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Orthopaedic Case Challenges Mini Series

Session 1: Understanding Joints and Diagnosing Joint Disease

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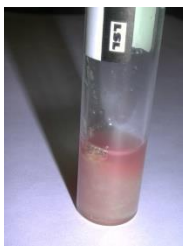

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Understanding arthritis

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Normal Synovial Joint Anatomy and Function

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Introduction

Joint disease is very common in small animals of all ages. An understanding of normal joint anatomy and function is a useful foundation for the clinician to make informed decisions regarding diagnosis and management of joint diseases. This section will briefly review synovial joint anatomy and function.

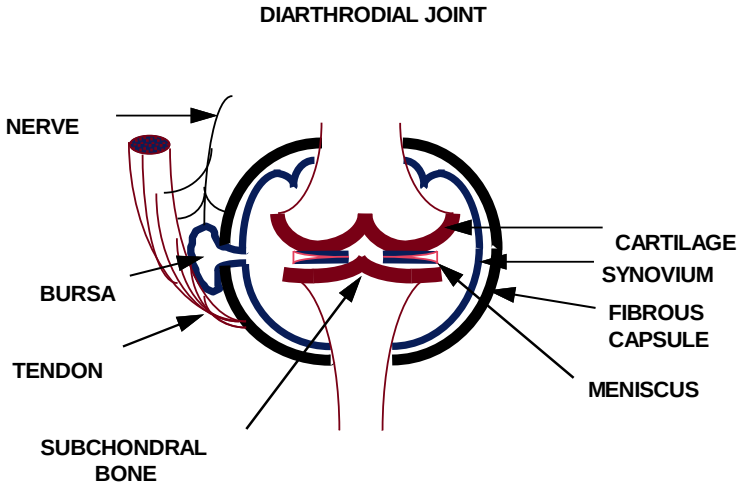

Figure 1: Schematic of a synovial joint

The synovial joint should be considered as an organ composed of various tissues which all provide a role in normal function but which also communicate with each other in pathological situations. The joint surface is lined by articular (hyaline) cartilage, a specialised tissue which allows the joint to move in an almost frictionless manner. Supporting the articular cartilage in a structural sense is the underlying subchondral bone plate beneath which lies cancellous bone. Encapsulating the joint space is the synovial capsule which is composed of a discontinuous lining layer, the synovium, supported by a fibrous joint capsule. The synovium is responsible for production of synovial fluid but also has a role in immunity, providing a response to injury or pathogen invasion.

In specific joints such as the femorotibial joint and coxofemoral joint, there are specialised intra-articular structures such as menisci, fat-pad and stabilising ligaments (e.g. cruciate ligaments, round ligament). These will be discussed in sections relating to those specific joints.

Articular cartilage

Articular cartilage is less than 1mm thick in the dog but this avascular tissue is key to normal joint function. The single architect of cartilage is the chondrocyte which produces the extracellular matrix of this specialised tissue. The majority (~70%) of the wet weight of cartilage is water. The organic matrix is composed of glycosaminoglycans (hyaluronan and proteoglycans) and collagens (mainly type II) which have complementary functions. The collagen forms a dense network that provides tensile strength to the tissue but also acts as a mesh within which is retained the glycosaminoglycans and some other glycoproteins. Of these, the major proteoglycan, aggrecan, is highly negatively charged and attracts water into the tissue. This creates a swelling pressure which is counteracted by the collagen network.

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Thus, whilst collagen provides tensile strength, the proteoglycan, and associated water, provide compressive stiffness to resist loading of the cartilage. In addition, when loaded, water is squeezed from the surface of the tissue, providing one of the lubrication mechanisms of cartilage.

In normal cartilage there is a very slow turnover of collagens but the proteoglycan is constantly being renewed. Aggrecan has a long, linear protein core and many side sugar chains of keratan sulphate and chondroitin sulphate. This core is, in turn, bound to long hyaluronan chains with each chain containing approximately 50 proteoglycan molecules.

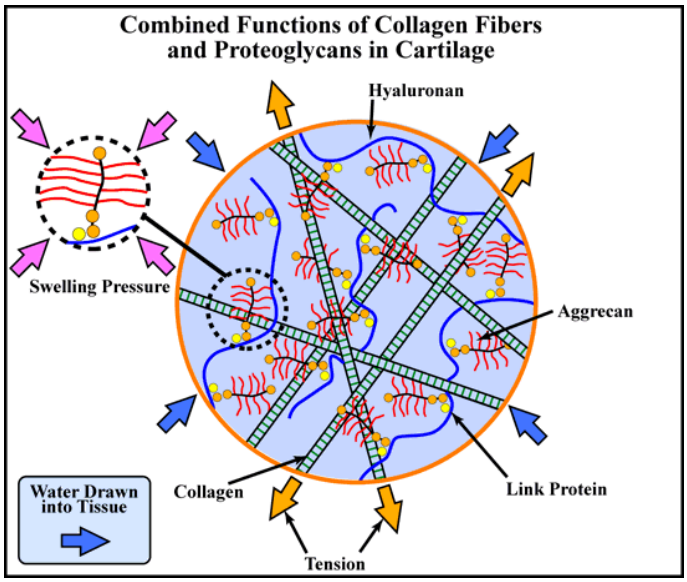

Figure 2: Components of articular cartilage. Aggrecan molecules attract water in to the tissue and create a swelling pressure. The type II collagen network resists this pressure.

The turnover of cartilage is controlled by the chondrocyte, acting in response to various stimuli including mechanical deformation and cytokine and growth factor signals. The chondrocyte can release proteolytic activities (e.g. matrix metalloproteinases [MMPs] and ADAMTS enzymes) which can degrade the organic matrix and this is part of normal homeostasis. However, the balance of synthetic and catabolic processes is crucial and this can be perturbed in pathology such as arthritis.

Synovium

The synovial intima is a discontinuous lining layer (i.e. not a true membrane) with two types of lining cells – the fibroblast-like synoviocytes and the macrophage-like synovoicytes. The former are responsible for production of hyaruronan which is secreted in to the joint cavity and, along with a dialysate of plasma, produces synovial fluid. The synovial macrophages provide phagocytotic capability and an innate immune response.

The innate immune system can respond to pathogen associated molecular patterns (PAMPs) such as bacterial lipopolysaccharide, providing a first line of defence against bacteria. Such a response is typically mediated through the toll-like receptors resulting in the release of various chemokines (e.g. CCL2) and inflammatory cytokines (e.g. TNFa, IL-1β). These signals produce an inflammatory response associated with effusion and cellular infiltration. However, it is increasingly recognised that the innate immune system can respond to so-called damage-associated molecular patterns (DAMPs) such as molecules released from extracellular matrix and necrotic cells, including fibronectin and high-mobility group box 1 protein (HMGB1).

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In the dog, the synovium appears particularly reactive and rapidly develops hyperplastic villi in response to joint injury or infection. Infiltration of intrinsic and extrinsic cells in to the joint cavity is part of the pathological response to various forms of arthritis and the evaluation of the numbers and types of such cells can provide the clinician with a useful insight in to the type of disease process that is active in the joint.

Development of joints

In the developing foetus, mesenchymal cells aggregate to form a cylindrical model of the future long bones. These cells differentiate into cartilage cells and synthesise an extracellular matrix of glycosaminoglycans and collagen. This cartilage model expands by multiplication of these cells and appositional growth at the periphery from the surrounding perichondrium.

The primary ossification centre starts at the mid-portion of the cartilage model and the cartilage cells die to be replaced by osteoblastic cells transported by invading vascular buds. The ossification continues in a centrifugal manner pushing the cartilage cells towards the ends of the developing bone. In this way the shaft of the bone is formed (the interior is later resorbed in the process of *tubulation*.). The remaining cartilage at either end becomes the *metaphyseal growth plate* (secondary centres of ossification). The metaphyseal growth plate separates the epiphysis from the diaphysis. The *epiphyseal growth plate* lies deep to the developing articular cartilage and contributes to the development of the epiphysis.

Normal metaphyseal growth plate activity involves distinct functional zones. The growth plate has distinct morphological zones that correspond with these functions. The epiphyseal-articular cartilage complex has similar zones called radiate and calcified zones. Proliferation of chondrocytes occurs at the radiate zone in a similar manner to the proliferative and hypertrophic zones of the metaphyseal growth plate. The calcified zone is comparable to the ossification zone and the metaphyseal zones. In the growing animal, there are vascular channels in the epiphyseal cartilage of the epiphyseal-articular complex.

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Arthritis

Introduction and classification of arthritis

Arthritis is a broad term that encompasses inflammatory disease processes within the synovial joint. The degree of inflammation may vary considerably between different types of arthritis such that some forms are traditionally described as “non-inflammatory” and some as “inflammatory”; in reality, all types of arthritis display some degree of inflammation, albeit in some cases, low-grade. Arthritis can be classified (Figure 4) to help the clinician determine the type of disease process that is driving the joint pathology. Such a classification is useful to provide a diagnostic and therapeutic framework although the clinician should realise that there are many pathogenic mechanisms in common between the various forms of arthritis although the relative importance of these different processes and the rate at which these progress may differ. The broad categories of arthritis include those termed as “degenerative”, “infective” and “immune-mediated”. This section will review these categories in turn.

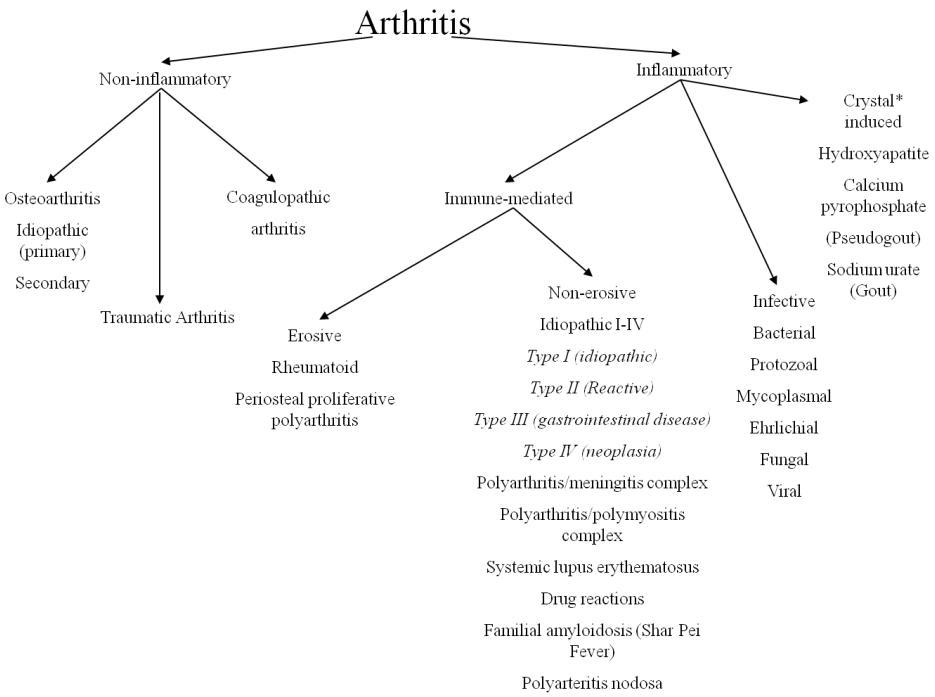

Figure 3: Classification of arthritis

Pathology of arthritis

The pathology of arthritis, whatever type, involves some generic changes in all tissues of the synovial joint. Central to this are the alterations in metabolism and morphology of articular cartilage but there are dramatic changes in subchondral bone metabolism and architecture, osteophyte and enthesophyte formation, and synovial inflammation and fibrosis. Current evidence increasingly implicates cross-talk between the various tissues of the joint, particularly the synovium and cartilage. In addition, it should be remembered that arthritis is associated with changes in other tissues such as surrounding muscles, ligaments and tendons as part of the process of disuse and inhibition of ipsilateral musculature. Furthermore, changes in the CNS caused by chronic pain can lead to the phenomenon of pain sensitisation.

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Articular cartilage
Degradation of articular cartilage is central to all types of arthritis. The speed of this degradation varies from relatively quick in aggressive infective arthritis through to relatively slow in osteoarthritis.

In the 'inflammatory' forms of arthritis, there is marked activation of inflammatory cytokines and the downstream consequences of this are the activation of various proteases that degrade the extracellular matrix of cartilage. In infective arthritis, bacteria can have a direct effect on articular cartilage also.

Much of our knowledge on the events in canine osteoarthritis comes from experimentally-induced models such as the Pond-Nuki cranial cruciate ligament transaction model [1]. Typical features of OA are the degeneration or progressive loss of the structure and functionality of articular cartilage. Grossly, the tissue loses compressive stiffness and tensile strength and the surface of the tissue begins to fibrillate. As the disease process progresses, cartilage tissue is lost and erosion and ulceration ensue. Overall, the pathophysiological process of OA can be divided in three overlapping stages: in the beginning, the extracellular matrix degrades on a molecular level, the water content increases, the size of aggrecan molecules within the tissue decreases [2], and the structure of the collagen network is damaged; all of which leads to reduced stiffness of the cartilage. Secondly, chondrocytes try to compensate for the damage by enhanced proliferation and metabolic activity - cell clusters, formed by cloning, appear surrounded by newly synthesized matrix molecules. This condition can remain for several months-years. In stage three, the chondrocytes are not able to keep up their repair activity and a complete loss of the cartilage tissue is the consequence.

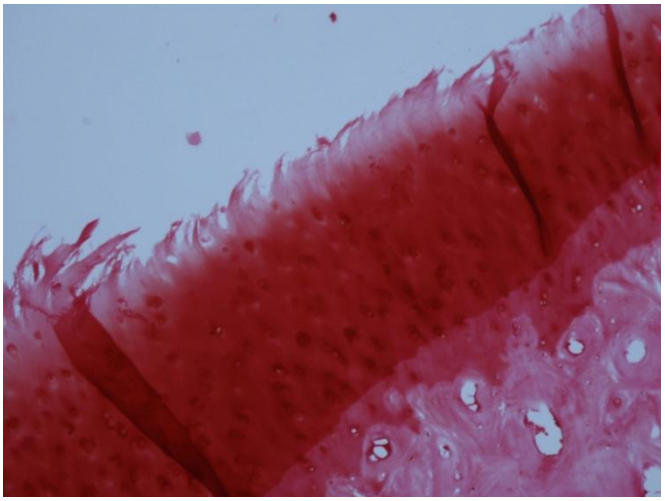

Figure 4: Cartilage fibrillation and loss of proteoglycan from the superficial zone (as demonstrated by loss of Safranin-O staining in this early patellar OA in a dog with patellar luxation)

Within arthritic cartilage, there is an imbalance between anabolic and catabolic processes in the tissue with both degradation and synthesis upregulated. Many cytokines and growth factors are produced by the synovial lining cells and chondrocytes. In the short-medium term (1-3 years), there is actually an increase in cartilage thickness [3] which is associated with tissue swelling as well as an anabolic response producing more cells and more extracellular matrix [4]. However, as disease progresses, cartilage tissue is lost and end-stage disease involves ulceration of cartilage and eburnation of subchondral bone [5].

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Degradation of the components of the extracellular matrix of articular cartilage and cell death are key processes in OA. Inflammatory cytokines such as interleukin (IL)-1β, IL-17, IL-18 and tumor necrosis factor-alpha (TNF-α) upregulate the synthesis of certain matrix metalloproteinases (MMP) and other proteolytic enzymes [6]; concomitantly, synthesis of their inhibitors (tissue inhibitors of metalloproteinases [TIMPs]) is decreased.

Given the potential role of inflammatory prostaglandins and the use of NSAIDs for the treatment of OA, there has been considerable interest in the role of cyclooxygenase (COX) in OA. Chondrocytes from human osteoarthritic cartilage explants express COX-2 and spontaneously produce prostaglandin E_2 [7]. In addition, it was recently reported that prostaglandin E_2 produced by osteoarthritic cartilage explants decreased proteoglycan synthesis and enhanced the degradation of both aggrecan and type II collagen. These effects are associated with downregulation of MMP-1 together with upregulation of MMP-13 and ADAMTS-5 [8]. In addition, there is some evidence that COX inhibition may provide beneficial effects in cartilage [9].

Among other inflammatory mediators that are of interest in the pathogenesis of OA are both oxygen and nitrogen-derived free radicals. Reactive oxygen species such as superoxide anion, hydrogen peroxide, and hydroxyl radicals directly promote chondrocyte apoptosis, most probably via mitochondrial dysfunction [10]. Nitric oxide (NO), produced by the inducible isoform of nitric oxide synthase (iNOS), appears to be another major catabolic factor produced by chondrocytes in response to cytokines such as IL-1β and TNF-α. Considerable evidence indicates that the overproduction of NO by chondrocytes plays a role in the progression of cartilage loss in OA. Although normal cartilage does not express iNOS, nor produce NO without stimulation by inflammatory cytokines, osteoarthritic cartilage explants spontaneously produce considerable quantities of NO. Nitric oxide exerts multiple effects on chondrocytes that promote articular cartilage degradation. These include inhibition of matrix synthesis; activation of MMPs and apoptosis. Several studies have implicated NO as an important mediator in chondrocyte apoptosis. However, NO and its derivatives may also play protective roles because protease activity and proteoglycan degradation are enhanced when NO production is blocked.

Degradation of aggrecan appears to be a very early event in canine OA [11] and is followed by disruption of the collagen network. Aggrecan can be degraded by MMPs such as MMP-13, but the ‘aggrecanase’ enzymes appear to be particularly important.

The aggrecanases [12], also known as ADAMTS-4 and ADAMTS-5, cleave the aggrecan protein core in the interglobular domain between G1 and G2 [13] and this action will release the majority of the molecule, including the negatively charged sugar side-chains, from the matrix [14]. It is currently thought that ADAMTS-5 is upregulated in murine models of OA and recent studies indicate that this enzyme may be critical to disease progression [15-17]. However, which of these enzymes is most important in canine and feline OA remains unknown.

The intact triple helix of type II collagen can only be degraded by MMP-1 and MMP-13, and possibly MMP-8 and MMP-14 [18-20]. The enzymes are secreted as pro-forms that are activated by partial proteolysis. In addition, the action of these enzymes is controlled by natural inhibitors, TIMPs, which are produced such that the balance between proteolyic activity and inhibitors is critical [20].

Cartilage oligomeric matrix protein (COMP) is the most abundant non-collagenous protein of articular cartilage. It putative role is in the assembly of collagen fibrils [21,22] and it has been extensively studied in human OA as a biomarker of human disease progression [23-25]. There are limited data on the role of COMP in canine OA but such that there is suggests increased COMP catabolism in early OA [26,27].

Anabolic changes in osteoarthritic cartilage probably represent a repair response. Although there is an anabolic response, there are disturbances to the anabolic mediators which are not fully understood at the current time.

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Synthesis of cartilage matrix molecules can be stimulated by various growth factors such as insulin-like growth factors (IGF-I and IGF-II) and transforming growth factor β (TGFβ). Both IGF and TGFβ can stimulate aggrecan and collagen synthesis. The availability of IGFs is controlled by circulating and locally-produced binding proteins (IGFBPs) which act to extend the circulating half-life of IGF but also act to control the local availability of IGF to bind to its receptor. There is disturbance to the IGF-IGFBP "system" in canine OA [28] such that the availability of IGF may be decreased. In addition, expression of TGFβ is reduced in OA [29].

Synovium

Arthritis involves variable synovitis and capsular fibrosis and indeed there is increasing interest in this aspect of the disease process [30,31]. As a species, the dog seems particular prone to development of synovitis. Synovial histologic changes include synovial hypertrophy and hyperplasia, with an increased number of lining cells, often accompanied by marked infiltration of the sublining tissue with foci of inflammatory cells [32-34]. Cartilage breakdown products, derived from the articular surface as a result of mechanical or enzymatic destruction of the cartilage, can provoke the release of collagenase and other hydrolytic enzymes from synovial cells and macrophages [19]. Indeed the macrophage is likely to be a key cell in driving the synovial control of cartilage metabolism through the release of catabolic cytokines such as IL-1β and TNF-α, which are probable contributors to the degradative cascade.

The inflammatory forms of arthritis have a more aggressive synovitis compared to osteoarthritis. Some types of immune-mediated arthritides (e.g. rheumatoid arthritis) can have an aggressive, invasive synovial response which can form a pannus over the joint surface and lead to erosion of cartilage and bone. Such erosive forms of IMPA carry a poor prognosis at the current time.

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Investigation of joint disease – general principles

Radiography

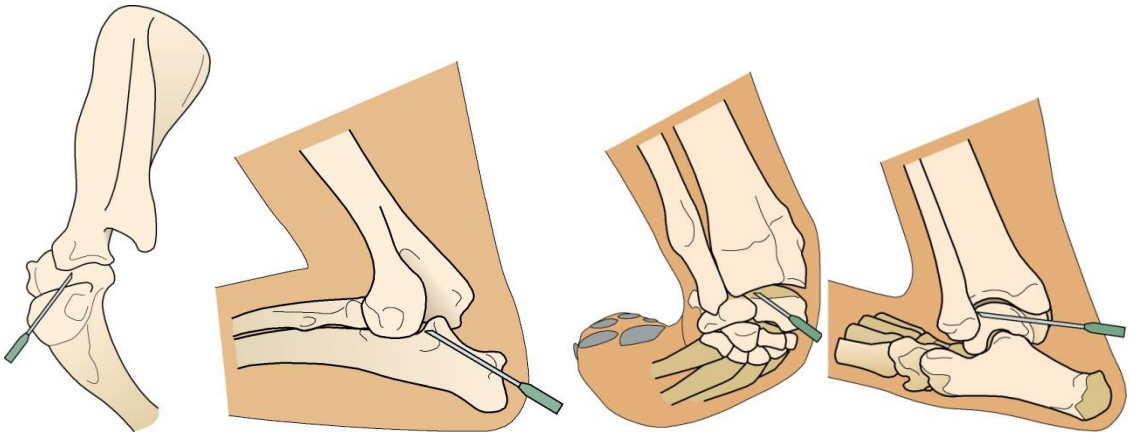
Radiography is the standard tool for initial investigation of joint disease. The changes seen in and around joints are listed below:

- Swelling of soft tissues
- Joint effusion
- Osteophytosis
- Enthesiophytosis
- Displacement of joint structures (e.g. sesamoids, tibia w.r.t. femur)
- Fractures
- Intra-articular mineralisation
- Joint mice
- Subchondral sclerosis
- Erosion
- Altered width of joint space
- Subchondral bone cysts

Two orthogonal views are the minimum requirement. Other more specialist views may be required in certain circumstances. Stressed views may be employed in ceratin situations such as carpal ligament injury. It is imperative that the radiographs are positioned correctly because otherwise features may be misinterpreted or pathology missed. Knowledge of normal variants should be acquired by reference to appropriate texts.

Principles of arthrocentesis

The analysis of synovial fluid is probably under-used. It is in most cases a very straightforward procedure and may be carried out under heavy sedation for most joints although the shoulder and hip may require general anaesthesia. The area for insertion of the needle should be clipped and washed with an antiseptic (e.g. chlorhexidine) and sprayed with alcohol. If the area is to be handled, gloves should be worn. 20’-22’ 1”-1.5” needles are used in most cases.



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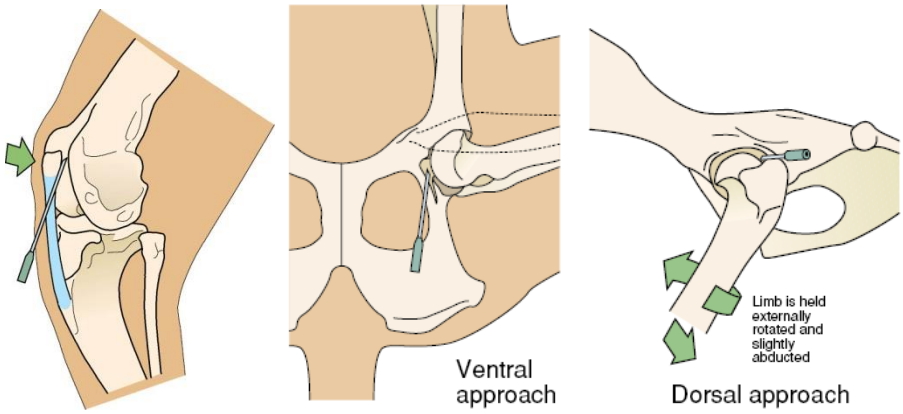

Figure 5: sites for arthrocentesis in the dog

(From BSAVA Manual of Canine and Feline Musculoskeletal Disorders)

The most common problem with fluid aspiration is iatrogenic blood contamination. This is recognised a "string" of blood within the fluid whereas a joint with haemarthrosis will have sanguinous fluid which is consistent in its colour.

The handling of the sample will depend somewhat on the differential diagnosis and the volume available. A subjective assessment of colour, turbidity and viscosity can be made. Direct smears may be made for cytological assessment and a differential count and this should be done promptly. A total cell count can be performed and the sample should be placed in an EDTA tube (since there may be fibrinogen present).

The viscosity of fluid may be assessed by the mucin clot test. This involves dropping some fluid into 5% acetic acid. Good viscosity produces a tight mucin clot whereas poor viscosity does not. The viscosity is a function of the length of the hyaluronic acid chains in the fluid. These are shorter than normal in inflammatory conditions such as infective arthritis or polyarthritis but near normal in osteoarthritis (OA). Effusion in OA may dilute the fluid and make it appear less viscus but the mucin clot test will be normal. However, the mucin clot test is of very little use clinically and the author does not use it.

The table below summarises the properties of normal and pathological SF. These are guidelines only.

Table 1: Properties of normal and pathological synovial fluid

	Normal	OA	Infective	Immune mediated
Volume	0-0.75ml	1-3ml	1-4ml	1-10ml
Viscosity	High	High[1]	Low	Low
TCC($x10^9$/L	0.75	0.75-5.0	5.0-100+	5.0-90
PMN's (%)	0-1	1-5	95-98	20-80

Arthrography

The use of positive contrast within joints may be employed when suspecting or investigating certain diseases. Arthrography can give information on:

- the articular surface
- integrity of the synovial capsule
- position of cartilaginous joint mice
- adhesions in bursae

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The shoulder joint is the most common site for the use of this procedure. To look at the articular surface, a low volume arthrogram is used (1-2ml in a shoulder) but to look at the bicipital bursa a high volume (5-6ml) is used to fill the bursa.

A needle is placed as for arthrocentesis (q.v.) and synovial fluid aspirated. The contrast is injected, the needle removed and the joint manipulated. Radiographs should be taken immediately.

Computed tomography
CT is very useful for evaluation of certain joint problems such as incomplete ossification of the humeral condyle (IOHC), elbow dysplasia and some cases of patellar luxation.

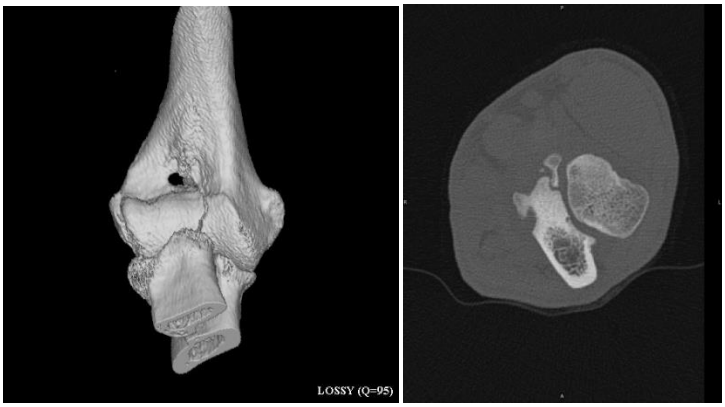

Figure 10: CT images of the canine elbow: 3-D rendered image (left) of IOHC and transverse slice (right) showing fragmented medial coronoid process.

Magnetic Resonance Imaging
MRI is becoming more available for imaging the joints of small animals. However, the expense limits the use of MRI in all but select cases and for research purposes. Probably the most common indications are for investigation of the internal structures of the stifle joint (menisci and cruciate ligaments) when the diagnosis is not clear, and for investigation of soft tissues in and around the shoulder joint [35,36].

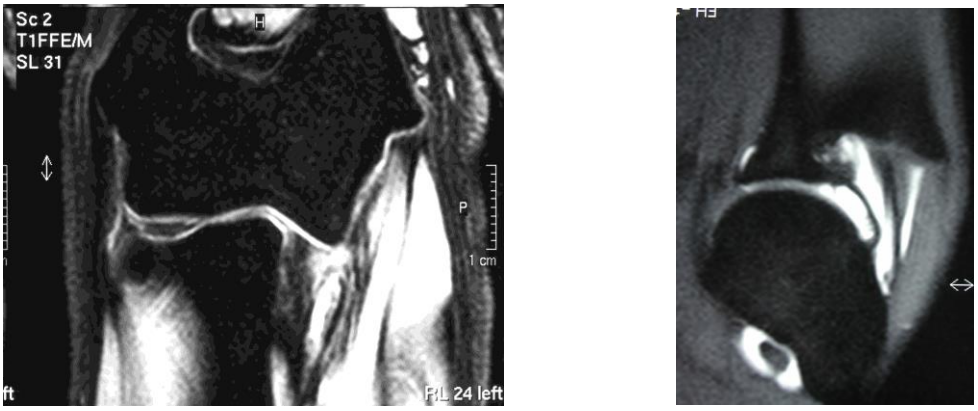

Figure 11: MR images of canine elbow (left) showing articular cartilage and canine shoulder (right) arthrogram to highlight lateral glenohumeral ligament/capsule.

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