voorjaarsdagen, 2011 - Amsterdam, Netherlands
Diagnostic evaluation

Diagnostic testing recommended in patients with neck pain will vary depending on the most likely differential diagnoses. An attempt should be made to determine whether, in addition to neck pain, the patient has muscle or joint pain, or pain on bulla palpation. Awake spinal radiographs should be performed to look for anomalies, obvious lytic lesions, or evidence of intervertebral disk disease. Screening clinicopathologic testing (CBC, biochemistry profile including creatine kinase(CK), urinalysis) is warranted. Additional tests may include synovial fluid and cerebrospinal fluid (CSF) analysis, appropriate infectious disease serology or antigen testing, systemic evaluation for infections or neoplastic disease, and advanced imaging (especially MRI).

Myositis. Muscular pain as the origin of neck pain can best be determined by finding that other muscle groups are painful. Palpate limb muscles for painfullness, swelling or atrophy. Immune mediated polymyositis and infectious myositis caused by the protozoal organisms Toxoplasma and Neospora are often painful. CK may be elevated. Diagnosis requires biopsy. Diskospondylitis usually causes neck pain with no neurologic deficits. Fever and leukocytosis occur in 30%. Multiple sites are usually infected. Diagnosis is based on radiographs. Blood and urine culture reveal the organism in 75% and 50% of cases. Brucella canis serology is recommended. If the causative organism cannot be found, presume Staphylococcus spp and treat with antibiotics (Cephalexin or Amoxicillin with clavulanic acid) as well as cage rest and analgesics. Resolution of pain and fever is expected within 3 to 5 days. When signs persist consider fine needle aspiration of the disk space under general anesthesia using fluoroscopic guidance to obtain a culture (80% positive). Treat bacterial diskospondylitis with antibiotics for 12 weeks.

Immune mediated polyarthritis involving the facetal joints can cause neck pain. Affected dogs may have a “walking on eggshells” gait but sometimes joints are not swollen and the dogs are not lame. Fever, inflammatory CBC and increased globulins are common. Diagnosis requires appendicular synovial fluid analysis. Degenerative joint disease of the articular facetal joints and synovial cysts in the cervical region are

Animals with neck pain often stand with their head and neck extended and they are reluctant to turn their neck to look to the side.

Neck pain should be assessed as part of every nervous system examination by deep palpation and by resistance to flexion, extension and lateral flexion of the neck. Obviously, if differentials causing cervical instability (cervical fracture/luxation, A-a luxation) are being considered, then manipulation should be delayed until after unsedated lateral radiographs have eliminated those diagnoses.

Traumatic and inflammatory lesions are most likely to be painful. Meninges, nerve roots, muscle and bone have a high density of pain receptors while central nervous system (CNS) tissues (brain and spinal cord) have few. Spinal cord compression is therefore not usually painful unless it results in meningeal traction, nerve root compression or muscular spasm.

Causes of neck pain
Muscle: Myositis, Muscle injury
Joint (facetal joints): Polyarthritis, Degenerative joint disease
Intervertebral disk: Type 1 or Type II disk extrusion or protrusion pinching nerve root or meninges
Nerve root: Neoplasia, Compression (by disk, tumor, fibrous tissue)
Meninges: Neoplasia, Inflammation (Immune, infectious)
Brain: Mass lesion (neoplasia, inflammatory), increased intracranial pressure

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often associated with neck pain. Young large breed dogs (Great Dane, Mastiff, Rottweiler, Bernese Mountain Dog, Scottish Deerhound) are typically presented for signs of cervical spinal cord compression by the enlarged facet joints but sometimes only exhibit cervical pain. Radiographs show periarticular osteophytes surrounding the articular facets and MRI establishes the diagnosis and reveals the degree of spinal cord/nerve root compression.

**Meningitis** (inflammation of the meninges) typically causes severe spinal pain. Neurologic deficits occur when the spinal cord parenchyma is involved (meningomyelitis) but cervical pain is often the only sign. Cerebrospinal fluid analysis is the most reliable antemortem diagnostic test to identify meningitis. Infectious and immune causes are possible. CSF cytology, culture and paired serum and CSF serology can be used to determine the cause of CSF inflammation.

**Steroid-responsive meningitis-arteritis (SRMA)** is a non-infectious immune-mediated meningitis that most commonly occurs in large breed dogs younger than 2 years of age. Breed associated in Beagles, Bernese Mountain Dogs, Boxers, German Shorthaired Pointers, and Nova Scotia Duck Tolling Retrievers. Clinical signs include fever, cervical rigidity, and vertebral pain. Neurologic deficits are uncommon. CSF analysis shows elevated protein and neutrophilic pleocytosis. IgA concentrations may be increased in CSF and serum. Some dogs have polyarthritis. Cultures and serology are negative. Treatment is with immunosuppressive doses of corticosteroids tapered to low-dose alternate-day therapy over 4 to 6 months. Dogs that do not respond completely to prednisone and dogs that relapse during prednisone tapering may benefit from azathioprine (Imuran) for 8 to 16 weeks. Prognosis for survival and complete resolution is excellent.

**Granulomatous meningoencephalitis (GME)** is a common idiopathic inflammatory disorder of the CNS. Most affected dogs have neurologic deficits reflecting involvement of the brain or cervical spinal cord. Marked meningeal inflammation and neck pain are common. CSF contains an increase in globulin and increased lymphocytes, monocytes, plasma cells, large mononuclear cells, and sometimes neutrophils. Cultures and serology are negative. MRI typically reveals a contrast enhancing mass or patchy inflammatory infiltrates. Prednisone administration often causes temporary dramatic improvement. More aggressive chemotherapy using cytosine arabinoside, cyclosporine or leflunomide has resulted in substantial clinical improvement and longer survival in some dogs. Prognosis for prolonged or permanent recovery is poor.

**Hemorrhage:** Hemorrhage into the subarachnoid space secondary to trauma, congenital or acquired bleeding disorders or primary or metastatic spinal neoplasia may cause severe neck pain and sterile meningitis.

**Intracranial masses.** Neck pain can be a prominent sign in dogs with intracranial masses (usually neoplasia) and also with other disorders causing increased intracranial pressure (like hydrocephalus). Diagnosis is suspected based on finding subtle concurrent neurologic forebrain abnormalities, and confirmed with MRI.

**ATYPICAL SEIZURE EVENTS IN DOGS**

Susan M. Taylor, DVM, Diplomate ACVIM (Small Animal Internal Medicine)
Professor of Small Animal Medicine
Western College of Veterinary Medicine, University of Saskatchewan
Canada
sue.taylor@usask.ca

A seizure is the clinical manifestation of abnormal electrical activity in the brain. Seizures can occur as the response of a normal brain to an intoxication or a metabolic disorder such as hypoglycemia, hepatic encephalopathy or hypocalcemia. Recurrent seizures (epilepsy) are most often secondary to structural brain disorders such as hydrocephalus, neoplasia or inflammation or can be a manifestation of idiopathic epilepsy.

**Generalized tonic-clonic seizures** typically including a loss of consciousness and sustained muscular contraction. The animal typically falls to its side in opisthotonus with the limbs extended. Salivation, urination and defecation may occur. There is rhythmic contraction of limbs resulting in paddling, and chewing movements lasting for seconds to several minutes. A post-
ictal phase may be characterized by confusion, excitement, blindness, ataxia or deep sleep.

Partial seizures, also called focal seizures, are thought to result from localized abnormal electrical discharges in the brain, with clinical signs reflecting the function of the portion of the brain generating the seizure. Simple focal motor seizures generally consist of abnormal movement of a body part such as repeatedly turning the head to one side, rhythmic contraction of a limb or a group of muscles, head tremor or chewing movements. It can be difficult to distinguish simple focal motor seizures from paroxysmal movement disorders known as dyskinesias. Dyskinesias are suspected in people based on a lack of postictal signs, normal merriment during episodes, normal electroencephalogram (EEG) between episodes, failure to respond to anticonvulsant medication and lack of progression to generalized seizure activity.

Focal seizures may also cause predominantly autonomic signs such as vomiting, diarrhea, excessive salivation, repetitive swallowing, retching, and apparent abdominal discomfort. Complex focal seizures (formerly called psychomotor seizures) are focal seizures with concurrent alterations of awareness. Affected dogs may seem confused or stunned and may not respond to their owners while engaging in abnormal motor activities such as head pressing, head bobbing, shaking or pacing (automatisms). Some complex focal seizures are manifested as bizarre behavior such as unprovoked aggression, confusion, extreme fearfulness, uncontrolled vocalizations, or hysteria.

In the past, generalized tonic-clonic seizures were considered the most common type of seizure in dogs with idiopathic epilepsy and partial seizures or partial onset generalized seizures were considered indicative of intracranial pathology. Recent reviews of seizure characteristics in dogs of many breeds with primary idiopathic epilepsy have demonstrated that a variety of partial or focal seizures can be seen, with episodes including behavioral, motor and/or autonomic symptoms. Although in most cases partial seizures evolve into generalized tonic clonic seizures, in some cases they do not, so it is important to recognize these partial seizures as seizure events.

Atypical seizures / paroxysmal dyskinesia of labrador retrievers
An episodic movement disorder that may be a form of focal motor seizure has been commonly recognized in Labrador Retrievers. This disorder has been called atypical epilepsy, paroxysmal dyskinesia or episodic dyskinesia. A significant proportion of Labrador retrievers with idiopathic epilepsy present either initially or during each episode with these atypical events. Some simply stagger and look dazed or confused for a few seconds or minutes and then recover, without ever falling over. Others have a 2 to 5 minute episode (occasionally longer) where they appear anxious and are unable to stand erect and walk but are able to crawl to their desired location. Affected dogs maintain consciousness and can obey commands during episodes. Episodes are most likely to occur when the dog is drifting off to sleep or when awaking from sleep in many dogs but exercise and excitement are common triggers in others. Some dogs have a dramatic decrease in their episode frequency when treated with chronic oral anticonvulsant therapy. Many affected dogs also develop more classical generalized tonic-clonic seizures later in life.

Focal seizures / dyskinesia causing head-bobbing
Episodic head bobbing syndromes in English bulldogs, Boxers (side to side in “no” direction) and Labrador retrievers and Boxers (up and down in “yes” direction) may be movement disorders or else focal motor seizures that do not respond very well to anticonvulsant therapy.

Focal seizures with autonomic signs
We have evaluated dogs with repetitive episodes of autonomic signs that we believe to have a focal seizure disorder. Signs may include vomiting, diarrhea, apparent abdominal pain, drooling, repetitive swallowing or gulping, and compulsive licking of the carpet or floor or eating grass. It is not uncommon for the signs to last for hours, rather than the seconds to minutes usually associated with seizure activity in epileptic dogs. Many affected dogs have had extensive evaluations for their recurrent gastrointestinal symptoms. Some affected dogs have responded well to chronic oral anticonvulsant therapy, supporting the suspicion that these are seizure events.

Episodic dyscontrol (rage syndrome) in dogs
Complex focal seizures (formerly called psychomotor seizures) can sometimes be manifested as episodes of
unprovoked aggression. This remains controversial because it is very difficult to distinguish episodic dyscontrol (“rage syndrome”) from severe aggression (a behavioral disorder).

Dogs with known aggressive tendencies or recognized dominance issues that exhibit owner-directed aggression may be suffering from a behavioral disorder. Some affected English Springer spaniels may have low brain levels of serotonin (a calming neurotransmitter).

A less common form of severe episodic aggression is seen in young male English Springer Spaniels, Cocker Spaniels, St. Bernards and Bull terriers. These dogs experience unpredictable outbursts of aggression, often when waking from sleep, during which they will attack surrounding people or inanimate objects. Just prior to the attack dogs may crouch, growl, have pupillary dilation and wag their tail for a few seconds. During the attack the dog cannot be distracted. After the outburst dogs may have a short period of apparent confusion but then return to their normal personality EEGs have demonstrated epileptiform in some affected dogs. Response to anticonvulsant therapy is generally poor and these dogs present a significant risk to household members - so are usually euthanized.

MEGAESOPHAGUS AND OTHER PROBLEMS CAUSING REGURGITATION
Reto Neiger
Dr. med. vet. PhD, DACVIM, DECVIM-CA
Small animal Clinic, Justus-Liebig University, Giessen, Germany
eto.neiger@vetmed.uni-giessen.de

Regurgitation is the typical clinical signs seen in dogs or cats with oesophageal disorders. It is important to differentiate regurgitation from vomiting (Tab 1), as the clinical assessment for both conditions is quite different. Causes of regurgitation can be due to intraluminal and extramural obstruction (Tab 2). Besides oesophageal foreign bodies, the most common diagnosis of oesophageal disorders in dogs is megaesophagus.

### Table 1. Differentiation between regurgitation and vomiting

<table>
<thead>
<tr>
<th></th>
<th>Regurgitation</th>
<th>Vomiting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preliminary signs</td>
<td>None</td>
<td>Retching, nausea</td>
</tr>
<tr>
<td>Abdominal compression</td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td>Localization of problem</td>
<td>Esophagus (pharynx)</td>
<td>Gastrointestinal, metabolic, neurological</td>
</tr>
<tr>
<td>Food</td>
<td>Non-digested Well formed</td>
<td>Digestion variable Mucous/bile/blood possible</td>
</tr>
<tr>
<td></td>
<td>Saliva covered</td>
<td></td>
</tr>
<tr>
<td>Time point after feeding</td>
<td>Immediate or later</td>
<td>Often delayed (for hours))</td>
</tr>
<tr>
<td>Acid, bile</td>
<td>Neutral to acid No bile</td>
<td>pH varies a lot +/- bile</td>
</tr>
</tbody>
</table>

Evaluation of oesophageal disorders can often be achieved with the use of plain radiographs. However, it is important to remember that dilation of the oesophagus can occur during sedation and anaesthesia. Some free air in the cranial oesophagus is frequently seen in...
Companion Animal Programme

anxious and stressed animals and is not equivalent with a diagnosis of megaeosophagus. Contrast studies with barium can help with the diagnosis of strictures as well as with intra- and extraluminal obstructions. In all cases where a megaeosophagus has been reliably diagnosed on plain radiographs, giving barium to confirm the diagnosis is not indicated as these patients tend to be at increased risk for reflux and aspiration. Giving an iodine-based liquid contrast bolus and taking radiographs immediately afterwards (lateral view) might be a better choice than barium because aspiration of liquid iodine contrast agent is of minor consequence as it will be absorbed very quickly (within few hours). In cases where a diagnosis cannot be reached with a contrast study, the patient may need to have its oesophageal peristalsis evaluated with fluoroscopy. Again liquid barium or barium mixed with food should be used. Finally, endoscopy is useful to visualise the mucosa (inflammation) and diagnose a tumour or granuloma.

Megaeosophagus

Idiopathic megaeosophagus is the most common cause of regurgitation in the dog. It is characterised by moderate to severe oesophageal dilation and ineffective oesophageal peristalsis. Several forms have been described: congenital idiopathic, acquired idiopathic, and acquired secondary megaeosophagus. Congenital idiopathic megaeosophagus is a generalised dilation and hypomotility of the oesophagus causing regurgitation and failure to thrive in puppies shortly after weaning. Increased breed incidences are reported for the Irish setter, Great Dane, Greyhound, German shepherd, Labrador and Golden retriever, Chinese Shar-Pei, and Newfoundland breeds, but heritability has been demonstrated only in the Miniature Schnauzer and Fox terrier breeds. The pathogenesis of the congenital form is incompletely understood, although recent studies point to a defect in the vagal afferent innervation to the oesophagus.

Acquired secondary megaeosophagus may develop in association with other conditions (Tab 2). Myasthenia gravis accounts for at least 25% of the secondary cases. In some cases myasthenia gravis is focal with no other clinical signs except for the signs of the megaeosophagus. Most cases of adult-onset megaeosophagus have no known aetiology and are referred to as acquired idiopathic megaeosophagus. Recent studies have suggested a defect in the afferent neural response to oesophageal distension. The responses of the upper and lower oesophageal sphincters to swallowing appear to be intact, but oesophageal distension does not initiate peristaltic contractions in affected animals. Haematology, serum biochemistry, and urinalysis should be performed in all cases to investigate possible secondary causes of megaeosophagus (e.g., hypoadrenocorticism, lead poisoning). A recent risk factor analysis suggests that oesophagitis increases the risk for the development of megaeosophagus. It is not yet clear whether oesophagitis is cause or consequence of megaeosophagus. In acquired secondary megaeosophagus the following diagnostic test should be performed: complete haematology and biochemistry, nicotinic acetylcholine receptor antibody testing (rule-out myasthenia gravis). Further possible tests are antinuclear antibody testing, electromyography, nerve conduction velocity and muscle biopsy. Although hypothyroidism and hypoadrenocorticism have been cited repeatedly as a potential cause or complicating factor in the development of canine megaeosophagus, hypothyroidism was not identified as a risk factor in a case-control study suggesting that hypothyroidism should be considered only on a case-by-case basis.

| Table 2. Major Causes of Regurgitation |
| See next page |

Treatment of a megaeosophagus is based on the cause, if one is found. In animals with aspiration pneumonia aggressive intravenous antibiotic therapy (e.g. cephalosporin and gentamycin), infusion and possibly inhalation is indicated. Prokinetic drugs such as metoclopramide or cisapride (where available) have no effect on oesophageal motility; bethanechol has been suggested but no long term success has been seen. We have used Pyridostigmin (0.2-2 mg/kg orally q8-12h) even in cases with negative acetylcholine receptor antibodies with success. Prognosis of an idiopathic megaeosophagus is always questionable. Mean survival of dogs diagnosed with megaeosophagus at the university of Giessen over 2 year period was around 4 months. Some animals might show few problems, especially if feeding regiment is strictly adhered. Animals must be fed from an elevated position and dogs should remain in a vertical position afterwards for about 10-15 minutes. Keeping the animals in this position might be difficult, especially in large breeds and thus construction of a special chair might help. Construction plans how to build such a Bailey Chair have been published online (http://www.
Continuous regurgitation might be better off with a gastric tube (PEG-tube) which is easiest placed endoscopically. The structure of the food (dry, wet, meat balls) with best results is different between patients and the owners must try various possibilities to find what works best. Patients with con-

<table>
<thead>
<tr>
<th>Intraluminal obstruction</th>
<th>Foreign body</th>
<th>Dog &gt;&gt; Cat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neoplasia</td>
<td></td>
<td>Dog &amp; Cat</td>
</tr>
</tbody>
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**Intramural abnormalities**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th>Dog &gt;&gt; Cat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Megaesophagus</td>
<td>idiopathic (congenital or acquired)</td>
<td>Dog</td>
</tr>
<tr>
<td></td>
<td>Myasthenia gravis (focal or generalised)</td>
<td>Dog</td>
</tr>
<tr>
<td></td>
<td>Lupus erythematosus</td>
<td>Dog</td>
</tr>
<tr>
<td></td>
<td>Endocrine disorder (hypothyroidism? hypoadrenocorticism?)</td>
<td>Dog</td>
</tr>
<tr>
<td></td>
<td>Neuropathy</td>
<td>Dog &amp; Cat</td>
</tr>
<tr>
<td></td>
<td>Myopathy</td>
<td>Dog</td>
</tr>
<tr>
<td></td>
<td>Infection (distemper, toxoplasmosis)</td>
<td>Dog</td>
</tr>
<tr>
<td></td>
<td>Intoxication (lead, organophosphate, thallium)</td>
<td>Dog</td>
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<thead>
<tr>
<th></th>
<th></th>
<th>Dog &gt; Cat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esophagitis</td>
<td>Reflux, chemical, heat</td>
<td>Dog &gt; Cat</td>
</tr>
<tr>
<td></td>
<td>Post anesthesia,</td>
<td>Dog &lt; Cat</td>
</tr>
<tr>
<td></td>
<td>Post esophagitis</td>
<td>Dog &lt; Cat</td>
</tr>
<tr>
<td>Granuloma</td>
<td>Spirocerca lupi</td>
<td>Dog</td>
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**Extraluminal obstruction**

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<thead>
<tr>
<th></th>
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<tr>
<td>Vascular ring abnormality</td>
<td></td>
<td>Dog &gt; Cat</td>
</tr>
<tr>
<td>Mediastinal mass</td>
<td>Lymphoma</td>
<td>Dog &lt; Cat</td>
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<tr>
<td></td>
<td>Thymoma</td>
<td>Dog &amp; Cat</td>
</tr>
<tr>
<td></td>
<td>Abscess</td>
<td>Dog &amp; Cat</td>
</tr>
<tr>
<td></td>
<td>Lymphadenomegaly</td>
<td>Dog &amp; Cat</td>
</tr>
<tr>
<td>Hiatel hernia</td>
<td></td>
<td>Dog &gt; Cat</td>
</tr>
</tbody>
</table>
VOMITING IN THE DOG AND CAT – CAUSE AND THERAPY
Reto Neiger
Prof. Dr. med. vet. PhD, DACVIM, DECvim-CA
Small animal Clinic, Justus-Liebig University, Giessen, Germany
reto.neiger@vetmed.uni-giessen.de

Definition
Vomiting is defined as retrograde, active, forceful ejection of food or fluid from stomach or small intestine (duodenum). It is imperative to make the distinction to regurgitation (see table in talk on Megaoesophagus for differentiation), which is passive and results in the expulsion of food and fluid mainly from the oesophagus.

Pathophysiology
Vomiting, a reflex act in dogs and cats requires the coordination of the gastrointestinal, musculoskeletal and nervous systems. Activation of the emetic centre, which lies within the reticular formation of the medulla oblongata, can happen by various stimuli. The neurons can be activated by certain blood-borne toxins or drugs through activation of the chemoreceptor trigger zone (CRTZ), which is located within the area postrema on the floor of the fourth ventricle. This stimulus is called the humoral pathway. Furthermore vagal and sympathetic neurons stimulated by receptors in the abdominal viscera and many other sites throughout the body can produce a vomiting reflex in the emetic centre, which is called the neural pathway. Receptor activation can occur as a result of inflammation, irritation, distension or hypertonicity, among other factors. Activation of the CRTZ is induced by a variety of humoral emetogenic substances (e.g. uremic toxins, apomorphine, cardiac glycosides, cytotoxic agents) but the reflex arch needs to be intact in order for animals to vomit, since ablation of the area postrema abolishes emesis. Finally impulses from the vestibular centre (inner ear) during motion sickness are thought to travel through the CRTZ to the vomiting centre.

Diagnostic plan
As mentioned, the first step in a vomiting patient is to differentiate between true vomiting and regurgitation. Vomiting is associated with salivation, retching, and violent abdominal contractions. Expulsion of yellow material suggests bile-stained duodenal contents and therefore vomiting. Measuring the pH of the expelled material is rarely helpful to differentiate between vomiting and regurgitation, since food, which has been lying in the oesophagus for a long time will ferment and become acidic as well.

The next step will be to determine if the animal has a self-limiting or possible life-threatening problem. This crucial assessment is based on a thorough history and a careful physical examination. Animals with an acute, self-limiting problem rarely require a thorough workup and symptomatic and dietary treatment is sufficient. Life-threatening acute vomiting, however, requires an in-depth diagnostic evaluation, specific, supportive and often antiemetic therapy. Finally, animals with chronic vomiting always require a work-up to find the cause of the problem.

Self-limiting acute vomiting in dogs and cats is mostly due to ingestion of incompatible food or any form of dietary indiscretion. These animals are mainly presented with a history of infrequent vomiting of food, mucus, bile or foreign material (grass, wood, bone, etc.). Questions concerning drug administration (non-steroidal anti-inflammatory medications, heart glycosides, etc.) or exposure to chemicals (herbicides, fertilizers, cleaning agents, etc.) are warranted. The presence of mild diarrhoea may indicate dietary indiscretion or gastrointestinal parasites (ascarids, Giardia). Laboratory evaluation in animals with self-limiting vomiting should include a packed cell volume and total protein. Faecal analysis including a fresh smear and zinc sulfate flotation for Giardia is recommended. In cats analysis of faeces for trichomonas fetus might be indicated.

Animals with life-threatening vomiting may show haematemesis, depression, fever, dehydration, abdominal pain and signs of shock. The initial minimum database includes a CBC, biochemical profile, urinalysis, faecal examination, blood tests for pancreatitis (PLI, TLI) and in many cases diagnostic imaging. This will help to eliminate infectious (e.g. parvovirus) or metabolic causes (e.g. renal insufficiency, hepatopathy, hypoadrenocorticism, acute pancreatitis) and will allow the assessment of electrolyte abnormalities and fluid derangements. Radiographs help to find radiodense foreign bodies, linear foreign bodies or intestinal obstructions with partial or total ileus. If these initial evaluations can not reveal the cause, additional diagnostic procedures such as upper gastrointestinal-barium series, abdominal ultrasound, endoscopy, ACTH-
stimulation test or surgical exploration of the abdomen are necessary.
In chronic vomiting cases, a similar work-up as in life-threatening disorders will be necessary. Since adverse reactions to food (food allergy, food intolerance) are a potential problem in dogs and cats with chronic vomiting, elimination of the suspected food, followed by recrudescence of the signs when the patient is subsequently challenged with the incriminated foodstuff, should be pursued. Other more chronic problems are inflammatory bowel disease or gastrointestinal neoplasm amongst others.

**Therapy**
With acute vomiting, the animal should be kept in a quiet place, food withheld for 12 to 24 hours and water given in small portions over the day. Starving over long periods is no longer adequate and feeding should start as soon as the animal can tolerate oral feeding. Refeeding should start with highly digestible diet three to four times daily in the first few days and then the original diet can be gradually reintroduced. If the animal is anorectic, tube feeding (naso-oesophageal intubation) might be necessary. If dehydration is present, parenteral fluid is necessary, often supplemented with potassium (10-30 mEq/l).

**Antiemetics**
Since most medical approaches to antiemetic therapy is based upon the neurotransmitter-receptor interactions, it is important to understand these mechanisms. In the chemoreceptor trigger zone (CRTZ), several neurotransmitters and receptors have been found, including dopamine (D1-dopaminergic), neurokinin1 (NK1), norepinephrine (α2-adrenergic), 5-hydroxytryptamine (5-HT3-serotonergic), acetylcholine (M3-cholinergic), histamine (H1 and H2-histaminergic), and enkephalins (ENKα, ENKβ, and ENKγ). In the emetic center, the only receptors shown to be present so far are NK1, 5-hydroxytryptamine3a, and α2-adrenergic. The α2-receptors in the emetic center and in the CRTZ may be antagonized by α2-antagonists (e.g., yohimbine, atipamezole) or by mixed α1/α2-antagonists (e.g., prochlorperazine, chlorpromazine). In the vestibular apparatus, muscarinic M3-receptors and acetylcholine have been demonstrated, and therefore mixed M1/M3-antagonists (e.g., atropine, scopolamine) and pure M1-antagonists such as pirenzepine may inhibit motion sickness in dogs and cats. Many receptors are found in the gastrointestinal tract, but the NK1, 5-HT1 receptors are likely to play the most important role in the initiation of vomiting. Cyto-
toxic agents cause the release of 5-HT from enterochromaffin cells in the gastrointestinal tract, which then activate the 5-HT3 receptors on afferent vagal fibers. Thus, vomiting induced by 5-HT3-receptor activation can be completely abolished by treating the patient with a 5-HT3-antagonists, such as dolesatron, ondansetron, granisetron, or tropisetron. Another antagonist of 5-HT3 is metoclopramide, but only in high concentrations.

Recently, substance P has been found to result in emesis by binding to the NK1-Receptor. NK1-receptor antagonists block central and peripheral vomiting both in dogs and ferrets.
Several antiemetic drugs have been formulated based on the neurotransmitter-receptor system just mentioned (Table 1). These antagonists are classified as α1-adrenergic, D2-dopaminergic, NK1, H1-histaminergic, H2-histaminergic, M1-muscarinic cholinergic, 5-HT3-serotonergic, and 5-HT4-serotonergic. Some of these drugs have several mechanisms of action as antiemetics. For example, the phenothiazines (e.g., prochlorperazine, chlorpromazine) are antagonists of α1- and α2-adrenergic, D2-dopaminergic, H1- and H2-histaminergic, and muscarinic cholinergic receptors. They are very potent but should be avoided in dehydrated or hypotensive animals without previous fluid support. Also, these drugs are contraindicated in animals with a known seizure history. Metoclopramide blocks receptors in the CRTZ, increases the threshold in the emetic center, and also has an effect on the visera. Metoclopramide increases the lower esophageal sphincter tone, decreases pyloric sphincter tone, and increases gastric and duodenal amplitude and contraction. This makes metoclopramide useful in controlling vomiting that is due to nonspecific gastritis or gastric motility disorders. The prokinetic activity of metoclopramide seems to be limited to the liquid phase of gastric emptying, as a study showed no effect on gastric emptying rate of digestible solids. Metoclopramide can be given orally, intravenously, or as a constant rate infusion.
A new NK1 receptor antagonist, maropitant, has recently been licensed for dogs in many countries. In various licensing studies, maropitant has been highly effective in abolishing vomiting induced through peripheral emetogenic stimuli, such as cisplatin or central emetogenic stimuli, such as apomorphine. Furthermore, even travel-sickness induced vomiting was successfully suppressed by maropitant.
GASTRIC EMPTYING PROBLEMS AND HOW TO ASSESS THEM
Reto Neiger
Prof. Dr. med. vet. PhD, DACVIM, DECVIM-CA
Small animal Clinic, Justus-Liebig University, Giessen, Germany
reto.neiger@vetmed.uni-giessen.de

Gastric emptying is a highly co-ordinated physiological response to the presence of food or liquid in the stomach. This emptying can be impaired in several pathological conditions. There are three general gastric motility disorders a) accelerated gastric emptying, b) retrograde transit and c) delayed gastric emptying. The latter can be due to mechanical or functional obstruction. Causes of mechanical obstruction are e.g. pyloric stenosis, chronic hypertrophic pyloric gastropathy, foreign bodies, pyloric or duodenal neoplasia, chronic hypertrophic gastritis, or intra-abdominal masses causing external compression of the pylorus. Functional disorders of gastric emptying result from one or more abnormalities in gastric motility. These motility disorders cause no morphological changes. Gastric motility may be affected by inflammatory and infiltrative lesions, gastric ulceration, inflammatory bowel disease, altered electrolyte concentrations and acid-base disturbances, recent abdominal surgery, diabetes mellitus and several drugs.

In normal monogastric animals the pylorus causes a sieving function during the postprandial period. Liquids pass easily and empty relatively rapid from the stomach by first-order kinetics. The rate of liquid expulsion from the stomach is proportional to its volume: the greater the gastric fluid, the more rapidly it is expelled. Solids are handled differently, requiring reduction to small particles (< 2mm in diameter) before passage through the pyloric canal. This emptying is determined by composition (carbohydrates empty faster than proteins, which in turn empty faster than fats); in general, however, emptying is based mainly upon caloric density of the ingesta. In dogs large food particles are normally retained in the stomach after feeding and will pass into the duodenum only during the interdigestive period. During this period, called the migrating motility complex (MMC) or “housekeeper contraction”, a special mechanism exists to expel these larger particles together with swallowed saliva, a small basal secretion of mucus and cellular debris. One MMC, which lasts about 2 hours, is divided in 4 phases, the third causing intense bursts of action potentials resulting in powerful distal gastric peristaltic contraction and emptying of larger particles. Abnormal gastric emptying is assumed to affect solid-phase gastric contents rather than liquids. Diagnosis of mechanical obstruction is generally straightforward whereas functional obstruction causing delayed gastric motility may be more difficult to confirm.

Several methods are available for evaluating gastric emptying. Contrast radiographic techniques are the most available means for diagnosing gastric motility disorders in veterinary practice and crude assessments of gastric emptying function are possible. Gastric emptying times for liquids, including barium suspension, are relatively short (~ 1 hour in cats, up to 3 hours in dogs). Studies using barium mixed with food have shown gastric emptying times varying from 4-16 hours in the dog and 4-17 hours in the cat, depending on the composition of the food, thus making it difficult to diagnose an emptying disorder unless gastric emptying times are markedly prolonged. Furthermore, when solid meals are mixed with barium granules or suspension the barium can dissociate from the food and redistribute into the liquid phase of the gastric contents. Barium-impregnated polyethylene spheres (BIPS) have been used to quantify gastric emptying in dogs and cats. BIPS are produced in two sizes: 1.5 mm and 5 mm in diameter. The small BIPS are designed to empty with small particles, thereby mimicking solid-phase gastric emptying. Large BIPS tend to be retained in the stomach longer than small BIPS, often remaining after the test meal has passed into the duodenum and then leaving the stomach once the MMC begins. The use of BIPS may be more useful for documentation of mechanical rather than functional obstruction. Ultrasonography is an excellent tool to assess gastric intramural abnormalities. It can also be used to reveal intraluminal foreign bodies and mucosal calcification. In human medicine ultrasonography has been used as an alternative method of measuring gastric emptying times. Evidence of delayed gastric emptying in the dog is provided by finding more than just a small amount of fluid in the stomach 18 hours after feeding.

Only recently gastric emptying has been evaluated by means of breath testing. The main advantages of breath test technology are that no radiation is required,
THERAPY OF FELINE HYPERTHYROIDISM – MEDICAL VERSUS RADIOACTIVE IODINE
Reto Neiger
Prof. Dr. med. vet. PhD, DACVIM, DECVIM-CA
Small animal Clinic, Justus-Liebig University, Giessen, Germany
reto.neiger@vetmed.uni-giessen.de

Key Points
Therapy of feline hyperthyroidism is accomplished with drugs or surgery but the best option is to use radioactive iodine. Success rate is 95-98% with few cases needing a second treatment. Hypothyroidism is exceedingly rare. Complications, such as renal failure, are not as common as thought and despite azotaemia radioactive iodine can be given.

Feline hyperthyroidism is the most common endocrine disorder in elderly cats. The exact reason for this problem is unknown but various environmental influences (litter, diet, antiparasitic drugs, etc.) have been thought to be involved. Most cats have either adenomatous hyperplasia or a uni- or bilateral adenoma of the thyroid gland. Carcinoma of a thyroid gland is rare (2-3% of hyperthyroid cats).

There are various therapy options available for treatment of hyperthyroidism, most commonly drugs, surgery of radioactive iodine.

Methimazole or carbimazole (a pro-drug of methimazole) act by blocking intrathyroidal conversion of iodothyronines into T3 and T4. The drug must be given live-long which might be a problem in certain cats. Animals developing side-effects to one of these medications should not be treated with the other as cross-sensitivity can occur. Side-effects with methimazole usually occur within the first month of therapy and include GI upset (anorexia and vomiting are the biggest problems), facial scratching and agranulocytosis. Reactions usually subside within 2 weeks after stopping medication but re-occur if the drug is re-introduced. Most gelenic forms are oral, but transdermal ointments are available in some countries.

Surgical excision of a unilateral or bilateral adenomatous gland has been well publicised. The following points should usually be done when surgery is anticipated: Treat the hyperthyroidism medically for 4-6 weeks prior to surgery. These cats are anaesthetic risks until euthyroid. Remove all abnormal thyroid tissue. If surgical excision is performed and initial hypothyroidism occurs, corticosteroids are indicated. If hypothyroidism persists, thyroxine may be indicated.

Scintigraphy is still the gold standard technique for measuring gastric emptying and, if available, is probably the best method currently available for evaluating gastric emptying in dogs and cats. 99Technetium is the isotope most widely used. Regardless of the method used, the investigator must be aware of the large inter-individual variability which exists in the rate of gastric emptying in normal healthy individuals and of the factors known to influence the gastric pattern.

Table 1: Methods to assess gastric emptying

<table>
<thead>
<tr>
<th>Technique</th>
<th>Information gained</th>
<th>Availability in pets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plain radiographs</td>
<td>*</td>
<td>+++</td>
</tr>
<tr>
<td>Contrast radiographs (barium)</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Contrast radiographs (BIPS)</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Ultrasonography</td>
<td>*</td>
<td>++</td>
</tr>
<tr>
<td>Endoscopy</td>
<td>*</td>
<td>**</td>
</tr>
<tr>
<td>Breath test</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Scintigraphy</td>
<td>+++</td>
<td><em>(referral institution)</em></td>
</tr>
<tr>
<td>Computed tomography (CT)</td>
<td>*</td>
<td><em>(referral institution)</em></td>
</tr>
<tr>
<td>Manometry</td>
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BIPS: barium-impregnated polyethylene spheres

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<tr>
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<td>*</td>
<td><em>(referral institution)</em></td>
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<tr>
<td>Manometry</td>
<td>+++</td>
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BIPS: barium-impregnated polyethylene spheres

Feline hyperthyroidism is the most common endocrine disorder in elderly cats. The exact reason for this problem is unknown but various environmental influences (litter, diet, antiparasitic drugs, etc.) have been thought to be involved. Most cats have either adenomatous hyperplasia or a uni- or bilateral adenoma of the thyroid gland. Carcinoma of a thyroid gland is rare (2-3% of hyperthyroid cats).

There are various therapy options available for treatment of hyperthyroidism, most commonly drugs, surgery of radioactive iodine. Methimazole or carbimazole (a pro-drug of methimazole) act by blocking intrathyroidal conversion of iodothyronines into T3 and T4. The drug must be given live-long which might be a problem in certain cats. Animals developing side-effects to one of these medications should not be treated with the other as cross-sensitivity can occur. Side-effects with methimazole usually occur within the first month of therapy and include GI upset (anorexia and vomiting are the biggest problems), facial scratching and agranulocytosis. Reactions usually subside within 2 weeks after stopping medication but re-occur if the drug is re-introduced. Most gelenic forms are oral, but transdermal ointments are available in some countries.

Surgical excision of a unilateral or bilateral adenomatous gland has been well publicised. The following points should usually be done when surgery is anticipated: Treat the hyperthyroidism medically for 4-6 weeks prior to surgery. These cats are anaesthetic risks until euthyroid. Remove all abnormal thyroid tissue. If surgical excision is performed and initial hypothyroidism occurs, corticosteroids are indicated. If hypothyroidism persists, thyroxine may be indicated.

Scintigraphy is still the gold standard technique for measuring gastric emptying and, if available, is probably the best method currently available for evaluating gastric emptying in dogs and cats. 99Technetium is the isotope most widely used. Regardless of the method used, the investigator must be aware of the large inter-individual variability which exists in the rate of gastric emptying in normal healthy individuals and of the factors known to influence the gastric pattern.

Table 1: Methods to assess gastric emptying

<table>
<thead>
<tr>
<th>Technique</th>
<th>Information gained</th>
<th>Availability in pets</th>
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<tbody>
<tr>
<td>Plain radiographs</td>
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<tr>
<td>Contrast radiographs (barium)</td>
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<td>Ultrasonography</td>
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<td>Endoscopy</td>
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<td>Breath test</td>
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thyroid scanning is not available and at the time of surgery you can see both thyroid glands, remove both of them. Normal thyroid tissue would have atrophied due to the increased level of T4. Some clinicians have advocated staged thyroidectomies though no studies have been published. Staged procedures should decrease the risk of hypoparathyroidism but they may also result in the need for a second surgical procedure to correct recurrent hyperthyroidism. Post-surgery: do not get overzealous with fluid therapy. If bilateral thyroidectomy was performed, measure serum calcium once daily for 7 days as iatrogenic hypoparathyroidism may not develop immediately. Signs of hypocalcemia include facial muscle twitching, ear twitching and rubbing of the face. Clearly the best therapy option for the treatment of hyperthyroidism is the administration of radioactive iodine. Thyroid concentrates iodine and radioactive iodine will destroy the functioning thyroid cells without destroying non-thyroidal tissue or normal suppressed thyroid tissue. Radioactive iodine is a beta-emitter and travels only short distances in tissue (few millimetres). Once given, it quickly accumulates in the active thyroid cells, but also in salivary tissue (and is excreted by saliva in the first days), in the gastric mucosa (and can be found in vomitus) and in the kidney where it is excreted via urine. Half-life of $^{131}$iodine is around 8 days. There are various ways of calculating the dose of radioactive iodine that should be given. The most complicated way is to perform a tracer study and calculate the dose based on the uptake. This method is cumbersome and is rarely used. More commonly, either a fixed dose (between 3 to 6 mCi) or a dose based on various parameters (thyroxin level, size or thyroid gland, clinical signs, etc.) is given both with equal effect. The advantage of radioactive iodine therapy is its high success rate (around 95-98%). Few cats need a second therapy and exceedingly few will develop permanent hypothyroidism that needs substitution therapy. Furthermore, due to the short distance effect of $^{131}$Iodine there a virtually no effect on the parathyroid glands and thus no hypoparathyroidism occurs. The effect of radioactive iodine is quick and most cats are euthyroid or initially hypothyroid within 7-10 days. $^{131}$Iodine can be given orally, subcutaneously or intravenously, depending on the availability of the compound. Most centres inject $^{131}$Iodine and the oral route is rarely used. The disadvantage of radioactive iodine use is that it can be given only in a specialised centre which has been licensed by law (and local radiation safety officer) to use radioactive compounds. On the continent, the following centres are available: Germany – university of Giessen and a private clinic in Norderstedt (close to Hamburg); Belgium – university of Gent; The Netherlands – university of Utrecht. Depending on the local regulations, cats need to be hospitalised for between 3 and 14 days and in some places, can be released only after their internal radiation level is below a specified threshold. The main safety hazard for the personnel dealing with the hospitalised cats is the incorporation of $^{131}$Iodine, i.e. it must be strictly forbidden to drink, eat or smoke in the cat ward and normal sanitary regulations (hand washing) needs to be enforced. To receive an excessive amount of radioactivity otherwise is very unlikely if normal precautionary measures are followed. A potential risk of therapy with $^{131}$Iodine is the development of renal failure. It is well known that humans with hyperthyroidism have an increased glomerular filtration rate (GFR) which normalises upon therapy. It has also been shown that in normal cats given thyroxin the GFR increases (and urea & creatinine decreases). As such, in cats with hyperthyroidism a subclinical renal failure may be masked due to the increased GFR. But the hyperthyroidism may also influence the kidney function negatively as the hypertension may lead to sclerosing of the nephrons. As such, there is a dual influence between hyperthyroidism and renal function. This problem has led to the question whether a cat with hyperthyroidism and azoteamia should be treated with radioactive iodine at all (a permanent therapy). Various studies have shown that in cats with hyperthyroidism GFR decreases irrespective of therapy (drug, surgery or radioactive iodine). Over 300 cats have been treated by the author with radioactive iodine irrespective of their urea and creatinine level. As long as the cats do not show classical signs of chronic renal failure therapy of the hyperthyroidism with the best available means seems to be safer that non-therapy, since the number of cats developing renal failure is not higher in the treated cats than in a control population of cats of the same age. However, if clinical signs of renal failure and especially an isosthenuria are present one should be careful and make sure that the thyroxin level does not decrease too much (aim for upper normal reference range). Before referral of a cat for radioactive iodine therapy the veterinarian should contact the centre to encounter the following points: what pre-therapy diagnostics are required, cost, duration of hospitalisation as to advice the owners to the best of their possibilities.
Feline adrenal problems are uncommon compared to the dog. Despite a scarcity of reports, it is important to know that these diseases are often fatal if not treated appropriately. Proper recognition and adequate testing are therefore crucial. Diseases with increased adrenal function are hypercortisolism, hyperaldosteronism and hyperprogesteronism.

Between 100 and 200 confirmed cases of naturally occurring, spontaneous, confirmed cases of hypercortisolism (Cushing’s disease) have been reported. More than 80% are due to a pituitary adenoma (very rarely adenocarcinoma) (PDH) while the remaining are commonly due to an adrenocortical tumor (equally divided between benign and malignant forms) (AT). There is no breed or sex predilection and most animals are older (mean 10 year, range 4.5-15).

Appearance:
The most common historical and clinical signs associated with feline hypercortisolism are polyuria/polydipsia (PU/PD), polyphagia, weight loss and lethargy. PU/PD is mostly due to concurrent diabetes mellitus but can also occur in cats not being diabetic. The typical Cushing’s syndrome related pot-bellied appearance with hepatomegaly, weight gain and generalised muscle wasting is common in cats, as it is in dogs. Dermatological abnormalities frequently recognised in cats include an unkempt hair coat with patchy alopecia. In addition, extreme fragility of the skin is relatively common in cats; the thin skin may tear with routine handling or during playing with other cats, leaving large denuded areas. Infections and abscesses are seen in about 40% of cases and can be found in the urinary system, skin, respiratory tract or oral cavity.

Diagnosis:
A stress leukogram (lymphopenia, eosinopenia and mature leucocytosis) occurs inconsistently. Despite clinical PU/PD, cats usually maintain urine specific gravities of greater than 1.020; they only occasionally exhibit the dilute urine and decreased blood urea nitrogen concentrations commonly seen in dogs with hyperadrenocorticism. Hyperglycaemia (about 80%) and hypercholesterolaemia (about 50%) are the most common laboratory abnormalities found on serum biochemistries. In contrast to dogs, high serum alkaline phosphatase activity is uncommon, developing in only 32% of cats.

Diagnostic imaging shows hepatomegaly (about 80%) on plain radiographs and – in the case of adrenal tumour – sometimes a mass cranial to the kidney. However, calcification of normal adrenals can occur in up to 30% of normal old cats. Abdominal ultrasound is useful to detect bilaterally enlarged adrenals (in PDH) or a unilateral mass with contra-lateral atrophied adrenal. MRI might help to find a pituitary mass.

Endocrinological evaluation of cats suspected of hyperadrenocorticism involves screening tests to confirm the diagnosis, and differentiating tests to distinguish PDH from AT. The ACTH stimulation has a sensitivity of about 80%; however, it can also give a positive result in ill cats with non-adrenal disease. However, values > 500 nmol/l are not commonly seen in these and point towards hypercortisolaemia. The urine cortisol-to-creatinine ratio (UCCR) has been commonly positive in cats with hypercortisolaemia; but false-positive test results may be seen in cats with moderate to severe non-adrenal illness. Urine should always be collected at home (not in hospital environment) as all stressful situations will elevate the UCCR. Sensitivity seems to be high, indicating that a normal value rules-out hypercortisolaemia.

In cats the low-dose dexamethasone suppression test is usually performed with a higher dose (0.1 mg/kg!!) as cats are more resistant to steroids. This dose results in a sensitivity of 78%. Serum cortisol values in all normal cats and all cats with non-adrenal illness are suppressed with this dose.

A higher-dose (1.0 mg/kg) dexamethasone suppression test or basal endogenous ACTH concentration has been used to differentiate cats with PDH from those with an AT. Normal to high plasma ACTH levels support a diagnosis of PDH, whereas low concentrations are consistent with AT.

Treatment:
Potential options for treatment of cats with hypercortisolaemia include the use of the adrenocorticotlytic agent mitotane (o,p’-DDD), drugs that block cortisol synthesis (ketoconazole, metyrapone or trilostane),
Enzymatic reactions, membrane transport and stability, blood coagulation, nerve conduction, neuromuscular transmission, muscle contraction, vascular smooth muscle tone, hormone secretion, bone formation and resorption, control of hepatic glycogen metabolism, and cell growth and division are all affected by calcium (Ca\(^2+\)). Intracellular Ca\(^2+\) is most important as intracellular messenger. Ca\(^2+\) in extracellular fluid regulates cell function in many organs (parathyroid gland, kidney, thyroid C cells).

1) Physiology
Main regulators of Ca\(^2+\) homeostasis are parathyroid hormone (PTH) [minute-to-minute control], calcitriol (1,25-dihydroxyvitamin \(D_3\)) [day-to-day control], less important calcitonin. Major target organs are intestine, kidney and bone with intake equal to excretion (via urine and faeces). Kidneys re-absorb in health > 98% or non-protein-bound filtered Ca\(^2+\). Osteoblasts (for rapid regulation) and osteoclasts (for prolonged release of Ca\(^2+\)) are important for regulation in bone.

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99% body Ca$^{2+}$ is in skeleton (hydroxyapatite) while most non-skeletal Ca$^{2+}$ is in ECF. Here are 3 forms: ionised (free) Ca$^{2+}$ (55%), complexed or chelated (bound to phosphate, bicarbonate, sulfate, etc.) Ca$^{2+}$ (10%), and protein bound Ca$^{2+}$ (35%). Intracellular Ca$^{2+}$ is found in exceedingly low levels (10’000-fold less than ECF) where it's rapidly buffered by cytosolic proteins (calbindin, calmodulin, troponin C) or subsequently sequestered in organelles (mitochondria and rough endoplasmatic reticulum).

**PTH: synthehsed and secreted by parathyroid gland chief cells (short half-live (3-5 min), closely regulated by calcitriol (negative effect) and extracellular Ca$^{2+}$.

PTH, a single chain polypeptide (almost identical AA-sequence between different species), is secreted intact into circulation (N-terminal side is active site). Biologically inactive COOH-terminal fragments of PTH are also secreted. Metabolism of active PTH to COOH-terminal fragments mainly in liver (macrophages), but also in kidney and bone. Both intact and COOH-terminal PTH cleared by glomerular filtration. COOH-terminal PTH has long half live in serum but no activity for Ca$^{2+}$-homeostasis.

The principal effects of PTH: increase blood Ca$^{2+}$ concentration by a) increasing tubular Ca$^{2+}$ reabsorption, b) increasing Ca$^{2+}$ resorption from bone and increase number of osteoclasts, and c) indirectly by accelerating formation of active Vit-D metabolite by kidney through trophic effect on 1α-hydroxylase in mitochondria of renal epithelial cells in proximal convoluted tubules.

**PTH-related protein (PTHrP):** many functions such as a) normal Ca$^{2+}$-regulating hormone in foetus (produced in foetal parathyroid gland and placenta), b) normal paracrine factor in foetal and adult tissue (skin, mammary gland, endocrine organs, muscle, lymphoid organs, kidney, bone, brain) and c) abnormal hormone in endocrine manner in hypercalcemia of malignancy (HCM). N-terminal side of PTHrP (AA 1-34) binds to PTH receptors with equal affinity as PTH and therefore has PTH-like effects.

**Vitamin D:** (synonym: calciferol) three major metabolites: 25-hydroxvitamin D$_3$ (calcidiol), 1,25-dihydroxvitamin D$_3$ (calcitriol) and 24,25-dihydroxyvitamin D$_3$.

Same metabolites from vitamin D$_3$ (ergocalciferol of plant origin) are equi-potent in domestic mammals. 25-hydroxylation (in liver) and 1α-hydroxylation (in kidney) are two most important enzyme systems to activate vitamin D. While humans can synthesise Vit.D (cholecalciferol) in skin from 7-dehydrocholesterol, this photo-synthesising (via UV light) is inefficient in pets and dietary Vit.D is required. Regulation of renal calcitriol synthesis is via serum PTH (reciprocal feedback mechanism), calcitriol itself, calcitonine, phosphorus and calcium concentrations. The principal effect of calcitriol (major biologic active Vit.D metabolite) is to increase serum Ca$^{2+}$ and phosphorus concentrations mainly via intestinal regulation of Ca$^{2+}$ absorption, but also via regulation of Ca$^{2+}$ resorption from bone and from kidney.

2) **Normocalcaemia**

For Ca$^{2+}$-analysis use only plain of heparinised serum (no EDTA, citrate or oxalate). Falsely high results possible with lipoaemia or hyperbilirubinaemia (always reconfirm high Ca$^{2+}$-value before start search of underlying cause). Growing animals often are mildly hypercalcemic. As 80-90% of bound Ca$^{2+}$ is bound to albumin, a correction for total Ca$^{2+}$ based on serum albumin levels might be necessary (mainly important for hypoalbuminaemia).

Ideally ionised Ca$^{2+}$ is measured, but in dogs with lymphoma and HCM there is close correlation between total and ionised Ca$^{2+}$ (less so in other hypercalcemic problems). Samples should be processed anaerobically as not to cause pH change. Acidic pH favours dissociation of Ca$^{2+}$ from protein and increased ionised Ca$^{2+}$ in sample and vice-versa with alkaline pH.

PTH is very label and must be shipped and stored frozen. Stability is best in EDTA plasma. For total PTH a two-site human immunoassay looking at the N-terminal and COOH-terminal sites works fine in dogs and cats. One-site assays (unless N-terminal site) are not useful as when PTH is metabolised, the COOH-terminal site circulates a long time in the blood. PTH needs to be interpreted in relation to serum Ca$^{2+}$ values.

Human two-site or N-site assays for PTHrP are useful for dogs and cats. PTHrP is in serum equally very label (as PTH). Metabolites of VitD are chemically identical between humans and pets, so human calcidiol or calcitriol assays are useful. Samples are stable during refrigeration but light should be avoided.
CHAPTER 2

Companion Animal Programme

In chronic renal failure (CRF), hypercalcaemia can be cause or effect. PTH is often increased in CRF with normal ionised Ca\(^+\), this in comparison to hyperparathyroidism with increased PTH and increased ionised Ca\(^+\). Causes of hypercalcaemia in CRF are manifold: decreased GFR leads to decreased load of filtered Ca\(^+\); CRF related increased PTH leads to increased Ca\(^+\) resorption from bone; increased concentrations of organic anions capable of complexing with Ca\(^+\) can lead to increased total Ca\(^+\) (but not ionised Ca\(^+\)); decreased calcitriol (due to CRF), its receptor and abnormal calcitriol-receptor interaction due to uraemic toxins leads to increased PTH set-point resulting in increased PTH secretion and hypercalcaemia. Low-dose calcitriol counteracts increased (potentially toxic) PTH secretion but has no effect on Ca\(^+\) absorption in intestine.

Hypercalcaemia due to neoplasia is a) due to hypercalcaemia of malignancy (T-cell lymphoma, apocrine gland adenocarcinoma of anal sac, and more rarely thymoma, carcinoma of lung, pancreas, thyroid gland, skin, mammary gland, nasal cavity and adrenal gland). b) due to haematologic malignancies (local bone resorption (lymphoma, multiple myeloma)). c) due to metastatic tumours in bone (local bone resorption) (rare in dogs, reported with mammary gland, prostate, liver and lung carcinoma). If diagnosis not possible but lymphoma suspected, trial-therapy with L-asparaginase (400 U/kg, subcutaneously) might be indicated (better than prednisolone-trial, as lymphoma might become more refractory to further chemotherapy).

Primary hyperparathyroidism: uncommon in dogs, rare in cats. Mostly adenoma (90%), rarely carcinoma (5%) or hyperplasia (5%). Keeshonds are over-represented (as are Siamese cats). Calcium-containing stones (urolithiasis) are seen in 30% of dogs or cats with hyperparathyroidism. Diagnosis made by ↑Ca\(^+\), ionised ↑Ca\(^+\), ↑PTH, ↓or normal phosphorus; ultrasound of neck to find one or more masses (90% sensitivity); scintigraphy (\(^{99m}\)Tc-sestamibi); surgical neck exploration.

Vitamin D toxicity from cholecalciferol (D\(_3\)), ergocalciferol (D\(_2\)), dihydrotachisterol, or calcitriol. Causes are: excessive dietary supplementation, iatrogenic (treatment of hypocalcaemia), toxic plants (Cestrum diurnum, Solanum malacoxylon, Trisetum flavescens), cholecalciferol-containing rodenticides. Diagnosis made by ↑↑Ca\(^+\), ↑phosphorus, mild azotaemia, ↑serum 25-hydroxyvitamin D.

Recently, idiopathic hypercalcaemia was reported in cats. Intensive investigations did not find a cause and steroid treatment results in long-term decrease of ionised and total Ca\(^+\).

Symptomatology: Common clinical signs of hypercalcaemia are polyuria/polydipsia, anorexia, lethargy, weakness and vomiting; uncommon signs are constipation, cardiac arrhythmia, seizures, calcium uroliths, renal failure or death. Rapidity of occurrence of hypercalcaemia important (slow onset less problematic). Long-term complications, i.e. mineralisation of soft tissue (kidney and heart) most severe if Ca\(^+\) times phosphorus product greater than 4.85.

Treatment: The higher the serum Ca\(^+\), the more aggressive the therapy should be. Serum phosphorus concentration must be evaluated as well to guide an immediate therapy. Removal of underlying problem should be the goal, but impossibility to do so (diagnosis not yet reached, surgery impossible or postponed, long acting vitamin D toxicity) might call for immediate supportive treatment. Increased renal Ca\(^+\) excretion, inhibition of bone resorption, promoting soft tissue deposition, shift within body compartments, reduced Ca\(^+\)-uptake via gut or combination of these should normalise serum Ca\(^+\). Treatment should be in a step-wise fashion.

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