MULTIMODAL MANAGEMENT OF CANINE OSTEOARTHRITIS

SECOND EDITION

STEVEN M. FOX

With a contribution on Regenerative Medicine
from Sherman Canapp and Brittany Jean Carr

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Preface

'Multimodal' has become a popular term in the recent medical literature. Arguably introduced as an acronym for 'balanced anesthesia', denoting induction by a multiple drug approach, multimodal is currently recognized to identify any protocol that includes multiple drugs, agents, adjuncts or delivery methods. Marketers have also come to embrace the term, as they tout the virtues of administering their products as part of a given protocol. Frequently this leads to advertising, where one is encouraged to incorporate a given product within 'your multimodal protocol'. Herein, at issue is actually identifying a foundation protocol.

The **Multimodal Management of Osteoarthritis** described in this work delineates an evidence-based approach for the canine patient with osteoarthritis (OA), pursuing the objective of the best available medicine. Appreciating that surgical intervention may initially be required, particularly for stabilizing a joint, the major focus of this work is the 'conservative' management of OA. A simplistic approach is taken with the overlapping of two three-pointed triangles of management: medical and non-medical. Medical management includes nonsteroidal anti-inflammatory drugs (NSAIDs), chondroprotectant and adjunct agents; while the non-medical management includes weight-control/exercise, an eicosapentaenoic acid-rich diet and physical rehabilitation. Each of these approaches has been independently shown to be effective, and while there are no published works on their collective synergism, the concept is intuitive and three actual case examples are overviewed.

As we learn more about the pathophysiology of OA, we are also becoming more aware of how to implement treatments to attack various components of these pathways. Our challenge as veterinary health professionals is to maintain awareness of contemporary issues in treating OA so that we can offer canine patients the care they need and deserve.

Since publication of this text's first edition (2010), several innovations are now potentially available for consideration in treating the OA patient. First, is introduction of a new Piprant Class, prostaglandin receptor antagonist. This new (2013) class of drugs specifically targets receptor subtypes for prostaglandin E_2; namely EP4, which has been identified as a major player in the pain pathway. This new class of drugs may offer the same analgesic features as NSAIDs, but without the associated adverse effects of many NSAIDs. Second, is availability of a new therapeutic and diagnostic tool to treat canine joint inflammation using radiosynoviorthesis. With the novel preparation of the radionuclide tin-117m suspended in a colloid (homogenous tin-117m colloid), comes a practical and safe treatment option for those patients that either respond poorly or have adverse side effects with traditional therapies. Because this treatment option is quite novel to companion animal practice, a detailed overview is provided in this revised text edition. The author would like to thank Drs. John Donecker and Nigel Stevenson for their inclusive contribution to insights on this treatment. Third, is recognition of the role that stem cells and platelet rich plasma are increasingly playing in the management of OA. The author expresses his deep appreciation for the segment on regenerative medicine provided by Drs. Sherman Canapp and Brittany Jean Carr (Veterinary Orthopedic Sports Medicine Group, Annapolis Junction, MD, USA).

This textbook is intended for veterinary healthcare professionals seeking to better understand the issues related to pain management associated with canine OA.

Disclaimer

Knowledge and information in this field are constantly changing. As new information and experience become available, changes in treatments and therapies may become necessary. The reader is advised to check current information regarding the procedures described in this book, the manufacturer of each product administered to verify the recommended dose or formula, the method and duration of administration, and any contraindications. Where a particular pharmaceutical is not approved for use in the target species and reader's country, the reader accepts full responsibility for administration. It is the responsibility of the reader to make an appropriate diagnosis, determine the dosages and the best treatments for each individual patient, and to take all appropriate safety precautions, including informed consent of the owner. To the fullest extent of the law, neither the Publisher nor the Authors assume any liability for any injury and/or damage to persons or property arising out of, or related to, any use of the material contained in this book.

Abbreviations

AA	arachidonic acid
ACE	angiotensin-converting enzyme
ADE	adverse drug event
ADPC	adipose derived cultured progenitor cells
AL-TENS	acupuncture-like transcutaneous electrical nerve stimulation
ALA	alpha-lipoic acid
ALT	alanine aminotransferase
AMA	American Medical Association
ANA	antinuclear antibody
ASU	avocado/soybean unsaponifiable
bFGF	basic fibroblast growth factor
BAPS	biomechanical ankle platform system
BMAC	bone marrow aspirate concentrate
BMSC	bone marrow derived stem cells
CAM	complementary and alternative medicine
CCL	cranial cruciate ligament
CCLT	cranial cruciate ligament transection
CK	creatine kinase
CNS	central nervous system
CODI	Cincinnati Orthopedic Disability Index
COX	cyclo-oxygenase
CT	computed tomography
DHA	docosahexaenoic acid
DJD	degenerative joint disease
DMOAA	disease modifying osteoarthritic agent
DMOAD	disease modifying osteoarthritic drug
ECG	electrocardiography
ECGC	epigallocatechin gallate (antioxidant)
EGF	epidermal growth factor
EMG	electromyography
EPA	eicosapentaenoic acid
ES	electrical stimulation
ESWT	extracorporeal shock wave therapy
FCP	fragmented coronoid process
FDA	Food and Drug Administration
GABA	γ-aminobutyric acid
GaAIA	gallium-aluminum-arsenide
GaAs	gallium-arsenide
GAG	glycosaminoglycan
GAIT	Glucosamine/chondroitin Arthritis Intervention Trial
GI	gastrointestinal
GS	glucosamine sulfate
HA	hyaluronic acid
HFT	high frequency transcutaneous electrical nerve stimulation
HRQL	health-related quality of life
HTC	homogenous tin-117m colloid
ICAM	intercellular cell adhesion molecule 1
IFN	interferon
IL	interleukin
iNOS	inducible nitric oxide synthase
IRAP	IL-1 receptor antagonist protein
IVD	intervertebral disc
keV	kiloelectron volt
LE	lupus erythematosus
LFT	low frequency transcutaneous electrical nerve stimulation
LLLT	low-level laser therapy
LOX	lipoxygenase
LPS	lipopolysaccharide
LR-PRP	leukocyte-rich platelet rich plasma
LP-PRP	leukocyte-poor platelet rich plasma
MMP	matrix metalloproteinase
MRI	magnetic resonance imaging
MSC	mesenchymal stem cell
nAchR	nicotinic acetylcholine receptor
NCCAM	U.S. National Center of Complementary and Alternative Medicine
NF-κB	nuclear factor kappa-light-chain-enhancer of activated B cells
NIH	National Institutes of Health
NMDA	N-methyl-D-aspartate
NMES	neuromuscular electrical stimulation
NNT	number needed to treat
NO	nitric oxide
NRS	numeric rating scale

NSAID	nonsteroidal anti-inflammatory drug
OA	osteoarthritis
OCD	osteochondritis dissecans
OTC	over-the-counter
PAG	periaqueductal gray
PBS	phosphate-buffered saline
PDGF	platelet-derived growth factor
PENS	percutaneous electrical nerve stimulation
PG	prostaglandin
Piprants	new (Y2013) drug class of prostaglandin E2 receptor antagonists
PKC	protein kinase C
PLA	phospholipase A
POMR	problem oriented medical record
PPI	proton pump inhibitor
PRGF	plasma rich in growth factors
PRP	platelet-rich plasma
PSGAG	polysulfated glycosaminoglycan
QOL	quality of life
RA	rheumatoid arthritis
RBC	red blood cell
RCCT	randomized, controlled, patient-centered clinical trials
RNA	ribonucleic acid
ROM	range of motion
RSO	radiosynoviorthesis
RSV	radiosynovectomy
SAP	serum alkaline phosphatase
SDS	simple descriptive scale
SMF	static magnet fields
SRI	serotonin reuptake inhibitor
SVF	stromal vascular fraction
TCA	tricyclic antidepressant
TCM	traditional Chinese medicine
TENS	transcutaneous electrical nerve stimulation
TGF	transforming growth factor
TIMP	tissue inhibiting metalloproteinase
Tin-117m (Sn-117m)	an artificially produced radionuclide of tin
TNF	tumor necrosis factor
TPI	total pressure index
TX	thromboxane
UAP	ununited anconeal process
US	ultrasound
VAS	visual analog scale
VCAM	vascular cell adhesion molecule
VCPG	viable cells per gram
VEGF	vascular endothelial growth factor
VRS	verbal rating scale

Chapter 1

Pain and Lameness

PAIN

Pain is the clinical sign most frequently associated with osteoarthritis (OA)[1]. The clinical manifestation of this pain is lameness. When an animal presents with clinical lameness, a determination must be made whether the animal is unable to use the limb, or is unwilling to use the limb. Inability to use the limb may be attributable to musculoskeletal changes, such as joint contracture or muscle atrophy. These anomalies are best addressed with physical rehabilitation. On the other hand, unwillingness to use a limb is most often attributable to pain. Herein, lameness is an avoidance behavior.

Ironically, articular cartilage is frequently the focus of studies regarding OA. However, clinical treatment of the OA patient is most often focused on the alleviation of pain. Appreciating that articular cartilage is aneural, the focus of OA pain management resides in the periarticular structures. No pain is elicited by stimulation of cartilage, and stimulation of normal synovial tissue rarely evokes pain[2].

OA pain is the result of a complex interplay between structural change, biochemical alterations, peripheral and central pain-processing mechanisms, and individual cognitive processing of nociception (**1.1**).

The source of pain in the joint 'organ' is multifocal: direct stimulation of the joint capsule and bone receptors by cytokines/ligands of inflammatory and degradative processes, physical stimulation of the joint capsule from distension (effusion) and stretch (laxity, subluxation, abnormal articulation), physical stimulation of subchondral bone from abnormal loading, and (likely) physical stimulation of muscle, tendon, and ligaments.

Bony changes at the joint margins and beneath areas of damaged cartilage can be major sources of OA pain. Subchondral bone contains unmyelinated nerve fibers, which increase in number with OA[3]. Increased pressure on subchondral bone (associated with OA) results in stimulation of these nociceptors. This is thought to contribute to the vague, but consistent pain frequently associated with OA. In humans OA is believed to be responsible for increased intraosseous pressure, which may contribute to chronic pain, particularly nocturnal pain. Human OA patients report pain, even at rest, associated with raised intraosseous pressure[4].

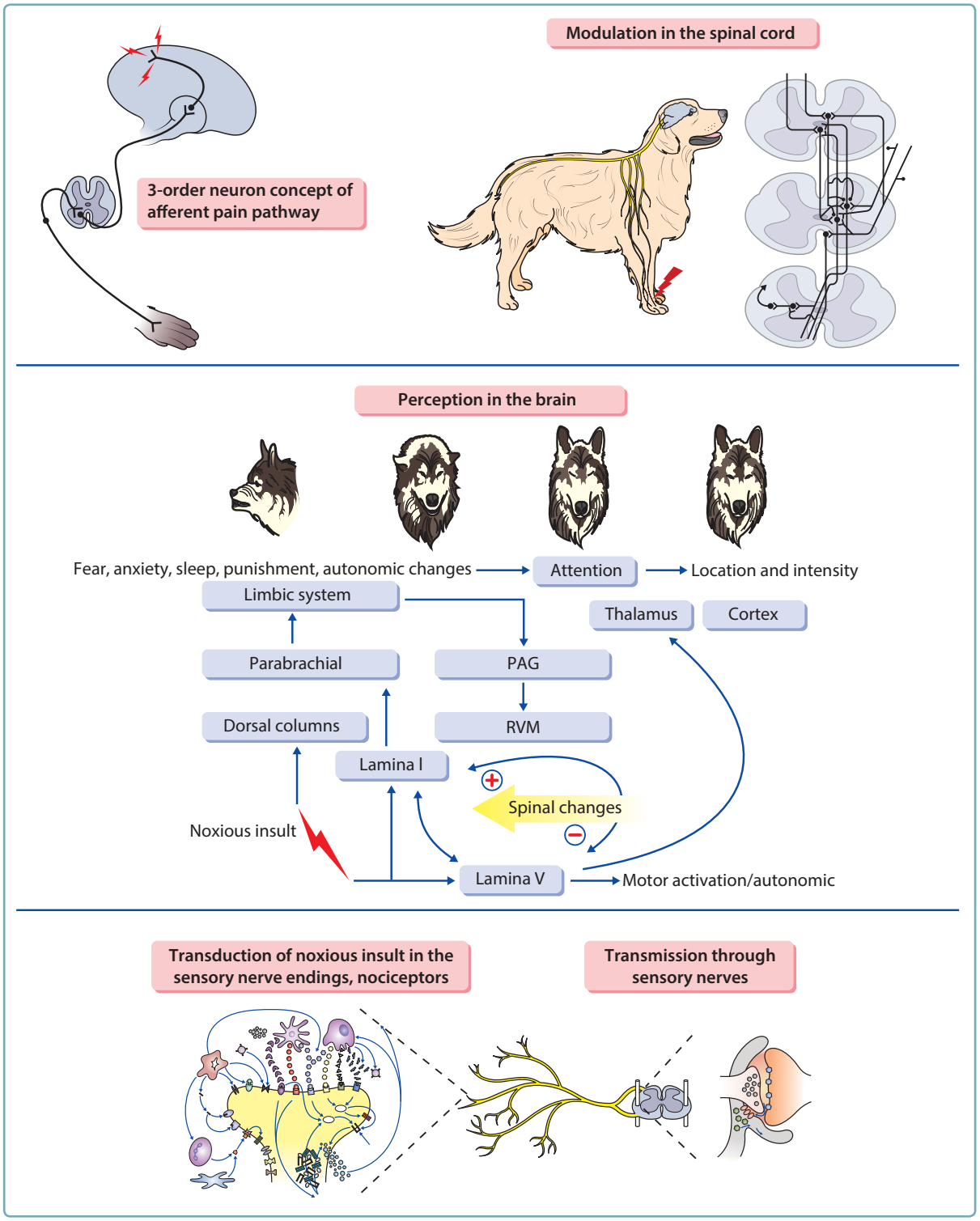
LAMENESS

Most often lameness in pets is identified by the owner, who subsequently seeks further consultation and advice from their veterinarian, or is identified by the veterinarian during routine examination. Most simply, dogs (and cats) are lame because they cannot or will not use one or more limbs in a normal fashion. Pain associated with OA is recognized to become more persistent and intense as the disease progresses. The condition may be asymptomatic in the early stages. With progression of the disease, discomfort may be continuous, or exacerbated by motion and weight bearing. In the later stages of OA, pain can become pervasive and affect nearly all activities and behaviors.

DIAGNOSIS OF OA

A proper diagnosis depends on a complete history and full assessment of the patient, possibly including:

- A complete physical, orthopedic, and neurologic examination.
- Radiographs of affected area(s).
- Advanced imaging, such as computed tomography, magnetic resonance imaging, nuclear scintigraphy.



1.1 The pain associated with osteoarthritis is far more complex than the 3-order neuron 'pathway'. Many sophisticated processes occur in the functions of transduction, transmission, modulation, and perception. PAG: periaqueductal grey; RVM: rostral ventromedial medulla.

- Advanced gait analysis, such as force plate (kinetic) analysis of gait and motion (kinematic) analysis.
- Clinicopathologic examination including hematology and serum chemistries, especially creatine kinase and electrolytes, and synovial fluid analysis.
- Electrodiagnostic testing: ultrasound, electromyography, nerve conduction velocity measurements, evoked potential recordings with repetitive nerve stimulation.
- Muscle biopsy examination including histopathology and histochemical analysis.
- Special tests: muscle percussion, serology for pathogens (e.g. *Neospora, Toxoplasma*), measurement of acetylcholine receptor antibody, immunohistochemistry, and molecular diagnostic techniques.

ANAMNESIS

The medical history, signalment, and owner's complaint(s) comprise the process of anamnesis. Most canine patients do not vocalize from their pain of OA, and many pet owners do not believe their pet is in pain if it does not vocalize. Nevertheless, signs suggesting animal discomfort include lameness, muscle atrophy, reluctance to exercise, general malaise, lethargy, inappetence or anorexia, change in temperament, licking or biting an affected joint, restlessness, insomnia, seeking warmth, seeking comfortable bedding, and difficulty posturing to toilet. Supraspinal influences are known to alter the behavior of humans with OA[1], and it is reasonable to presume the same occurs in dogs.

Pet owners often recognize lameness only when there is gait asymmetry; however, dogs with bilateral OA, such as with hip or elbow dysplasia, have a symmetrically abnormal gait and do not favor a single limb. These patients shift weight from hind to forelimbs or vice versa with resultant muscle atrophy of the affected limbs and increased development in compensating limbs. Rarely are dogs nonweight bearing simply due to OA. Pet owners do often report that their dog is stiff after resting, particularly following strenuous exercise, but they report that the pet will 'warm out of the stiffness'. The amount of time required to warm out of this stiffness gradually increases with progression of the disease. Pet owners also frequently report a shortened stride and stiff gait. This is associated with a decreased range of motion (ROM) in the joint, often due to joint capsule fibrosis and osteophyte formation.

EXAMINATION

For many years degenerative joint disease (DJD) (often used interchangeably with the term OA) was considered a disease of the cartilage. DJD is most appropriately considered a disease of the entire joint, with the influence of multiple structures including articular cartilage. Pain is a hallmark of DJD, provoked by instability, and therefore a comprehensive physical examination is the essential diagnostic tool.

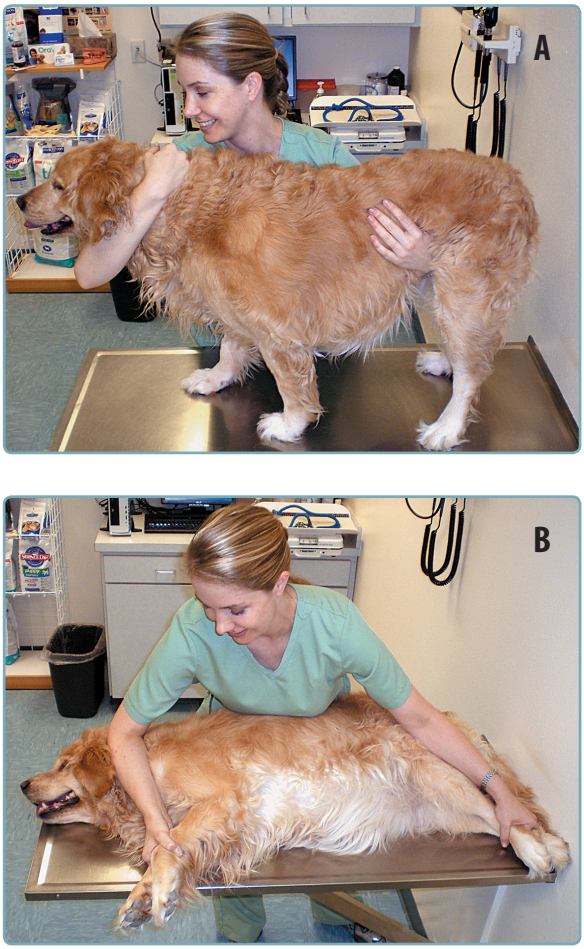
An orthopedic examination should be part of every routine examination and should be conducted in conjunction with a neurologic examination (when appropriate) to identify neurologic causes for pain or lameness, such as a nerve root signature sign secondary to a laterally herniated intervertebral disc (IVD) or brachial plexus pathology.

A consistent 'routine' for examining a patient is advised, and it is also recommended that the 'lame' limb be examined last. A consistent examination pattern (e.g. distal limb to proximal limb, and left side to right side or vice versa) is helpful to avoid missing a structure during the examination, and leaving the most painful limb for last in the examination avoids the early elicitation of pain which may render the patient noncompliant for further examination. A thorough examination also requires the aid of an assistant who is adequately trained to hold and restrain the animal. The assistant is also important for identifying the animal's painful response to examination, such as body shifts and change of facial expression.

Animal restraint

Appropriate animal restraint by the assistant (with the patient standing on the examination table) is with one arm over or under the patient's trunk, while the other arm is placed under and around

the patient's neck (**1.2A**). This constraint allows the assistant to quickly tighten his/her grip to control the animal and avoid the patient from harming anyone, should it become confrontational. In lateral recumbency the assistant should be at the animal's dorsum, 'lightly leaning' on the animal with his/her forearms while holding the hind and forelimbs (**1.2B**). One forearm should be placed on the animal's neck, with that hand grasping the forelimb that is closest to the table, or the 'down limb'. The other arm is placed over the top of the abdomen and the hand grasps the 'down' hindlimb. With this restraint, the assistant can rapidly increase his/her amount of weight on their forearms, thereby controlling the animal's movements. Regarding restraint, large dogs are analogous to horses: if you control their head, you control their body.



1.2 Restraint for examination. Standing restraint (**A**) of large dogs is done with the neck cradled close to the assistant's chest with one arm, while the other arm controls the patient's trunk by placement either under or over the trunk. If the patient struggles or becomes aggressive, the assistant holds the dog as tight as possible. Lateral restraint (**B**) of large dogs is done with the assistant's forearm over the dog's neck. If the patient struggles, more weight is applied on the forearm.

THE ORTHOPEDIC EXAMINATION

Forelimb examination

In the growing dog, forelimb lameness differentials mostly reflect abnormal stressors on normal bone or normal stressors on abnormal bone (excluding fractures and minor soft tissue injuries) and include:

- Osteochondritis dissecans (OCD): shoulder.
- Luxation/subluxation shoulder: congenital.
- Avulsion: supraglenoid tubercle.
- OCD: elbow.
- Ununited anconeal process (UAP).
- Fragmented coronoid process (FCP).
- Ununited medial epicondyle.
- Elbow incongruity:
  - congenital.
  - physical injury.
- Premature closure of growth plates, such as with radius curvus.
- Retained cartilaginous core (ulna).
- Panosteitis* (a disease of diaphyseal bone).
- Hypertrophic osteodystrophy*.

In the adult dog, forelimb lameness differentials mostly reflect abnormal stressors on normal bone or normal stressors on abnormal bone (excluding fractures and minor soft tissue injuries) and include:

- Arthritis.
- OCD: shoulder.
- Luxation /subluxation: shoulder.
- Avulsion: supraglenoid tubercle.
- Bicipital tenosynovitis*.
- Calcification of supraspinatus tendon*.
- Contracture of infra- or supraspinatus*.
- Medial glenohumeral laxity.
- OCD: elbow.
- UAP.

- FCP.
- Ununited medial epicondyle.
- Elbow incongruity.
- Angular limb deformity.
- Hypertrophic osteopathy.
- Bone/soft tissue neoplasia*.
- Inflammatory arthritis.

* denote pathology/disease conditions which are not considered OA, but often manifest similar clinical presentations.

For the purpose of examination, the forelimb can be anatomically segmented into the paw, antebrachium, brachium, scapula, and interpositional joints. Although the entire limb should be examined in every patient, the orthopedic examination can be focused more on areas prone to disease and signalment of the individual patient.

Paw

The paw should be thoroughly examined with flexion and extension of each digit, as well as inspection of each nail and nail bed. Findings incidental to those suggesting OA might include:

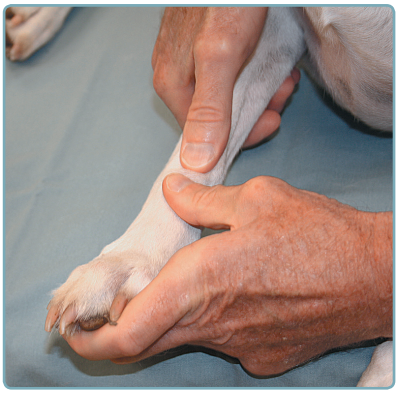
- Pad lacerations.
- Foreign bodies.
- Split nails.
- Overgrown nails.
- Nail bed tumors.
- Phalangeal luxations/fractures.

Some patients resist manipulation of the paws. Here, the assistant can be very helpful by talking to the patient or scratching the patient to distract him/her from the examination.

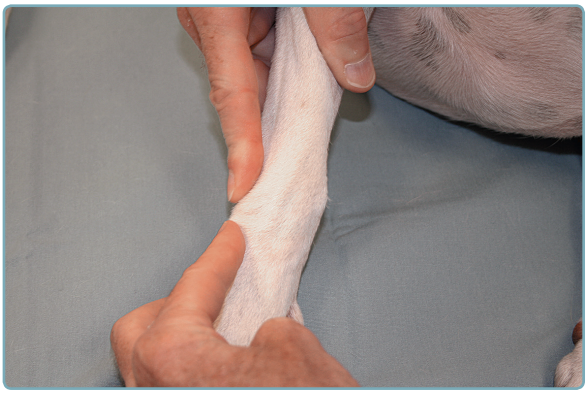
Carpus

The carpus should be placed under stress in flexion, extension, valgus, and varus (**1.3–1.6**). The normal

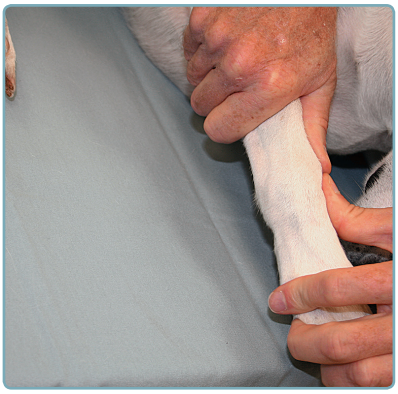
1.3 Carpus flexion. The carpus should be comfortably flexed with the palmar surface nearly touching the flexor surface of the antebrachium.



1.4 The carpus should be stressed in extension, looking for signs of discomfort/pain.



1.5 Placing the carpus in valgus stress identifies integrity of the medial radial collateral ligament.



1.6 Placing a varus stress on the carpus challenges the integrity of the lateral ulnar collateral ligament.

carpus should flex comfortably until the palmar surface of the paw nearly touches the flexor surface of the antebrachium. Findings from the carpal examination may include:

- Young dog 'carpal laxity syndrome'.
- Carpal flexural deformity of young dogs.
- Degenerative joint disease.
- Hyperextension.
- Inflammatory arthritis.
- Luxation.
- Fracture (including an intra-articular fracture, possibly mistaken as OA).

Joint capsule distension is easily palpated and suggests joint inflammation.

Antebrachium

Periosteum of bone is a sensitive tissue, well innervated with nociceptive axons. Therefore, examination of both the radius and ulna should focus on deep palpation for a response of bone pain (**1.7**). Panosteitis is commonly revealed in this manner. Osteosarcoma is another condition that results in pain on palpation of the metaphyseal region of bones. Although an orthopedic examination would include assessment of the antebrachium, OA includes only diarthrodial joints. Nevertheless, joint pain should be localized and differentiated from the pain of long bones and soft tissues.

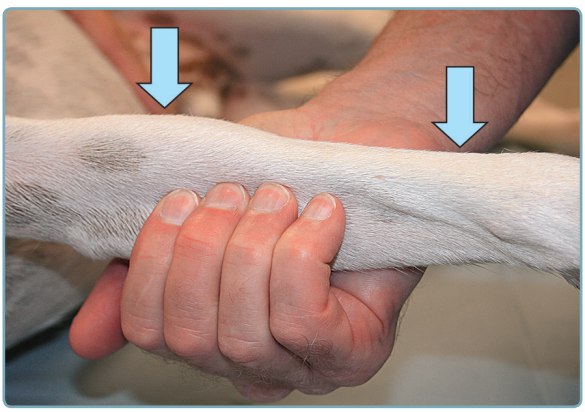
Physeal disturbances are relatively common in the growing dog, the severity of which depends on the amount of growth remaining following injury until physeal closure. Resultant aberrant growth is expressed as angular limb deformities of the carpus and/or the elbow. In general, the plane of the elbow joint should be parallel to the plane of the carpal joint.

Sources of lameness within the radius/ulna include:

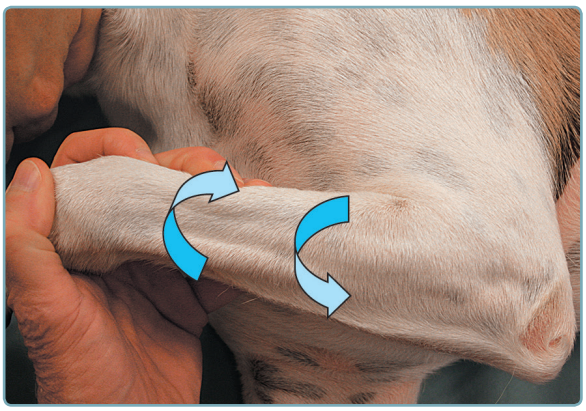
- Hypertrophic osteopathy.
- Angular limb deformities.
- Panosteitis.
- Neoplasia.
- Hypertrophic osteodystrophy.

Elbow

The elbow is the most common forelimb joint responsible for lameness, especially in growing dogs of predisposed breeds (i.e. large breeds, sporting dogs, and Rottweilers). The elbow should be



1.7 Digital palpation is made on the antero-medial aspect of the antebrachium, where there is minimal muscle cover. In the normal dog the elbow joint is parallel to the carpal joint.



1.8 Examination of the elbow joint includes manipulation through a full range of motion.