Osteoarthritis (OA) is a chronic, progressive disease that affects both dogs and cats. It has been noted that up to 20% of adult dogs and 60% of adult cats have radiographic evidence of OA.1,2 Owners, themselves are becoming increasingly aware that bone and joint problems are and issue with their pet. Much of this increased awareness has come through the use of the Internet and social media. The overall outcome of osteoarthritis is centered on destruction of the articular cartilage and breakdown of the joint. Because of this OA must be thought of as a global disease process rather than an isolated disease entity. There is considerable cross talk among the tissues that make up a joint. For this reason the joint must be thought of as an organ and the final pathway of OA is organ failure of the joint.

OA primarily affects diarthrodial joints. A diarthrodial joint is composed of the joint capsule, synovial lining, articular cartilage, and the surrounding muscles, ligaments, tendons, and bone. The joint capsule is composed of two layers: the outer fibrous layer and the inner subsynovial layer. Both layers have a rich blood and nerve supply. One explanation of pain associated with OA is distention of the joint capsule due to joint effusion. The synovial lining covers ever structure in the joint except for the cartilage/menisci. It provides a low friction lining and is responsible for the production of synovial fluid. Two major cell populations are present in the synovial lining: type A synoviocytes and type B synoviocytes. Type A synoviocytes are macrophage-like cells that are responsible for phagocytosis. The type B synoviocytes have a more fibroelastic-like appearance and are responsible for producing hyaluronic acid (HA) and other enzymes.

Articular cartilage forms a smooth, compressible surface, which has the primary function of transmitting compressive forces onto the underlying subchondral bone. It is important to note that articular cartilage lacks blood flow, lymphatics and nerves. In fact the oxygen tension in articular cartilage is about 6-7% thus making chondrocytes survive in a hypoxic environment. Cellular destruction and apoptosis has been noted if the oxygen concentration drops below 1-2%. Because the lack of blood flow, articular cartilage must receive its nutrition from the synovial fluid. Histologically, articular cartilage is made up mainly of water (about 80%); a smaller portion is composed of the extracellular matrix (around 10-15%), and chondrocytes (around 5-10%). The chondrocytes are the only metabolically active component of articular cartilage, and are responsible for the production of the extracellular matrix (ECM). The ECM is composed of the proteoglycan matrix and type II collagen.

At the very basic level the proteoglycan matrix is composed of an aggrecan. An aggrecan is a core protein with glycosaminoglycans attached (GAGs) such as chondroitin 5 or 6 sulfate. Multiple aggrecan’s are then attached to a hyaluronic acid backbone (produced from type B synoviocytes) to form an aggrecan aggregate. These aggrecan aggregates have a gel-like consistency and are responsible for resisting compression. The proteoglycan matrix is contained within a type II collagen framework. This lattice type framework gives added support by forming interlocking loops. Having the knowledge of phenotypic make up of cartilage is important when evaluating in-vitro studies. When type II collagen from articular cartilage is taken from an in-vivo condition and placed in-vitro it tends to change its phenotypic expression and begins to produce type I collagen. Many studies utilizing OA models for various treatment modalities are in-vitro. It is very important when evaluating these studies that the study authors have proven that the collagen in-vitro has the same phenotypic expression as collagen in-vivo.

Mature cartilage is classified into 3 un-mineralized zones. Zone 1 (superficial or tangential zone) contains the highest concentration of chondrocytes. These chondrocytes are small, flat, and oriented with the long axis parallel to the joint surface. During joint compression such as with weight bearing the chondrocytes in this zone undergo tension parallel to the joint surface. Chondrocytes in Zone 2 (transitional zone) begin to become larger and more rounded. As the zones become deeper the long axis moves from being more parallel to the joint surface to becoming more perpendicular to the joint surface to compensate for the shearing and compressive forces that predominate in this area as the load on the joint increases. Chondrocytes in the deeper zone 3 (radial zone) contain larger chondrocytes that are predominately oriented perpendicular to the joint surface. This zone forms a rigid mesh and can be partially mineralized. The primary force in this area is compression. The tidemark marks the completion of cartilage maturity as it transitions to the underlying subchondral bone. In a nutshell, mature cartilage forms a pre-stressed, wear-resistant protective diaphragm in zone 1 that helps withstand tension in the plane of the articular cartilage. The middle and deeper layers have the fibrils becoming more organized perpendicular to the plane of the cartilage to withstand compressive loading.

The physiology of cartilage is important because damage to chondrocytes will not only lead to death of that particular chondrocyte but also an inflammatory response that creates problems with neighboring chondrocytes. Thus a downward, progressive spiral occurs which leads to destruction of the “work-horse” (chondrocytes) and loss of extracellular matrix production. The loss of ECM production leads to the loss of cartilage’s ability to soften and transfer loads to the underlying subchondral bone.
The pathophysiology of OA is described as a non-infectious disorder of diarthrodial joints. It is categorized by deterioration of articular cartilage, bone formation at synovial margins (osteophytes), peri-articular fibrosis, and a localized inflammatory response. For OA to develop there has to be some insult to the articular cartilage such as hip dysplasia, a cranial cruciate ligament tear, elbow dysplasia, or an articular fracture. Once the chondrocyte is damaged the inflammatory cascade begins and is followed by the release of multiple cytokines. The two main cytokines involved with OA are interleukin 1 beta (IL-1β) and tumor necrosis factor alpha (TNF-α). IL-1β is responsible for the breakdown of the matrix, while TNF-α drives the inflammatory response. Furthermore, prostaglandins are released, particular prostaglandin E2 (PGE2), which increases the release of metalloproteinases (MMPs). MMPs are responsible for the continued breakdown of the ECM.

This brings into mind one fundamental question; if inflammation is such a key driving force with OA then why don’t anti-inflammatories slow down or eliminate the problem? The answer is there must be one piece of the puzzle missing to the pathophysiology. One such puzzle piece that has been investigated is the concept of oxidative stress. Oxidative stress is an early event during the evolution of many diseases. It occurs when reactive oxygen species (ROS) outweigh the antioxidants. On a daily basis cells under go oxidative stress to help with normal cellular metabolism, which is kept in balance by the cells natural antioxidants. If at any point the ROS outweigh the antioxidants through either excessive ROS production or antioxidant depletion then oxidative stress will occur. This manifest itself as lipid peroxidation, protein, DNA or RNA oxidation. What has been shown in human medicine is that the effects of oxidative stress on chondrocytes along with MMPs are the 2 main mediators in matrix degradation. Furthermore, inducible nitric oxide synthase expression can occur by a single stimulation of IL-1β or TNF-α.4 This concept has also been proven in the canine where it was shown that the same inflammatory mediators that cause an inflammatory response also cause an oxidative stress response. Furthermore, oxidative stress to the cell causes a reduction to the cells natural antioxidants. With treatment of certain antioxidants the cells natural antioxidants are able to recovery and thus minimize the oxidative stress response.5

It is important to remember that OA is usually always secondary to some other disease process so it is important to eliminate the problem if one is able. Technically, any problem that involves or disrupts the joint will lead to OA. Because of this it is important to make owners aware. For example, it is common to explain to owners why their dog may rupture its cranial cruciate ligament and what treatment options exist. Its equally important to also make the owner aware that no matter what treatment option is elected the patient will still possibly develop some degree of OA.

Owners will typically complain about their pets have a reluctance to exercise, stiffness, lameness, inability to jump, or even some behavioral changes. Remember that cats are not small dogs, and they can have fewer signs. The biggest complaint from owners with cats suffering from OA is a reduction in activity, reluctance to jump, an unkempt appearance, and aggression. Orthopedically, dogs may show disuse muscle atrophy (ensure to rule out any neurogenic atrophy), a reduced range of motion, pain or discomfort on range of motion, crepitus, and joint effusion. Cats can be tricky to examine so allowing them performance tests is encouraged to see how the cat moves and interacts with its environment. One true test is to place the cat on exam table with its carrier below. Most cats will easily jump from the exam table to their carrier. Any reluctance to want to do so raises concern about possible joint pain.

Radiographs are key to aiding in the diagnosis of OA. However, just as with any diagnostic modality there are limitations. Radiographs only provide bony information, they are taken in a non-weight bearing position, and osteophytes are useful to diagnose OA but they are not pathognomonic for OA. Furthermore, the value of osteophytopsis for staging OA is controversial and does not correlate with OA progression. Probably the biggest issue with radiographs is that they do not correlate with clinical signs. The radiographic key features of OA are: osteophytopsis, enthesophytopsis, effusion, soft tissue swelling, subchondral sclerosis, intra-articular mineralization (especially in cats), and subchondral cyst (rarely seen).

Other additional diagnostic modalities include CT, MRI, and arthroscopy. Arthroscopy is probably the most valuable means to objectively evaluate the cartilage. However, it is a surgical procedure and can be costly to perform. It does allow the evaluation of the cartilage, which can then be classified by the Modified Outerbridge score. One looming question is if you don’t perform arthroscopy and radiographs are helpful to diagnose but don’t help stage for monitoring for progression of OA is there some type of subjective based assessment? The answer is yes, the Canine Orthopedic Index (COI) was developed and validated in 2014 to provide reliable assessment of dogs with OA in terms of staging as well as response to treatment. It can be downloaded at www.canineorthopedicindex.com.

In regards to treatment there must be a multimodal approach. There is no “cook book” or one size fits all treatment plan. Treatment must be patient centered and patient specific. What works for one dog may not work for another dog. Furthermore, patients may respond initially to a treatment plan then become less responsive. In these cases the treatment plan has to be changed. In some cases it can really be trial and error. When I approach OA patients I break it into 1 of 2 categories. Am I seeing a patient that has a primary problem and has or will develop OA (such as cranial cruciate ligament rupture) or Am I seeing a patient that had a primary problem and now suffers from OA (the typical “OA consult”).

For those patients that have a primary problem and either have OA or will develop OA I give owners clear expectations for the future. If I can correct the primary problem such as fixing an articular fracture, or addressing a ruptured cruciate ligament then that is
recommended. Following surgery I give owners my 4 pillars of OA management: Joint supplements, Omega-3 fatty acids (150-175 mg/kg of DHA/EPA), daily exercise and weight management. Furthermore, formal rehabilitation therapy is key for post-operative patients. Hopefully, once the primary problem is corrected and following these 4 pillars, nothing more will need to be done.

For patients that had a primary problem that either was or was not addressed but now they suffer from OA I will initially recommend joint supplements, omega-3 fatty acids, Adequan, weight management, and daily exercise. Furthermore, if the patient is having a flare-up then I will recommend formal rehabilitation the control the inflammatory response, improve range of motion and improve comfort. I only like to initially use NSAIDS at the lowest possible dose as infrequently as possible. Unfortunately, many of these patients will progress to a daily need for NSAIDS. During times of flare-ups patients will also benefit from additional analgesics such as Codeine or Tylenol 3 (both at 1 mg/kg q8-12h) or Tramadol (5 mg/kg q 8h). The biggest benefit in these patients is owner education. It is very important that owners are aware that this will be progressive and we can’t cure it. Flare-ups will occur and management must be stepwise.

If I have patients that don’t respond initially, or have more frequent flare-ups then NSAID use becomes more frequent. I will consider adding in gabapentin (5-10 mg/kg q8-12h) as well as formal rehabilitation. Other potential considerations are given to using amantadine (3-5 mg/kg q24h) with an NSAID, or intra-articular injections.

Potential intra-articular therapies include regenerative medicine (platelet rich plasma with or without stem cell treatment), hyaluronic acid, or steroids. Discussion of regenerative medicine is beyond the scope of this proceeding. HA is a viscosupplementation that restores the physiochemical properties to the joint. From a molecular standpoint it stimulates production of ECM as well as continued production of HA from resident synoviocytes. It will also inhibit inflammatory mediators. It is important to use a product that closely mimics a dog’s HA such as Evervisc from Everost (sold through Patterson). Evervisc is about 2 million Daltons in size and is made from a fermentation process rather than rooster combs. Until further research is completed it is not recommended to combine an HA injection with any other drug as this may decrease the molecular weight of the HA or could lessen its efficacy. What has been shown is that approximately 80% of dogs respond well to HA, 10% respond fair, and 10% don’t respond. The duration of response is about 4-6 months of relief. When compared to regenerative medicine a response of about 9 months is expected following a platelet rich plasma injection and about 12 months or longer following a platelet rich plasma and stem cell injection.

In summary, OA is a chronic progressive disease and the goal of management needs to be to slow and minimize the progression. Owners need to be well educated to know that it will progress and there will be flare-ups. Treatment needs to be multimodal and patient centered.

References
Developmental orthopedic diseases (DOD) are those, which are identified during postnatal skeletal growth. The common DOD discussed here are hypertrophic osteodystrophy (HOD), panosteitis, craniomandibular osteopathy, retained ulnar cartilaginous cores, Legg-Calve-Perthes disease, and osteochondrosis/osteochondritis dessecans (OCD). While elbow dysplasia is a type of DOD disease, given its complex nature it is beyond the scope of this proceeding to try and describe elbow dysplasia.

**Hypertrophic osteodystrophy (HOD)**

A DOD in young, rapidly growing dogs also referred to as metaphyseal osteopathy, skeletal scurvy, juvenile scurvy, infantile scurvy, Moller Barlow’s disease, and osteodystrophy II. The incidence is roughly 2.8/100,000 with patients presenting between 2 and 6 months of age. HOD is predominantly seen in large and giant breed dogs. Great Danes, Chesapeake Bay Retrievers, Irish Setters, Boxers, German Shepherd, Golden Retrievers, Labrador Retrievers, and Weimaraners are at an increased risk with males 2.3 times more likely to develop HOD than females.

There are numerous proposed causes such as vitamin C deficiency, over nutrition, heritability, infections, and vaccines; however, no single cause has been determined. More recent studies have refuted the vitamin C and over nutrition theories. Heritability has been suggested for at risk breeds and has been shown in a family of Weimaraners. Infection is thought because many of the patients have a history of systemic illness with the addition of leukocytosis, although in most studies an infectious process has not been identified. One study did document an association with HOD and canine distemper virus; however, a large multi-institutional study did not support a link between HOD and canine distemper.

Diagnosis of HOD is based on signalment, history, clinical signs, and radiographs. The distal radius, ulna, and tibia are the most commonly affected bones. Clinical signs include swelling of the metaphyseal region of the bone and the lesions are often bilateral. The swelling may be warm upon palpation with varying degrees of pain and lameness (from mildly lame to a having a reluctance to walk. Some patients may exhibit systemic signs of illness such as hyperthermia, depression, inappetence, anorexia, and diarrhea. The pathognomonic radiographic sign is a lucent line in the metaphysis parallel to a narrow zone of increased radiodensity just adjacent to the physis (the so called “double physeal line”). There can be varying degrees of periosteal and endosteal proliferation. Differential diagnosis includes secondary nutritional hyperparathyroidism, septic polyarthritis, retained cartilaginous cores, and hypertrophic osteopathy.

In the majority of cases HOD is self-limiting within days to weeks, but can persist for months. The prognosis is typically good to excellent; however, in very severe cases death has been reported. For mild cases, analgesics along with a balanced diet should be provided. In more severe cases supportive treatment may be needed especially if the patient is reluctant to eat. Furthermore, owners should be warned about the possibility of angular limb deformity in severe cases. In Weimaraners specifically with severe HOD without bacteremia may respond better to corticosteroids than to NSAIDS.\(^1\)

**Panosteitis**

Panosteitis is a self-limiting inflammatory disease of the bone marrow of long bones. It is sometimes referred to as enostosis, eosinophilic panosteitis, and shifting leg lameness with an incidence of about 2.6/1000 patients. Breeds that are at an increased risk or Airedale Terriers, Irish Setters, German Shorthair Pointers, Doberman Pinschers, Afghans, Great Danes, Saint Bernard’s, Bernese Mountain Dogs, Newfoundland’s, Mastiffs, Bassett Hounds, Rottweiler’s, Cocker Spaniels, Golden Retrievers, Labrador Retrievers, and German Shepherds. Given the list of pre-disposed breeds panosteitis is primarily a disease of large to giant breed dogs; however, it has been reported in small breed dogs. Age at presentation is typically between 5-12 months of age but up to 2 years of age has been noted. Males are affected more than females with a ratio of 4:1.

Histologically, the first changes noted consist of empty spaces in the adipose bone marrow, vascular proliferation with local bone formation around the nutrient foramen. These changes are thought to lead to vascular congestion and secondary increases in intraosseous pressure. The exact origin and etiology is still unknown.

Much like HOD the diagnosis is derived from the signalment, history, and clinical signs along with radiographs. The hallmark clinical sign is a shifting leg lameness with pain on palpation of affected long bones. The degree of the lameness and pain can be variable from mild to inability to walk. Typically the owner will report an acute lameness with no history of trauma. The most commonly affected bone is the ulna (42%), followed by the radius (25%), humerus (14%), femur (11%), and tibia (8%). Radiographs are helpful to differentiate panosteitis from other conditions (such as HOD, OCD, etc.). The appearance on radiographs will depend on the stage of the disease. In the early stage of disease radiographs may be normal or have a decrease in radiodensity in the medullary...
cavity near the nutrient foramen. As the disease progresses, the increase in medullary opacity will develop a granular pattern with loss of normal trabecular pattern. Other findings include periosteal bone formation. After 4-6 weeks the densities will regress leaving a trabecular pattern that is coarser than normal.

Treatment consists of rest and analgesics; however, treatment does not influence the outcome. Recurrence is possible, but the severity will decrease over time as the dog matures.

**Craniomandibular osteopathy**

Craniomandibular Osteopathy is also known as craniomandibular osteoarthropathy, craniomandibular osteodystrophy, mandibular periostitis, lion jaw, Westie jaw, and Scotty jaw with an incidence reported as 1.4/100,000 cases. There is no reported sex predisposition; however, puppies less than 6 months of age are at the highest risk. The incidence is reported to decrease with age. West Highland White Terriers and Scottish Terriers are at an increased risk; other breeds reported to be affected are Boxers, Labrador Retrievers, Great Danes, Boston Terriers, Great Danes, and German Shepherd’s. Given the strong breed predisposition in West Highland White Terriers, a heritable etiology has been suggested, and an autosomal recessive mode of inheritance has been demonstrated in this breed.

The disease is characterized by either unilateral or bilateral symmetric irregular osseous proliferations of mainly the mandible, but the tympanic bullae can also be affected. Osteoclastic resorption of lamellar bone occurs, which is followed by the presence of primitive bone that will expand beyond the periosteum. The bone is replaced by a fibrous-type stroma and inflammatory cells invade the border of the lesion destroying adjacent connective tissue and muscle.

Clinical signs will vary from minor difficulty eating and chewing to complete inability to open the mouth and thus the inability to eat or drink. Because of the lack of nutrition additional clinical signs include weight loss, salivation, depression, and pain while eating. Physical examination will reveal enlargement or irregularity of the mandibles. The patient’s mouth may be able to be opened only partially or not at all, and the teeth are unaffected. Often times blood work and urinalysis are unremarkable. Radiographs will demonstrate bony proliferation of the mandible and/or bullae. CT can be useful to identify lesions and to better delineate the areas affected.

It can be self limiting when the dog is 11-13 months of age; however, patients may need varying levels of supportive care such as feeding soft food/gruel, syringe feeding, or placing a feeding tube. Nutrition and hydration are key parameters to monitor. Given the pain involved with trying to open or close the mouth analgesics are indicated. Over time the bony proliferations will regress completely or partially. Surgical excision of the proliferation is not recommended due to the recurrence within 3 weeks. Rostral hemimandibulectomy has been reported for a severe case that facilitated lapping of food. Euthanasia has been performed for patients with uncontrollable discomfort or with lesions that do not resolve and affect quality of life.

**Retained ulnar cartilaginous cores**

Also known as retained endochondrial cartilage cores, this is a cone of growth plate cartilage that projects from the distal ulnar growth plate into the distal metaphysis. Histologically, the retained cartilaginous core consists of viable hypertrophic chondrocytes. It is essentially failure of the growth plate cartilage to convert to metaphyseal bone, while some consider it a growth plate manifestation of osteochondrosis. Like most DOD it occurs predominately in large to giant breed dogs.

If the retained ulnar cartilaginous core is associated with reduced ulnar length then changes similar to premature closure of the distal ulnar growth plate are noted. These changes consist of cranial bowing of the radius, external rotation, and valgus deviation of the paw; additional subluxation of the carpus and elbow may be seen.

Radiographs are mainstay for the diagnosis, where a radiolucent core (typically triangle in shape) of cartilage is noted in the distal ulnar metaphysis. There may be an area of sclerosis surrounding the area. The core may extend up to 3-4 mm into the metaphysis. This must be differentiated from premature closure of the distal ulnar growth plate. No correlation has been noted between the size of the lesion, histopathology and severity of deformity.

Treatment is based off the degree of deformity. If no deformity is noted then no treatment is recommended, and the core may disappear spontaneously. In these cases it is recommended to closely monitor patients for the development of deformities, especially of the carpus and elbow. In cases with moderate to marked deformity the surgical correction of the deformity may be required.

**Legg-calve perthes disease**

Avascular necrosis of the femoral head is noted as a noninflammatory localized ischemia of the femoral head and neck, which results in deformation of the femoral head and neck leading to a pelvic limb lameness. It has also been referred to as aseptic necrosis of the femoral head, coxa plana, osteochondrosis, and osteochondritis coxae juvenilis. Small breed dogs are the most commonly affected with toy breeds and Terriers predisposed. Initially, the disease is histologically characterized by necrosis of the trabeculae of the
femoral head, followed next by the fragmentation phase where loading of the affected hip causes collapse of the epiphysis and secondary thickening and cleft formation of the articular surface.

**Osteochondrosis/osteochondritis dessecans (OCD)**

In short OCD is a disturbance of endochondral ossification. There is failure of the cartilage matrix calcification and vascular ingrowth, which results in cartilage retention. The cartilage retention results in thickening of the articular epiphyseal cartilage. There are two distinct areas of osteochondrosis: the growth plate-epiphyseal complex (GEC), and the articular-epiphyseal complex (AEC).

Proposed causes of osteochondrosis include genetics (especially with large and giant breed dogs), rapid growth, calcium supplementation, hormonal influences, ischemia and trauma. The incidence of AEC osteochondrosis is 8.1/1000 patients with male dogs more affected than female dogs with a typical age at presentation of 4-9 months.

Proposed mechanisms for the pathogenesis of AEC osteochondrosis is it is a result of generalized disease; however, this does not adequately address the species and site-specific nature of osteochondrosis. The other proposed mechanism is it starts as a focal disease from vascular trauma and subsequent necrosis of the subchondral bone or necrosis of the epiphyseal cartilage canals. This necrosis may possibly lead to cartilage ischemia and necrosis. The necrosis may occur at a development stage when the vessels from the perichondrium are being replaced by vessels from the adjacent epiphyseal bone marrow. As this is occurring the vessels are susceptible to damage by conformational forces and/or microtrauma. If the vessels become damaged and thus necrotic then a cartilaginous infarct develops, which prevents endochondrial ossification.

Osteochondrosis latens is used to describe the initial cartilage necrosis, at this stage the disease process can be resolved or progress to osteochondrosis manifesta where larger areas of necrotic cartilage resists vascular invasion. This will then persist during growth and can be detectable. If the overlying articular cartilage fissures or fractures (thus developing a flap) then the commonly known osteochondrosis/osteochondritis dissecans (OCD) lesion develops.

The most commonly affected joint is the shoulder, followed by the elbow, tarsus, and stifle. The caudocentral or caudomedial aspect of the shoulder is affected the most commonly and it is bilateral in 27-68% patients, while the lesions of the medial aspect of the humeral condyle are common areas affected in the humerus; 96% of lesions in the stifle affect the medial femoral condyle, and in the talus the medial or lateral trochlear ridge is affected.

Clinical signs associated with osteochondrosis typically become apparent when a cartilage flap (OCD) develops. One theory is the motion between the flap and the subchondral bone, or the altered loading may provoke pain. If the flap detaches it can become what is known as a “joint mouse”, which may further contribute to synovitis and OA progression. Patients tend to present from 4-9 months of age with a compliant of lameness or exercise intolerance. Many cases will show signs of a unilateral lameness; however, the disease is commonly noted bilaterally so careful examination of the contralateral joint is warranted. Once a patient presents with clinical signs of a lameness the OCD lesion is considered chronic and a defect in the subchondral bone is well developed. Radiographs are a sensitive diagnostic method that may demonstrate disruption of the subchondral bone with flattening or concavity of the normal contour. Sclerotic margins may be seen around the defect. Contrast arthrograms can be used to demonstrate unmineralized cartilage flaps and joint mice, effusion, and new bone formation. CT is also useful in demonstrating an OCD lesion. Arthroscopy is useful as both a diagnostic and therapeutic modality.

Aims of treatment need to include elimination of pain and lameness, restoration of the cartilage surface with tissue of similar nature to the native tissue, normalization of joint biomechanics, and prevention of further joint degeneration. Conservative management may be recommended with small subchondral lesions and when the patient is mildly lame or asymptomatic. This form of treatment is only recommended for dogs younger than 6 months of age. Conservative management consists of NSAIDS, exercise restriction, chondroproctants, rehabilitation therapy, and weight control. Persistence of clinical signs suggests the patient should be treated with a surgical approach.

Surgical management consists of either an arthrotomy or arthroscopy (the authors preferred method). Surgical treatment consists of flap excision and joint mouse removal. Additional treatment may consist of removing peripheral cartilage that is not firmly adhered and stimulation of fibrocartilage to the underlying subchondral bed.

OCD of the shoulder usually carries a good to excellent prognosis; however, other joints affected with OCD carry a guarded prognosis with continued progression of OA and an intermittent lameness.

**References**

Regenerative Medicine in Orthopedics: A New Approach to an Old Problem
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Orthobiologics also referred to, as regenerative medicine is a new emerging treatment modality for a variety of disease problems. It has usage in orthopedics from an orthopedic soft tissue and osteoarthritis (OA) perspective. It is important to understand with regenerative medicine we are not cloning things or growing new tissue. This is the biggest misconception among the general public so it is important to make sure we are not misleading people. To get the best response from regenerative medicine one must have a definitive diagnosis and must be able to treat the underlying condition. It’s not a magic silver bullet that is going to replace conventional medicine but only to augment other therapies. Therefore, combination therapy is key when considering regenerative medicine such as medical and surgical intervention, incorporation of regenerative medicine and rehabilitation therapy.

Platelet rich plasma (PRP)
The terminology can at times be confusing especially with platelet products. Platelet rich plasma (PRP) is referred to as autologous blood plasma enriched with platelets (contains and releases through degranulation) with numerous growth factors and anti-inflammatory cytokines. Autologous protein solution (APS) has a high concentration growth factors (TGF-B; EGF; PDGF), while autologous conditioned serum (ACS) has a high concentration growth factors and anti-inflammatory cytokines (IL-1 receptor antagonist, IGF-1, etc.). Autologous conditioned plasma (ACP) is plasma with a high concentration of platelets. Essentially PRP is blood plasma concentrated with platelets. Within these platelets there are huge reservoirs of bioactive proteins and growth factors. These proteins have been shown to initiate and/or accelerate tendon, ligament, and cartilage repair. It has been stated that it can induce some regeneration but I would be very cautious about using this statement. Primarily PRP is great in decreasing inflammatory mediators especially in OA along with initiating reparative cytokines. Furthermore, they reduce pain and improve articular function in OA.

Within PRP we are primarily interested in the growth factors found in the alpha granules of the platelets such as transforming growth factor β (TGF-β), platelet derived growth factor (PDGF), insulin like growth factor (IGF-1), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), and fibroblast growth factor (FGF). So why should we care about these growth factors? The answer is simple in that knowing what is contained in the granules and what growth factors are involved help understand the healing properties of PRP. For example VEGF and FGF promote angiogenesis while PDGF, FGF, and TGF-β enhance cellular proliferation. Lastly TGF-β and IGF-1 promote extracellular matrix formation, which is especially important in OA. The primary roles and functions of PRP are to enhance recruitment, proliferation, and differentiation of cells associated with tissue healing and regeneration. Furthermore, it provides fibrin to serve as a matrix and scaffold. This becomes very important when we talk about combination therapy with stromal cells (MSC) a little later.

The protocol for PRP collection begins with collecting 10-30 ml of blood from the patient, then centrifuging the blood or filtrating it to produce the PRP. This typically increases the concentration of the PLT and growth factors by 5-10%. For OA PRP is typically injected via blind intra-articular, fluoroscopic or digital radiography guided but rarely IV. For soft tissue injuries the PRP has to be injected into the lesion via ultrasound guidance not just into the local area. If you are not familiar with neuromuscular ultrasound I would encourage you to learn how. The diagnosis of “soft tissue injury” is now obsolete as we can identify exact lesions.

Ideally in any product we want the PLT concentration to increase 7-10 fold (too high such as greater than 12 fold can actually cause issues such as a joint flare, although even this is being questioned). In the PRP product there should be no neutrophils, which can cause an inflammatory reaction. Also, there should be no RBC’s in the product. In terms of separation we want to spin the blood to allow gravity to separate the cells based on weight. When considering what centrifuge to buy we want something that is cost effective but more importantly is HAS to be validated in dogs, not humans. My wants in the post spin PRP are (which are every evolving) an increased concentration of platelets that have primarily alpha granules with plenty of growth factors. Monocytes areacceptable in that they are associated with an increase in cellular metabolism and collagen production in fibroblasts. Also, we want a decrease in the release of anti-angiogenic cytokines, which makes sense in that one of the properties of PRP, is angiogenesis. My dislikes in the post spin (again, which are every evolving) PRP are that there be no RBC’s which have been shown to cause direct damage to the cartilage and synovium via iron-catalyzed formation of ROS. Also, I don’t want the PRP to contain any WBC’s that cause an inflammatory reaction and I don’t want any inflammatory mediators in the PRP, which have been shown to cause synoviocyte death. However, in human sports medicine they are investigating the concept of “dirty PRP” where they may actually have some RBC or certain WBC’s for various soft tissue injuries.
Neutrophils are probably the biggest concern in that they increase the concentration of inflammatory mediators in the area. Furthermore, an increase of neutrophils in PRP is positively correlated with an increase in MMP-9, which is a major mediator in cartilage degradation in OA. Currently the thought on lymphocytes in the PRP is unknown. Platelets (PLT’s) have been shown to activate peripheral blood mononuclear cells, which when mediated by an increase in IL-6 expression can help stimulate collagen production.

There is certainly some controversy behind using PRP, mainly because of the public’s perception while seeing professional athletes getting the treatment. The problem is the lack of standardization makes treating individuals with the exact same product is difficult. Furthermore, validation is a huge problem in veterinary medicine. Our group of VOSM has recently validated canine PRP systems. This is the only currently published study to evaluate (at the time) all of the commercially available products looking at PLT concentration, white blood cell concentration (WBC), and red blood cell (RBC) concentration by following manufacturer recommendations. We found that the highest yield of PLTs was with the SmartPReP® ACP and Companion Regenerative Therapies (CRT) Pure PRP. While the SmartPReP® ACP increased PLT’s by 219%, it failed to reduce WBC (especially neutrophils). The CRT Pure PRP increased PLT’s by 550%, removed greater than 95% of RBC’s, 19% of WBC’s (85% of the neutrophils).

So why care about the research, it’s boring and frankly we just want to buy the product and use it, right? Because, first we want to do no harm to the patient, and because injecting products that contain substances that may cause a clinical issue is not recommended. As a profession we need to do what is in the best interest of the patient, so; therefore, we have an ethical responsibility to know what we are using and why. Also, we have an ethical responsibly to practice evidence based medicine and not rely on companies to benefit financially while we “test” their products.

Mesenchymal stem cell (MSC)

In a simple term a stem cell is characterized by its ability to self-renew and its ability to differentiate along multiple lineage pathways. Ideally, to use a stem cell for clinical use it should be found in abundant quantities, be able to be harvested in a minimally invasive way, be able to differentiate along multiple cell lines in a predictive and reproducible way, be able to safely and effectively transplanted to either autologous or allogeneic host, and be able to be manufactured in accordance with current good manufacturing practice guidelines.

Work to characterize stromal/stem cells dates back to over 30 years. To identify MSC used in vitro, cells must have 3 specific characteristics. The first characteristic is the ability of cultured MSC to readily adhere to plastic culture dishes and form fibroblast like colonies, hence the term colony forming unit-fibroblastic is applied to cultured MSC that are not induced into specific lineages. The second characteristic is that cells have the capacity to differentiate into various specialized cell lineages. MSC have been induced into adipogenic, chondrogenic, osteogenic, myogenic, and neurogenic like lineages among others. The last characteristic is the expression of defined cell surface marker profiles. Cluster of differentiation is what is used to aid in the identification and classification of cell surface markers. Cell surface markers on cultured MSC have been identified using immunohistochemistry and flow cytometry. The required positively expressed markers are CD73, CD90, and CD105 and lack the markers CD11b and CD14 as well as numerous others. One big problem with this is that cell surface marker expression can vary because of different isolation techniques and a function of culture time. Also there is variation among species and cell of origin. In a more broader sense, stem cells have 3 principal characteristics: 1. They are capable of self-renewal, 2. Are unspecialized cells, and 3. Can give rise to other specialized cell types.

Stem cell therapy has been investigated in every body system including musculoskeletal, cardiovascular, endocrine, integumentary, and CNS. In human medicine phase I clinical trials have demonstrated safety and some promise. Much remains to be learned about stem cells. In order to understand how to use stem cells, knowledge of what stem cells are is needed. Three broad classifications of stem cells have been identified. These are embryonic stem cells, fetal or perinatal stem cells and adult stem cells. Furthermore, adult stems cells include different classifications depending on origin such as mesenchymal, hematopoietic, neural, and the newest addition the induced pluripotent stem cells (iPS). MSC can be obtained from a number of sources such as the bone marrow, adipose tissue, umbilical cord blood, muscle, cartilage, tendon, and a number of other tissues. Bone marrow MSC was the original source of MSC and lately adipose derived MSC have come into light. MSC are said to be multipotent in that they can give rise to multiple but limited number of lineages. They are the most extensively investigated and have the majority of clinical applications.

The original thought of MSC was simply just to replace lost tissue and the stem cells would regenerate new tissue. However, research has shown that the #1 mechanism of repair is the release of trophic factors. These trophic factors in the form of cytokines and chemokines release different growth factors and also provide an anti-inflammatory environment as well as help with immune system modulation. The trophic support provided from MSC helps to diminish tissue injury, promote neovascularization, recruit and induce proliferation of resident stem cells, inhibit fibrosis, and act as a carrier for therapeutic genes. One of defining characteristics of stems cells is their ability to undergo unlimited or extensive proliferation. However, this raises the problem of tumor formation in the recipient. Therefore, methods to monitor and control proliferation are of paramount importance. The general concern for tumor
formation is that embryonic stem and iPS cells can easily form teratomas, which is a feature of their pluripotency. To date no definitive reports have described tumor formation following stem cell therapy.

As stem cell therapy emerges, new problems arise in perfecting the science. Methods of cell delivery such as IV, versus IM, SQ, or intra-articular need to be addressed. Some evidence suggests that stem cells injected IV have the ability to hone in to a specific site of injury. However a direct approach such as intra-articular may make more sense for a more targeted approach. To improve stem cells capabilities much research is focusing on different growth factors to promote proliferation of in vitro performance of the these cells; along with mechanical force testing. Lastly unrealistic expectation to cure everything with stem cells may act as a burden in the research setting.

Autologous stem cell therapy is essentially harvesting the source of the tissue, isolating and expanding the MSC then returning it back to the same patient. Currently, there are 2 major sources in the dog: bone marrow or adipose tissue. Bone marrow derived stem cells actually contain both hematopoietic stem cells and MSC. The two ways to collect MSC from bone marrow are culture expanded and bone marrow aspirate concentrate (BMAC). Adipose derived stem cells contain MSC and are called ASC by the international fat applied technology society. The two ways to collect MSC from fat are culture expanded and stromal vascular fraction (SVF).

Currently, until more research as been done I don’t recommend shock wave therapy, class IV laser (class IIIb is encouraged), no cold or warm pack, no therapeutic ultrasound, and no NSAIDS (8 weeks with MSC or PRP/MSC or 2 weeks with PRP alone) following regenerative medicine treatment.
References