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Animal Welfare 2010, 19: 437-448
ISSN 0962-7286

Relationships between pathology and pain severities: a review

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Abstract

The relationships between pathology severity and pain severity are reviewed using the literature available for humans. The aim is to help veterinary radiologists, physicians and pathologists recognise the disorders in which severity of a lesion is likely to be related to the severity of pain or to incipient pain. Specific features or lesions within the following conditions showed a relationship with pain score, which was usually assessed with a visual analogue scale: inflammation; pancreatitis; ileitis; mucositis; fasciitis; synovitis; arthritis; lower back pain; disc herniation; sciatica; scoliosis; myalgia; cancer; arteriosclerosis; skin ulcers; mastalgia; skin and oral neuropathies; endometriosis; hepatopathy and chronic pulp diseases of the teeth. As experience with magnetic resonance imaging grows, there will be further opportunities to look for quantitative relationships in humans between pathology and pain severities. This information will be useful to veterinarians and other people working with animals in evaluating pain in animals in their care.

Keywords: *animal welfare, correlation, disease, human, pain, pathology*

Introduction

Disease is arguably the single most important cause of suffering in animals. That suffering includes pain, which is one of the more difficult features of suffering to recognise in animals simply from their behavioural signs. Veterinarians and researchers sometimes strive to appreciate the severity of pain an animal is experiencing or has experienced by examining lesions in the live animal or at post mortem. However, this often calls for assumptions about the quantitative relationship between the severity or extent of a lesion and pain severity. Those assumptions may be valid for some conditions and not for others. For example, in some conditions there might be a threshold in lesion severity at which pain emerges, and more severe forms of the lesion do not necessarily add to the pain. Conversely, as necrosis progresses, pain can sometimes become less pronounced, for example in gangrene (Gregory 2004).

With the advent of radiography, Doppler ultrasonography, magnetic resonance (MR) imaging, arthroscopy and many other organ and tissue examination procedures, it has become possible to examine lesions in living people and track the lesions as they change. This has allowed research clinicians in human medicine to cross-relate the development and decline of lesions with the presence of reported pain. The relationships have been examined in both cross-sectional as well as longitudinal studies, and pain assessments have often been made with the VAS (visual analogue scale).

This review brings together cases where quantitative relationships between pain and pathology severities have been established in human medicine.

Materials and methods

Over 90 papers have been included in the review. They were identified by following up lead references and by searching through PubMed. Papers were selected if they reported quantitative relationships between pain and a lesion which were statistically significant. The statistical methods used for evaluating the quantitative relationships relied on gradations of pain and gradations of the lesions, and included linear regression, multiple linear regression, logistic regression, Spearman's rank correlation, Pearson's rank correlation, and Kendall's τ correlation. Qualitative relationships based on ungraded associations, such as a 2×2 matrix, or a biserial correlation coefficient, were not included. For example, in the study by Elias *et al* (2008), a correlation of 0.77 was cited for the relationship between bone marrow oedema and pain at the ankle. This was a qualitative relationship based on an analysis of four outcomes; pain vs no pain and bone marrow oedema vs no bone marrow oedema, and a phi (φ) correlation coefficient was derived.

Pain has usually been evaluated with a visual analogue scale (VAS), but other systems such as the Likert scale, WOMAC-pain scale (Western Ontario McMaster Osteoarthritis), Constant and Murley score, ASES (American Shoulder & Elbow Surgeons') score, D'Abignè and Postel grade and Ritchie Articular Index were included, all of which were based on pain severity assessed by the affected individual. In the VAS system, the subject is asked to enter a line on a scale which usually extends from 0 to 10, where 0 corresponds to 'no pain' and 10 is 'unbearable pain' or 'the worst possible pain'. Descriptors are used at the two extremes, but there are

https://doi.org/10.1017/S0962728600001925 Published online by Cambridge University Press

no descriptors for the values inbetween. In paediatrics, smiley symbols were substituted for the wording. The Likert scale has descriptors assigned to each number. The patient recorded the level of agreement with a description. Most of the pain assessments related to ongoing spontaneous pain either at the time of an interview or recalled by the subject. Others included pain assessment during manipulation or application of pressure, but only a few studies used algometry (eg McBeth & Gratt 1996). In some situations, severe pain has been less responsive to pain-relieving therapies than mild pain. This has also been used in a limited number of studies as a retrospective way of assessing pain severity, for example in cancer (Akhan *et al* 1997).

Results

Inflammation

The degree of inflammation is often assessed from the size of the area showing reddening, swelling or heat. Swelling can itself be partly responsible for pain through tissue tension, but in other respects these signs are not direct causes of pain. Instead, the link that they may have with pain is either through common mediators which lead to both types of effect, or through localised secondary ischaemia. The features that can be used post mortem to assess the severity of inflammation have to be carefully considered when retrospectively relating this to pain in the live animal. Some conditions are obscured by post mortem changes whilst others may only be obvious in the live state. Notwithstanding this, the following observations are helpful.

Attempts have been made at identifying quantitative relationships between pain severity and each of the three main gross signs of inflammation. Mohammadian *et al* (1998) performed a classic study in which they tried to find which of three signs of increased perfusion during inflammation related best to pain. The model they used was the inflammatory response to capsaicin cream applied to the skin. Flare size was used as a measure of redness, laser-Doppler measurements were taken to assess hyperaemia and skin temperature was assessed by camera thermography to monitor local thermogenesis and increased perfusion. These responses were measured at the capsaicin site and at areas of secondary hyperalgesia. The important conclusion was that the area of skin flare produced the best relationship with spontaneous pain intensity (VAS; $r = 0.97$; $P < 0.005$). Both the area of hyperalgesia and the area of allodynia were correlated with the area of visible flare ($r = 0.87$ and 0.94; $P < 0.01$). Skin temperature was not correlated with hyperalgesia, allodynia or visible flare.

Tenderness and pain severity have been directly correlated to oedema and the severity of swelling, in leg ulcers and psoriatic dactylitis, respectively (Howlader *et al* 2003; Healy *et al* 2008). Oedema has been weakly correlated to chemical markers, such as plasma vascular endothelial growth factor (Howlader *et al* 2003). The redness of actinic skin lesions was significantly related to pain intensity when the affected area was subjected to photodynamic irradiation therapy (Sandberg *et al* 2006).

Subsidence of inflammatory hyperaemia in arthritic joints (assessed from Doppler ultrasonography) has been correlated with declining VAS score for pain (Terslev *et al* 2003).

The severity of pain in chronic pancreatitis has been correlated to the extent of perineural infiltration of the pancreatic nerves by immune cells (Di Sebastiano *et al* 1997). Immune cell infiltration was determined histologically as absent, scattered, dense and follicle-like. There was also a significant relationship between growth associated protein GAP-43 immunoreactivity in nerve fibres and pain intensity.

In the live subject, the temperature difference between the side of the face that was affected by an inflammatory temperomandibular disorder and that on the non-affected side was positively correlated with pain severity assessed with a muscle and joint palpation severity scoring system (McBeth & Gratt 1996). The relationship was strongest in those regions of the face that overlay a well-developed muscle.

The inflammatory responses are co-ordinated by cytokines. Increased concentrations of the acute pro-inflammatory cytokine IL-8 in cerebrospinal fluid were correlated with a short duration of pain in subjects with spinal disc herniation. There was no relationship with the intensity of pain, but IL-8 was linked to the severity of the herniation (Brisby *et al* 2002). Similarly, the staining score for IL-1β in endothelial cells within sections of articular disc and synovial biopsy specimens was correlated to the severity of arthralgia in patients affected by temperomandibular joint disorders (Suzuki *et al* 1999).

In temperomandibular joint disorders, the severity of joint pain has also been directly correlated to nitric oxide concentration in the joint fluid (Spearman's $\rho = 0.73$; Suenaga *et al* 2001). Nitric oxide formation serves as a measure of the inflammatory response, but because of its rapid decay it is not easy to measure precisely.

Calcitonin gene-related peptide (CGRP) can contribute in bringing about inflammatory responses. It is present in nociceptive unmyelinated afferent C-fibres, and is released into surrounding tissues when these fibres are activated. Positive correlations have been found between the extent of CGRP-positive staining cells in sections of synovial tissue and VAS joint pain in subjects affected by temperomandibular joint disorders (Sato *et al* 2004).

With some diseases, pain sometimes continues beyond an inflammatory episode. For example, there can be tissue scarring and stenosis which presents masses that are painful on palpation. In Crohn's disease, the severity of pain in the inactive disease has been correlated to the length of the diseased segment in the gut, as determined by double-contrast X-rays (Prantera *et al* 1984). This relationship did not exist in the active disease.

Specific inflammatory conditions — synovitis

Synovitis can be assessed with arthroscopy, contrast-enhanced ultrasonography, power Doppler sonography or MRI. Arthroscopy can give a reliable overall assessment, and MR images can assess synovial thickening (Ayral *et al* 2005). In some instances the painful lesion is

https://doi.org/10.1017/S0962728600001925 Published online by Cambridge University Press

confined to one aspect of a joint and there is a risk of dismissing it because of its limited size relative to the joint surface as a whole. Whereas, conditions, such as effusion into a joint will be more general and can be correlated to pain especially during activity (Song *et al* 2008, 2009). Effusion may, however, be more difficult to recognise from gross post mortem pathology.

There are a multitude of steps in the biochemical cascade that control an inflammatory response, and several biochemical markers show promise as indicators of pain severity in synovitis. For example, in rheumatoid arthritis, monocyte chemoattractant protein-1 (MCP-1) acts as a monocyte, and a B and T lymphocyte chemoattractant. It is located in macrophages, endothelium, synovial fibroblasts and chondrocytes in inflamed joints, and its concentration in plasma and synovial fluid has been correlated with the Ritchie Articular Index (pain response when pressure was applied to the joint) (Ellingsen *et al* 2001).

When synovial inflammation is followed by a reactive capsular fibrosis, the shoulder can become 'frozen'. There is restriction in both active and passive shoulder movement from an adhesive capsulitis. When the uptake of Tc-99m human immunoglobulin at the inflammatory site was assessed by scintigraphy, it was found to be related to the patients' ASES pain score (Şenocak *et al* 2002).

When synovitis is assessed by arthroscopy it can be graded for capillary hyperaemia and synovial hyperplasia. When this was done in a sample of subjects with either osteoarthritis or rheumatoid arthritis, joints that were tender on palpation showed a correlation with the presence of synovitis (Gynther *et al* 1997).

In a cross-section of subjects affected by osteoarthritis of the knee, there was no correlation between baseline synovitis and baseline pain score (Hill *et al* 2007). However, as treatment progressed there was a correlation between change in VAS pain score and change in synovial thickening. Increasing synovitis was associated with increasing pain, but not with loss of cartilage in the joint.

Specific inflammatory conditions — fasciitis and mucositis

Hyperaemia in plantar fasciitis of the heel (assessed by power Doppler ultrasonography) has been directly correlated with VAS for pain (Spearman's $\rho = 0.71$; $P < 0.0001$; Walther *et al* 2004). This condition is often due to overloading of the heel. As with many other inflammatory reactions, the relationship with hyperaemia probably only occurs during the acute phase response. In other words, the relationship will be less obvious during the chronic phase when there is less or no inflammation.

Oral mucositis can be an unpleasant side-effect of cancer therapy. When the severity and extent of mucositis was assessed with a scoring system based on ulceration, pseudomembrane and erythema, it was found to be strongly correlated with pain severity (Sonis *et al* 1999).

Specific inflammatory conditions — sinusitis

There have been mixed reports as to whether pain is correlated to the severity of sinusitis assessed with CT scans (Kenny *et al* 2001; Wabnitz *et al* 2005). There has, however, been a highly significant correlation between a composite of five other symptoms (fatigue, lack of sleep, nasal discharge, blocked nose, decreased sense of smell) and CT scan score for sinusitis (Kenny *et al* 2001).

Arthritis

In general, rheumatoid arthritis is more likely to be associated with severe pain than osteoarthritis. Rheumatoid arthritis involves inflammation of the joints, whereas osteoarthritis involves cartilage changes, loss of flexibility of subchondral bone, and neuromuscular changes leading to articular degeneration (Ay *et al* 2008). Both can be chronic conditions.

In the early stages of osteoarthritis, functional ability is influenced more by disease activity than by joint destruction. Thus, at the early stage, the relationships between pain and pathology may lie in the acute phase responses, but they will change as the disease progresses and becomes less active. In rheumatoid arthritis, involving pannus, there is progressive degradation of bone, cartilage matrix and joint capsule with soft tissue detachment and atrophy. Fatty infiltration and tears within supporting muscles (eg *supraspinatus* and *infraspinatus* in shoulder rheumatoid arthritis) can be correlated with pain severity (van de Sande *et al* 2008). This, no doubt, is symptomatic of how advanced the disease has become, rather than fatty infiltration or degeneration directly causing pain.

Osteoarthritis can involve some localised inflammatory responses and in this situation there can be a quantitative relationship between pain severity and PGE_2 concentration in synovial fluid (Brenner *et al* 2004).

Many studies have reported significant relationships between knee or temperomandibular joint pathology and pain severity. The pathological features have included bone marrow lesions in the subarticular marrow, osteophyte formation, articular cartilage lesions, condyle erosion, abnormal positioning of the articular disc, and joint hyperaemia (Bakke *et al* 2001; Emshoff *et al* 2002; Hunter *et al* 2003, 2008; Terslev *et al* 2003; Kettunen *et al* 2005; Raynauld *et al* 2006; Duncan *et al* 2007). Many of these conditions no doubt involved an inflammatory response, and increasing pain was often associated with increasing disability. In one study, the cartilage lesion scores were classified according to fragmentation and fissuring and according to the total cartilage lesion area as shown in Table 1, and they correlated generally with pain severity (Kettunen *et al* 2005).

Arthritis has sometimes been scored on a scale involving composites of lesions instead of individual lesions, and this makes application of the findings more complex especially when stepping across species boundaries. One such scale is the Pettersson scale, which is a composite of eight

https://doi.org/10.1017/S0962728600001925 Published online by Cambridge University Press

Table 1 Relationship between articular cartilage lesion score at the knee and VAS pain score (0 to 100).

Lesion score	Lesion description	VAS (± SEM) pain score
0	Normal	10 (± 9.6)
1 + 2	1: softening + swelling (closed), 2: fissuring + small erosions	16.0 (± 16.5)
3	Fragmentation, fissuring, deeper erosions but not to subchondral bone	35.0 (± 11.3)
4	Erosions down to subchondral bone	64 (± 15.2)

features: osteoporosis; increase in the epiphyseal endplate; irregularity in the subchondral surface; reduction in joint space; presence of subchondral cysts; erosion of joint edges; incongruity of joint surfaces and joint deformity. This radiographic score produced strong correlations with VAS pain score for the knee, but less so for the ankle and elbow (eg Wallny *et al* 2005). The narrower Kellgren-Lawrence scale has not always produced such clear relationships with pain (Link *et al* 2003).

One of the complications of radiographic examination of joints is that they sometimes require ongoing pain for identifying the underlying pathology. In this situation, radiographic examination in the anaesthetised state has limitations. An example is the case where reduced joint space width in the osteoarthritic knee was only evident in the standing position when the affected knee was causing pain (Mazzuca *et al* 2002). This raises limitations in veterinary applications, and in using post mortem pathology when assessing the likelihood of a history of pain.

Bone marrow oedema can be seen in MRI scans of subjects with advanced hip osteoarthritis. It is coincident with subchondral lesions, bone marrow fat necrosis, subchondral pseudocysts or geodes, bone marrow fibrosis, microfractures in different stages of healing, and it should not be considered as a separate lesion. Using bone marrow oedema as a marker of these changes, it has been found to be correlated to pain severity (Taljanovic *et al* 2008).

Bone-wasting diseases and osteonecrosis

Bone-wasting disorders are not always painful. However, in people afflicted with fibromyalgia, reduced bone mineral density in the femoral neck and the spine (assessed by DEXA scanning) have been associated with VAS pain rating (Jensen *et al* 2003).

Femoral head necrosis is likely to be painful, and pain severity can be graded from the area of the lesion in a two-dimensonal MR image. Early (presymptomatic and preradiologic) stages of osteonecrosis can be identified with MRI, and at the preradiologic stage, collapse of the hip can be correlated with the incidence of pain (Nishi *et al* 2002). As hip deterioration progressed, the correlation persisted. The frequency of subjects reporting hip pain rises as the lesion becomes more severe (Nam *et al* 2008).

Advanced neuropathic arthritis is often painless, and this can lead to self-neglect in care for the affected joints. However, in its early stages pain can be present and it has been related to the severity of bone marrow oedema (Schlossbauer *et al* 2008).

Back pain, pelvic disorders and sciatica

The severity of back pain has been correlated with the severity of back and pelvic pathology in a number of studies. The pathological features have included lumbar spinal stenosis, spinal disc disease, lumbosacral angle, and asymmetric sacroiliac laxity during pregnancy (Damon *et al* 2001; Kapural *et al* 2007; Sarikaya *et al* 2007; Scuderi *et al* 2008). No relationship was reported between pain severity and the extent of post-surgical epidural fibrosis (Coskun *et al* 2000).

The relationships may apply to some regions of the back and not to others. For example, there was a relationship between severity of low back pain and radiographic score for L3–L4, but no relationship for any of the other lumbar vertebrae (Scuderi *et al* 2008). Similarly, the relationship between pain severity and lumbosacral angle applied in the case of manual workers involved with lifting and carrying, but not in workers who did prolonged standing, walking and bending (Sarikaya *et al* 2007). Relief from pain did not always follow the reverse lesion score sequence. For example, patients with mild or moderate spinal stenosis had greater reduction in pain compared to subjects with severe stenosis, when treated with lumbar epidural steroid injections (Kapural *et al* 2007).

Two studies have found a positive linear relationship between the concentration of substance P in cerebrospinal fluid and VAS pain score. In one of the studies ($r = 0.32$; $P < 0.05$), the patients were suffering from lumbar disc herniation, lumbar spinal canal stenosis, cervical myelopathy, cervical radiculopathy or lower limb fracture (Imasato *et al* 1997). The cohort making up the second study ($r = 0.71$; $P < 0.01$) is not clearly explained in the paper, and it appears that it was made up of patients suffering from osteoarthritis of the hip or knee (Lindh *et al* 1997). If this interpretation is correct, then it suggests the cerebrospinal fluid substance P concentration might be an indicator of sensitisation at the spinal level.

Vertebral compression fractures are a hazard in subjects with osteoporosis. Bone marrow oedema sets in after a compression fracture as part of the inflammatory response, and it resolves with time. A study in subjects treated for compression fractures with vertebroplasty has shown that pain relief from the procedure was correlated to the severity of the bone marrow oedema (Tanigawa *et al* 2006). The implication is that this feature of the inflammatory response following bone trauma could be an indicator of pain severity.

https://doi.org/10.1017/S0962728600001925 Published online by Cambridge University Press

Macromastia can lead to back pain, as well as shoulder and neck pain. Long-lasting pain relief after surgery in subjects undergoing breast reduction was significantly correlated with the weight of tissue removed (Bruhlmann & Tschopp 1998). The implication is that in cases of oversize, the larger the burden the greater the potential pain.

Back pain can be associated with long-term abnormalities in posture and gait. This, in turn, can be associated with either hypertrophy, in particular postural or locomotor muscle groups, or atrophy, depending on which side or aspect of the body is being favoured. Subjects with unilateral back pain showed a positive correlation ($r = 0.61$; $P < 0.01$) between cross-sectional area of the *psoas* muscle group on the affected side and pain rating (Barker *et al* 2004). The *psoas major* inserts along the lumbar spine and probably increases intradiscal pressure when contracted. Wasting of the muscle can reflect the duration of painful conditions such as sciatica (Dangaria *et al* 1998).

Sciatica can arise from poor perfusion of the discs supplied by the lumbar arteries. In subjects with unilateral sciatica, eight lumbar arteries were scored for occlusion from MRI scans and this was found to be weakly (but significantly) correlated to pain severity in the leg or the back (Kurunlahti *et al* 2004). This supports other work where atherosclerosis of the lumbar arteries and calcification of the abdominal aorta have been linked to low back pain.

The degree of lumbar spinal stenosis is not closely related to the severity of back pain (Athivirahan *et al* 2007). However, when stenosis exceeds a critical threshold, there is significantly greater functional disability. Disc narrowing can be associated with pain, and logistic regression analysis has revealed an association between the severity of the narrowing and the severity of back pain (Pye *et al* 2004).

Oedema in the dorsal root ganglia (DRG) can contribute to back pain when there is disc herniation. This has been assessed as swelling of the DRG in MRI scans in comparison with the unswollen contralateral side. When assessed in this way, the swelling has correlated with leg pain (Spearman's $\rho = 0.39$; Aota *et al* 2001).

In scoliosis, inflammatory endplate changes, endplate angle, lumbar lordosis and thoracic spinal curvature have been correlated with back pain (Schwab *et al* 2002; Watanabe *et al* 2005; Buttermann & Mullin 2008).

Logistic regression analysis has revealed a relationship between the extent of development of anterior osteophytes at T4–L5 and back pain (O'Neill *et al* 1999). Osteophytes may form at vertebral fractures or at small peripheral tears in the annulus which allow a mobile nucleus to press forward and stimulate bone formation near a stress point in the longitudinal ligament.

In subjects affected by chronic back pain there was a strong negative correlation between pain intensity and the relative volume of grey matter to white matter in MRI scans of the brainstem plus somatosensory cortex (Schmidt-Wilcke *et al* 2006). This might have been due to grey matter shrinkage or accelerated neurodegeneration in the worst affected individuals.

Table 2 Spearman's correlation coefficients between muscle and serum parameters and delayed onset muscle soreness.

Muscle or serum parameter	VAS per pain
Volume of muscle oedema	0.60, $P < 0.05$
Change in serum creatine kinase	0.79, $P < 0.001$

To summarise, the clearest relationships with non-specific low back pain have been with degenerative conditions involving disc narrowing, osteophytes and sclerosis. In a review of 35 publications, van Tulder *et al* (1997) somewhat surprisingly concluded that spondylolisthesis, spondylosis, spondylolysis and transitional vertebrae were not quantitatively associated with pain in a clearly recognisable manner.

Myalgias

Neck and shoulder pain in women is often due to insufficient peripheral circulation in the upper *trapezius* muscle. Kadi *et al* (1998) showed that there was a quantitative relationship between these features. The number of capillaries per unit of muscle area for Type I myofibres was inversely correlated to the magnitude of pain assessed by VAS ($r = –0.45$; $P < 0.05$). In disorders linked to non-cardiac peripheral artery insufficiency, walking distance before pain set in was positively correlated with the proportion of Type I myofibres in the dependent muscles ($r = 0.72$; Sjöström *et al* 1980). This implies that different fibre types in muscle are used selectively, and they are adapted differentially to insufficient blood supply.

Muscle soreness can develop when there has been unusually strenuous exercise. The soreness is often delayed and becomes obvious the day after the event. When muscle oedema (MR imaging) and the change in serum creatine kinase activity were assessed two days after strenuous elbow flexion exercise, they were both found to be related to pain score (Table 2; Evans *et al* 1998).

Although muscle tension cannot be assessed in cadavers, it may be useful to note that muscle hardness in the live state can be related to local tenderness score (Ashina *et al* 1999).

Cancer

Pain intensity or duration has been positively correlated to tumour size or spread in pancreatic, skin, alimentary tract, cauda equina cancers and lymphomas. In the case of pancreatic cancer, pain is not always present but it can arise from invasion of the intra-pancreatic nerves, stretching of the pancreatic capsule, peritoneal involvement and impinging on surrounding organs and tissues (Okusaka *et al* 2001). The prevalence of abdominal pain in subjects with small pancreatic tumours (≤ 3 cm) was not related to their malignancy (Lee *et al* 2008).

In subjects with skin cancer, when the tumour area was larger than 130 mm^2, there was significantly higher mean VAS pain scores during photodynamic therapy (Grapengiesser *et al*

https://doi.org/10.1017/S0962728600001925 Published online by Cambridge University Press

Table 3 Association between spontaneous pain, pain during dressing change and size of a leg ulcer or duration of the ulcer.

	Mean VAS pain score	
	Spontaneous	Dressing change
Ulcer size (cm^2)		
< 5	42[a]	48[a]
5–9	50[ab]	62[ab]
10–29	47[ab]	53[ab]
> 30	57[b]	69[b]
Ulcer duration (months)		
< 3	39[a]	47[a]
3–5	46[ab]	49[ab]
6–12	53[ab]	53[ab]
> 12	54[b]	64[b]

Means within the column for ulcer size and for ulcer duration were significantly different at $P < 0.05$ if they did not have a common superscript letter.

2002). The patients experienced a burning sensation in the tumours, but not in the normal skin that was also irradiated. The implication is that they experienced more pain when more malignant cells were in the treated field.

In a study on a range of subjects who had tumours of the cauda equina (including schwannoma, ependymoma, meningioma, neurofibroma and ganglioblastoma), pain duration was correlated with tumour size ($r = 0.46$; Shimada *et al* 2006).

In a group of patients with either lymphomas, pancreatic, stomach, colon, bile duct, or hepatocellular carcinomas, the relief from pain achieved with coeliac ganglionic blockade (with 70% ethanol) was found to be inversely related to tumour size (Akhan *et al* 1997). The implication is that larger carcinomas provoke a more stubborn, if not more severe, pain.

Squamous cell carcinomas in the mouth can be painful. However, no correlation has been found between the size of the carcinoma and VAS pain suggesting that the pain is not a result of the stretching effect of the tumour (Connelly & Schmidt 2004). Where there had been metastases, there was a correlation between the extent of lymph node involvement and increased levels of spontaneous pain and functional throbbing. This could have been due to either perineural infiltration or nociceptor hypersensitivity.

Hepatic metastases can stretch the liver capsule causing discomfort if not pain. However, there was no quantitative relationship between the number of metastases and pain severity when the former was assessed by CT scanning (Harris *et al* 2003).

Bone density has been inversely correlated with pain severity in bone cancer patients before they received treatment ($r = –0.57$; Vassiliou *et al* 2007). Following radiotherapy, the increase in bone density at metastatic sites was accompanied by marked pain reduction.

Artery disease

The matrix metalloproteinase MMP-2 is involved in the degradation of the basement membrane and the extracellular matrix of arterioles during progressive systemic sclerosis. MMP-2 activity in tenosynovial arterioles has been positively related with Likert pain severity in carpal tunnel syndrome in the absence of inflammation (Hirata *et al* 2005). This association may be a feature of repeated transient ischaemia-reperfusion injury, leading to tissue degeneration.

Ulcers, cysts and organomegaly

Pain severity has been significantly correlated with the size of upper or lower limb ulcers and the extent of oedema associated with lower limb ulcers (Howlader *et al* 2003; Guarnera *et al* 2007; Toffolo *et al* 2008). Pain severity has also been related to the length of time the subject has had the ulcer (Table 3, after Guarnera *et al* 2007).

It is well recognised that when a gross inclusion body is reduced or removed there is prompt pain relief. This applies to a wide range of painful conditions, for example to drainage of liver and arachnoid cysts, post-surgical reduction in swelling, thermal ablation of tumours, and reduction of hypertrophy (with erythema) in cutaneous lupus erythematosus (Erdogan *et al* 2007; Grieco *et al* 2007; Helland & Wester 2007; Bonilla-Martinez *et al* 2008; Phillips *et al* 2008). These findings imply that there is a quantitative relationship which either involves a threshold at which pain is evoked by tissue stretching or a gradation in pain severity with lesion size.

Patients with enlarged prostates tend to feel more pain during pressure applied by transrectal ultrasound-guided prostate biopsy (Yun *et al* 2007).

Mastalgias

Mastalgia is often recognised in animals affected by trauma, mastitis and mammary carcinoma, and no doubt it occurs in some other conditions. In a study on women who were being screened for breast cancer, but retrospectively were asymptomatic, it was found that there was a relationship between intensity of pain and maximum width of the milk duct assessed by ultrasonography (Pearson's $r = 0.50$; $P < 0.001$; Peters *et al* 2003). In some individuals, milk duct dilatation may have been associated with mammary duct ectasia within the gland in response to an inflammatory condition. Tension-mediated pain in response to cyclical prolactin-induced gland oedema would not be expected to explain the association, because it is likely to have a milk duct constricting effect (Peters *et al* 2003).

Neuropathic pain and neuralgias

In the past, it has been considered that nerve fibre loss has been associated more with loss of sensation than with loss of pain. This view is now changing, and a number of studies have shown inverse relationships between intraepidermal nerve fibre density and levels of neuropathic pain (Polydefkis *et al* 2002; Devigili *et al* 2008; Vlčková-Moravcová *et al* 2008).

https://doi.org/10.1017/S0962728600001925 Published online by Cambridge University Press

Table 4 Proposed relationship between salivary sodium, potassium and VAS score for pain (1–5) in children.

Salivary Na^+ (mmol L^{-1})	Salivary K^+ (mmol L^{-1})	VAS score	Pain description
173.2	12.2	1	No pain
172.3	13.2	2	Mild pain
171.4	13.5	3	Moderate pain
170.4	14.2	4	Moderate high pain
165.3	16.2	5	Severe pain

Post-herpetic neuralgia (PHN) and anaesthesia dolorosa are considered by some to be two of the worst forms of pain in people. In PHN, varicella zoster virus causes inflammatory damage to DRG cells, and pain usually develops in or near the dermatome affected by the virus. Pain and allodynia severity in PHN have been inversely correlated with skin innervation density at dermatome sites (Kendall's $\tau = -0.40$ to -0.46; Rowbotham *et al* 1996). Subsequent work failed to confirm the quantitative relationship, but it did confirm a relationship with the presence or absence of pain (Pearson's $r = -0.66$ to -0.69; Oaklander *et al* 1998).

Burning mouth syndrome is a chronic small-fibre neuropathy associated with nerve fibre loss in the lingual mucosa. It can lead to over-expression or over-activity of capsaicin receptors. The VAS pain score for this condition has been correlated with the capsaicin fibre area in the lingual mucosa (Spearman's $\rho = 0.55$; Yilmaz *et al* 2007). It was also related to sensitivity to capsaicin-induced pain.

In general, the size of a neuroma has not been correlated with pain severity (Sharp *et al* 2003).

Some painful neuropathies are associated with delayed motor nerve conduction. The reduced velocity could be due to either degeneration of motor nerves or progressive post-synaptic damage. In patients with myofascial pain syndrome, which is a chronic muscular pain accompanied by referred pain and weakness, there was a significant correlation between the duration of the painful condition and the delay in motor end plate conduction (Chang *et al* 2008). Although this does not relate directly to a pathological lesion, it could serve as a promising lead.

Reproductive tract

A large volume of work has examined relationships between pain severity and lesion scores in endometriosis in an attempt to understand the cause of the associated pain. In the veterinary area this has most relevance in primate health care. Endometriosis has only occasionally been reported in non-primate species.

The pain takes the form of back pain, dysmenorrhoea and dyspareunia. Severe pain is often linked to growth of nerve fibres into ectopic implants and so advanced stages of the disease can be more painful. Pain is more severe when there is deep invasion by the endometrioma into surrounding tissue (Muzii *et al* 1997). In cases of deep endometriosis, pain score was significantly correlated to a severity score for adhesions. The spread of adenomyosis has been correlated with pelvic pain and with dysmenorrhoea, and the diameter of ovarian endometriomas has been inversely related to the severity of dysmenorrhoea (Sammour *et al* 2002; Vercellini *et al* 2007).

Hepatopathy

The severity of portal fibrosis, assessed histologically from liver biopsies, was related to abdominal (right upper quadrant) pain in children with fatty liver disease (Schwimmer *et al* 2003).

Teeth

In human dentistry, pulpal disorders that are usually considered to be treatable include intact-uninflamed pulp, atrophic pulp or pulposis, acute pulpitis and transitional stages to corresponding chronic conditions. Untreatable disease includes chronic partial or total pulpitis, total pulp necrosis and acute pulpitis superimposed on a chronic pulpitis. There is a general relationship between pain in response to cold stimulation (ethyl chloride) and untreatability of the pulpal state, with more likelihood of a pain response in untreatable conditions (Cisneros-Cabello & Segura-Egea 2005).

When root canal surgery was followed by generalised swelling there was an increased odds of post-obturation pain (Ng *et al* 2004). No relationship was found between teeth wear and temperomandibular pain (Schierz *et al* 2007).

An interesting relationship between salivary electrolytes and toothache severity in children was reported by Gupta *et al* (2006). The proposed scale between salivary sodium, potassium and VAS pain score is shown in Table 4. The reason for the relationship was not clear but it could have been linked to decreasing food intake in the more severely affected children.

Discussion

The findings in this review on humans indicated that pain severity and pathology severity are related to each other for the conditions listed in Table 5. This table gives the main pathological features within each condition that are quantitatively correlated to pain, and the pain may be in terms of severity or duration, as explained in the *Results* section.

Needless to say, the likelihood of obtaining a significant correlation between a lesion and pain depends on the cohort that is being considered. The likelihood increases when the cohort includes both symptomatic and asymptomatic cases, and this has not been the situation in all studies that were

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Table 5 Pathological features related quantitatively to pain severity or duration in humans.

Disease or condition	Pathological feature correlated to pain
Inflammation	Flare size
	Redness; hyperaemia
	Oedema, Swelling
Pancreatitis	Perineural infiltration by immune cells
	GAP-43 in nerve fibres
Ileitis	Length of gut affected by disease
Mucositis	Ulcers, pseudomembrane, hyperaemia
Synovitis	Effusion
	Synovium IL-1β, immunoglobulin binding
	Synovial fluid NO, CGRP, MCP-1, PGE_2
	Synovium thickening
	Hyperaemia + hyperplasia
Arthritis	Articular cartilage lesions
	Condyle erosion, Reduced joint width
	Joint hyperaemia, Osteophytes
	Ectopic articular disc, Bone marrow lesions
	Bone marrow oedema
	Fatty infiltration in supporting muscles
Back pain	Lumbar spinal stenosis
	Spinal disc narrowing
	Abnormal lumbosacral angle
	Anterior osteophytes
	Asymmetric sacroiliac laxity
	Psoas major asymmetry
	Bone marrow oedema*
	Grey:white matter in brain
	Cerebrospinal fluid substance P concentration
Disc herniation	Cerebrospinal fluid IL-8, DRG oedema
Sciatica	Stenosis of lumbar arteries (arteriosclerosis)
Scoliosis	Inflammatory endplate
	Abnormal endplate angle
	Back curvature
Macromastia	Gland size*
Myalgia	Capillaries/area Type I myofibres
	Serum CK
	Muscle oedema
Cancer	Invasion of an organ by nerves
	Pancreatic, skin, gut, hepatic, bile duct, cauda equina tumour size
	Low bone density
Arteriosclerosis	MMP-2 in arterioles
Skin ulcers	Ulcer size
Cysts	Cyst size*
Mastalgia (non-lactating)	Teat duct dilatation
Skin neuropathy	Reduced intra-epidermal nerve fibre density
Oral neuropathy	Reduced small fibre population
Endometriosis	Nerve fibre growth into the implant
	Depth of penetration of endometrioma
	Extent of adhesions
	Size of ovarian endometrioma
	Adenomyosis spread
Hepatopathy	Portal fibrosis
Tooth pain	Chronic pulp disease
	Swelling
	Salivary electrolyte

* A quantitative relationship with pain is implied, and not proven.

reviewed. On reflection it is thought there were many studies in which no significant relationship existed between pathology severity and pain severity simply because there were no asymptomatic patients in the study.

The reports have been dominated by research into osteoarthritis, rheumatoid arthritis, synovitis, tempero-mandibular joint disorders, lower back pain and endometriosis. The findings for almost all of the 23 general disease categories have relevance to animal welfare and veterinary science. There are three ways in which this information can be applied to animals. Firstly, it can help practitioners decide when analgesic treatment, slaughter or euthanasia are appropriate courses of action, and it could influence the advice they give to clients. For example, facial eczema is a potentially painful condition in dairy cattle, and the evidence described in the section on inflammation suggests that the focus should be on skin redness when offering advice to the client on pain control. In addition, the focus in deciding when pain relief should be given to patients with leg ulcers should be based on the severity of swelling, and in the case of patients with cancer the size of the tumour and its likely innervation are more relevant than the number of tumours when considering the immediate or imminent need for pain control or euthanasia.

Secondly, the information can be used as supporting evidence in testimonies that a particular condition could have been painful. For example, skin flare can be a helpful feature when considering cases where accommodation hygiene has been neglected and a statement about the likelihood of pain is expected. In addition, in cases of femoral head necrosis in poultry or small breeds of dog, collapse of the hip would be an appropriate criterion for the likelihood of pain.

Thirdly, the approach adopted in this review can be used in research into potentially painful conditions. For example, osteochondrosis dissecans can be a painful condition in breeding pigs, and strategies being developed to reduce its impact could include synovial thickening associated with synovitis as a post mortem feature that retrospectively indicates likely pain severity. In non-inflammatory osteoarthritis, cartilage erosion would be a more relevant feature. In animals used in competitive sports, recreation and draught work, serum creatine kinase may be of value as an indicator of muscle soreness besides its more usual use as an indicator of exertion or muscle injury.

These are a few examples of how the information in this review could be applied, and no doubt more will emerge in future as the approach is adopted and explored further.

Animal welfare implications

The welfare compromise associated with a particular painful condition depends on the number of animals affected by the condition, the severity of the pain, and the capacity of the species to experience pain for that particular feature. Learning about pain severity in humans and applying those principles in animals is one of the main ways of understanding the extent of pain in animals. This approach has limitations and needs to be supported with

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observations in affected animals to be confident that the interpretations are correct.

The conditions that can cause pain in man are well recognised (Wall *et al* 1994), and that knowledge is used widely in recognising whether animals with comparable conditions may be experiencing pain. However, it is less widely used in attempting to assess the severity of pain or welfare compromise in animals. This review was concerned with estimating pain severity. It provided a starting point in establishing quantitative relationships between pain and pathology that could be examined and developed for animals.

Acknowledgements

This work was performed as part of a project on recognising pain in clinical conditions seen in donkeys that was commissioned by the Donkey Sanctuary.

References

Akhan O, Altinok D, Özmen MN, Oguzkurt L and Besim A 1997 Correlation between the grade of tumoral invasion and pain relief in patients with celiac ganglia block. *American Journal of Roentgenology 168*: 1565-1567

Aota Y, Onarii K, An H and Yoshikawa K 2001 Dorsal root ganglia morphologic features in patients with herniation of the nucleus pulposus: assessment using magnetic resonance myelography and clinical correlation. *Spine 26*: 2125-2132

Ashina M, Bendtsen L, Jensen R, Sakai F and Olesen J 1999 Muscle hardness in patients with chronic tension-type headache: relation to actual headache state. *Pain 79*: 201-205

Athiviraham A, Yen D, Scott C and Soboleski D 2007 Clinical correlation of radiological spinal stenosis after standardisation for vertebral body size. *Clinical Radiology 62*: 776-780

Ay S, Tur BS and Küçükdeveci A 2008 Evaluation of disability in patients with degenerative and inflammatory arthritis. *International Journal of Rehabilitation Research 31*: 159-163

Ayral X, Pickering EH, Woodworth TG, Mackillop N and Dougados M 2005 Synovitis: a potential predictive factor of structural progression of medial tibiofemoral knee osteoarthrtitis – results of a 1 year longitudinal arthroscopic study in 422 patients. *Osteoarthritis and Cartilage 13*: 361-367

Bakke M, Zak M, Jensen BL, Pedersen FK and Kreiborg S 2001 Orofacial pain, jaw function, and temperomandibular disorders in women with a history of juvenile chronic arthritis or persistent juvenile chronic arthritis. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology 92*: 406-414

Barker KL, Shamley DR and Jackson D 2004 Changes in the cross-sectional area of multifidus and psoas in patients with unilateral back pain: the relationship to pain and disability. *Spine 29*: E515-E519

Bonilla-Martinez ZL, Allbrecht J, Troxel AB, Taylor L, Okawa J, Dulay S and Werth VP 2008 The cutaneous lupus erythematosus disease area and severity index. *Archives of Dermatology 144*: 173-180

Brenner SS, Klotz U, Alscher DM, Mais A, Lauer G, Schweer H, Seyberth HW, Fritz P and Bierbach U 2004 Osteoarthritis of the knee – clinical assessments and inflammatory markers. *Osteoarthritis and Cartilage*, *12*: 469-475

Brisby H, Olmaker K, Larsson K, Nutu M and Rydevik B 2002 Proinflammatory cytokines in cerebrospinal fluid and serum in patients with disc herniation and sciatica. *European Spine Journal 11*: 62-66

Bruhlmann Y and Tschopp H 1998 Breast reduction improves symptoms of macromastia and has a long-lasting effect. *Annals of Plastic Surgery 41*: 240

Buttermann CR and Mullin WJ 2008 Pain and disability correlated with disc degeneration via magnetic resonance imaging in scoliosis patients. *European Spine Journal 17*: 240-249

Chang C-W, Chen Y-R and Chang KF 2008 Evidence of neuroaxonal degeneration in myofascial pain syndrome: a study of neuromuscular jitter by axonal microstimulation. *European Journal of Pain 12*: 1026-1030

Cisneros-Cabello R and Segura-Egea JJ 2005 Relationship of patient complaints and signs to histopathologic diagnosis of pulpal condition. *Australian Endodontic Journal 31*: 361-367

Connelly ST and Schmidt BL 2004 Evaluation of pain in patients with oral squamous cell carcinoma. *Journal of Pain 5*: 505-510

Coskun E, Süzer T, Topuz O, Zencir M, Pakdemirli E and Tahta K 2000 Relationship between epidural fibrosis, pain, disability, and psychological factors after lumbar disc surgery. *European Spine Journal 9*: 218-223

Damon L, Buyrik HM, Güler-Uysal F, Lotgering FK, Snijders CJ and Stam HJ 2001 Pelvic pain during pregnancy is associated with asymmetric laxity of the sacroiliac joints. *Acta Obstetrica et Gynecoligica Scandinavica 80*: 1019-1024

Dangaria TR and Naesh O 1998 Changes in cross-sectional area of *psoas major* muscle in unilateral sciatica caused by disc herniation. *Spine 23*: 928-931

Devigili G, Tugnoli V, Penza P, Camozzi F, Lombardi R, Melli G, Broglio L, Granieri E and Lauria G 2008 The diagnostic criteria for small fibre neuropathy. *Brain 131*: 1912-1925

Di Sebastiano P, Fink T, Weihe E, Friess H, Innocenti P, Beger HG and Büchler MW 1997 Immune cell infiltration and growth-associated protein 43 expression correlate with pain in chronic pancreatitis. *Gastroenterology 112*: 1648-1655

Duncan R, Feat G, Thomas E, Hay E, McCall I and Croft P 2007 Symptoms and radiographic osteoarthritis: not as discordant as they are made out to be. *Annals of Rheumatic Disease 66*: 86-91

Elias I, Zoga AC, Raikin SM, Peterson JR, Besser MP, Morrison WB and Schweitzer ME 2008 Bone stress injury of the ankle in professional ballet dancers seen on MRI. *BMC Musculoskeletal Disorders* 9: 39

Ellingsen T, Buus A and Stengaard-Pedersen K 2001 Plasma monocyte chemoattractant protein-1 is a marker for joint inflammation in rheumatoid arthritis. *Journal of Rheumatology 28*: 41-46

Emshoff R, Innerhofer K, Rudisch A and Bertram S 2002 The biological concept of 'internal derangement and osteoarthritis': A diagnostic approach in patients with temperomandibular joint pain? *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology 93*: 39-44

Erdogan D, van Delden OM, Rauws EAJ, Busch ORC, Lameris JS, Gouma DJ and van Gulik TM 2007 Results of percutaneous scleropathy and surgical treatment in patients with symptomatic simple liver cysts and polycystic liver disease. *World Journal of Gastroenterology 13*: 3095-3100

Evans GFF, Haller RG, Wyrick PS, Parkey RW and Fleckenstein JL 1998 Submaximal delayed-onset muscle soreness: correlations between MR imaging findings and clinical measures. *Radiology 208*: 815-820

Grapengiesser S, Gudmendsson F, Larkö O, Ericson M, Rosén A and Wennberg A-M 2002 Pain caused by photodynamic therapy of skin cancer. *Clinical and Experimental Dermatology 27*: 493-497

Gregory NG 2004 *Physiology and Behaviour of Animal Suffering*. Blackwell Publishing: Oxford, UK

Grieco CA, Simon CJ, Mayo-Smith WM, Di Petrillo TA, Ready NE and Dupny DE 2007 Image-guided percutaneous thermal ablation for the palliative treatment of chest wall masses. *American Journal of Clinical Oncology 30*: 361-367

Guarnera G, Tinelli G, Abeni D, Pietro CD, Sampogna F and Fabolli S 2007 Pain and quality of life in patients with vascular leg ulcers: an Italian multicentre study. *Journal of Wound Care 16*: 347-351

Gupta V, Chandrasekar T, Ramani P and Anuja P 2006 Determining toothache severity in pediatric patients. *Journal of Indian Society of Pedodontics and Preventive Dentistry 24*: 140-143

Gynther GW, Holmlund AB, Reinholt FP and Lindblad S 1997 Temperomandibular joint involvement in generalised osteoarthritis and rheumatoid arthritis: a clinical arthroscopic, histologic and immunohistochemical study. *International Journal of Oral & Maxillofacial Surgery 26*: 10-16

Harris JN, Robinson P, Lawrence J, Carrington BM, Hopwood P, Dougal M and Makin W 2003 Symptoms of colorectal liver metastases: correlation with CT findings. *Clinical Oncology 15*: 78-82

Healy PJ, Groves C, Chandramohan M and Helliwell PS 2008 MRI changes in psoriatic dactylitis – extent of pathology, relationship to tenderness and correlation with clinical studies. *Rheumatology 47*: 92-95

Helland CA and Webster K 2007 Intracystic pressure in patients with temporal arachnoid cysts: a prospective study of preoperative complaints and postoperative outcome. *Journal of Neurology Neurosurgery and Psychiatry 78*: 620-623

Hill CJ, Hunter DJ, Niu J, Clancy M, Guermazi A, Genant H, Gale D, Grainger A, Canaghan P and Felson DT 2007 Synovitis, detected on magnetic resonance imaging and its relation to pain and cartilage loss in knee osteoarthritis. *Annals of Rheumatic Diseases 66*: 1599-1603

Hirata H, Tsujii M, Yoshida T, Yoshida KI, Morita A, Okuyama N, Nagakura T, Sugimoto T, Fujisawa K and Uchida A 2005 MMP-2 expression is associated with rapidly proliferative arteriosclerosis in the flexor tenosynovium and pain severity in carpal tunnel syndrome. *Journal of Pathology 205*: 443-450

Howlader MH and Coleridge Smith PD 2003 Symptoms of chronic venous disease and association with systemic inflammatory markers. *Journal of Vascular Surgery 38*: 950-954

Hunter DJ, Lo GH, Gale D, Grainger AJ, Guermazi A and Conaghan PG 2008 The reliability of a new scoring system for knee osteoarthritis MRI and validity of bone marrow lesion assessments. *Annals of Rheumatic Diseases 67*: 206-211

Hunter DJ, March L and Sambrook PN 2003 The association of cartilage volume with knee pain. *Osteoarthritis and Cartilage 11*: 725-729

Imasato, H, Nagata K, Hashimoto S, Komori H and Inoue A 1997 Objective evaluation of pain in various spinal diseases: neuropeptide immunoreactivity in the cerebrospinal fluid. *Spinal Cord 35*: 757-762

Jensen B, Wittrup IH, Bliddal H, Danneskiold-Samsøe B and Faber J 2003 Bone mineral density in fibromyalgia patients – correlations to disease activity. *Scandinavian Journal of Rheumatology 32*: 146-150

Kadi F, Waling K, Ahlgren C, Sundelin G, Holmner S, Butler-Browne GS and Thornell L-E 1998 Pathological mechanisms implicated in localized female *trapezius* myalgia. *Pain 78*: 191-196

Kapural L, Mekhail N, Bena J, McLain R, Tetzlaff J, Kapural M, Mekhail M and Polk S 2007 Value of the magnetic resonance imaging in patients with painful lumbarspinal stenosis (LSS) undergoing lumbar epidural steroid injections. *Clinical Journal of Pain 23*: 571-575

Kenny TJ, Duncavage J, Bracikowski J, Yildirim A, Murray JJ and Tanner SB 2001 Prospective analysis of sinus symptoms and correlation with paranasal computed tomography scan. *Otolaryngology — Head and Neck Surgery 125*: 40-43

Kettunen TA, Visuri T, Harilainen A, Sandelin J and Kujala UM 2005 Primary cartilage lesions and outcome among subjects with patella femoral pain syndrome. *Knee Surgery Sports Traumatology Arthroscopy 13*: 131-134

Kurunlahti M, Karppinen J, Haapea M, Niinmäki J, Autio R, Vanharanta H, Suramo I and Tervonen O 2004 Three-year follow up of lumbar artery occlusion with magnetic resonance angiography in patients with sciatica: associations between occlusion and patient-reported symptoms. *Spine 29*: 1804-1808

Lee CJ, Scheiman J, Andersen MA, Hines OJ, Reber HA, Farrell J, Kochman ML, Foley PJ, Drebin J, Oh YS, Ginsberg G, Ahmad N, Merchant NB, Isbell J, Parikh AA, Stokes JB, Bauer T, Adams RB and Simeone DM 2008 Risk of malignancy in resected cystic tumors of the pancreas $\leq$ 3 cm in size. *Journal of Gastrointestinal Surgery 12*: 234-242

Lindh C, Liu Z, Lyrenäs S, Ordeberg G and Nyberg F 1997 Elevated cerebrospinal fluid substance P-like immunoreactivity in patients with painful osteoarthritis, but not in patients with rhizopatic pain from a herniated lumbar disc. *Scandinavian Journal of Rheumatology 26*: 468-472

Link TM, Steinbach LS, Ghosh S, Ries M, Lu Y, Lane N and Majumdar S 2003 Osteoarthritis: MR imaging findings in different stages of disease and correlation with clinical findings. *Radiology 226*: 373-381

Mazzuca SA, Brandt KD, Lane KA and Katz BP 2002 Knee pain reduces joint space width in conventional standing anteroposterior radiographs of osteoarthritic knees. *Arthritis and Rheumatism 46*: 1223-1227

McBeth SB and Gratt BM 1996 Thermographic assessment of temperomandibular disorders symptomatology during orthodontic treatment. *American Journal of Orthodontics and Dentofacial Orthopedics 109*: 481-488

Mohammadian P, Andersen OK and Arendt-Nielsen L 1998 Correlation between local vascular and sensory changes following tissue inflammation induced by repetitive application of topical capsaicin. *Brain Research 729*: 1-9

Muzii L, Marana R, Pedullà S, Catalano GF, and Mancuso S 1997 Correlation between endometriosis-associated dysmenorrhea and the presence of typical or atypical lesions. *Fertility and Sterility 68*: 19-22

Nam KW, Kim YL, Yoo JJ, Koo K-H, Yoon KS and Kim HJ 2008 Fate of untreated asymptomatic osteonecrosis of the femoral head. *Journal of Bone and Joint Surgery of America 90*: 477-484

Ng Y-L, Glennon JP, Setchell DJ and Gulabivala K 2004 Prevalence of and factors affecting post-obturation pain in patients undergoing root canal treatment. *International Endodontic Journal 37*: 381-391

Nishi T, Sugano N, Ohzono K, Sakai T, Haraguchi K and Yoshikawa H 2002 Progression and cessation of collapse in osteonecrosis of the femoral head. *Clinical Orthopaedics and Related Research 400*: 149-157

Oaklander AL, Romans K, Horasek S, Stocks A, Hauer P and Meyer RA 1998 Unilateral postherpetic neuralgia is associated with bilateral sensory neuron damage. *Annals of Neurology 44*: 789-795

https://doi.org/10.1017/S0962728600001925 Published online by Cambridge University Press

Okusaka T, Okada S, Ueno H, Ikeda M, Shimada K, Yamamoto J, Kosuge T, Yamasaki S, Fukushima N and Sakamoto M 2001 Abdominal pain in patients with resectable pancreatic cancer with reference to clinicopathologic findings. *Pancreas 22*: 279-284

O'Neill TW, McCloskey EV, Kanis JA, Bhalla AK, Reeve J, Reid DM, Todd C, Woolf AD and Silman AJ 1999 The distribution, determinants, and clinical correlates of vertebral osteophytosis: a population based survey. *Journal of Rheumatology 26*: 842-848

Peters F, Diemer P, Mecks O and Behnken LJ 2003 Severity of mastalgia in relation to milk duct dilatation. *Obstetrics and Gynecology 101*: 54-60

Phillips C, Blakey G and Jaskolka M 2008 Recovery after orthognathic surgery: short-term health-related quality of life outcomes. *Journal of Oral and Maxillofacial Surgery 66*: 2110-2115

Polydefkis M, Yinnoutsos CT, Cohen BA, Hollander H, Schifitto G, Clifford DB, Simpson DM, Katzenstein D, Shriver S, Hauer P, Brown A, Haidich AB, Moo L and McArthur JC 2002 Reduced intraepidermal nerve fiber density in HIV-associated sensory neuropathy. *Neurology 58*: 115-119

Prantera C, Luzi C, Olivotto P, Levenstein S, Cerro P and Fanucci A 1984 Relationship between clinical and laboratory parameters and length of lesion in Crohn's Disease of small bowel. *Digestive Diseases and Sciences 12*: 1093-1097

Pye SR, Reid DM, Smith R, Adams JE, Nelson K, Silman AJ and O'Neill TW 2004 Radiographic feature of lumbar disc degeneration and self-reported pain. *Journal of Rheumatology 31*: 753-758

Raynauld J-P, Martel-Pelletier J, Berthiaume M-J, Beaudoin G, Choquette D, Haraoui B, Tennenbaum H, Meyer JM, Beary JF, Cline GA and Pelletier J-P 2006 Long term evaluation of disease progression through the quantitative magnetic resonance imaging of symptomatic knee osteoarthritis patients: correlation with clinical symptoms and radiographic changes. *Arthritis Research and Therapy 8(R21)*: 1-12

Rowbotham MC, Yosipovitch G, Connolly MK, Finlay D, Forde G and Fields HL 1996 Cutaneous innervations density in the allodynic form of postherpetic neuralgia. *Neurobiology of Disease 3*: 205-214

Sammour A, Pirwany I, Usubutun A and Arseneau J 2002 Correlations between extent and spread of adenomyosis and clinical symptoms. *Gynecologic and Obstetric Investigation 54*: 213-216

Sandberg C, Stenquist B, Rosdahl I, Ros A-M, Synnerstadt I, Karlsson M, Gudmundson F, Ericson MM, Larkö O and Wennberg A-M 2006 Important factors for pain during photodynamic therapy for actinic keratosis. *Acta Dermato-Venereologica 86*: 404-408

Sarikaya S, Özdolap Ş, Gümüştaş Ş and Kroç Ü 2007 Low back pain and lumbar angles in Turkish coal miners. *American Journal of Industrial Medicine 50*: 92-96

Sato J, Segami N, Kaneyama K, Yoshimura H, Fujimura K and Yoshitake Y 2004 Relationship of calcitonin gene-related peptide in synovial tissues and temperomandibular joint pain in humans. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology 98*: 533-540

Schierz O, John MT, Schroeder E and Lobbezoo F 2007 Association between anterior tooth wear and tempero-mandibular disorder pain in a German population. *Journal of Prosthetic Dentistry 97*: 305-309

Schlossbauer T, Mioc T, Sommerey S, Kessler SB, Reiser MF and Pfeifer KJ 2008 Magnetic resonance imaging in early charcot arthropathy – correlation of imaging findings and clinical symptoms. *European Journal of Medical Research 13*: 409-414

Schmidt-Wilcke T, Leinisch E, Gänßbauer S, Draganski B, Bogdahn U, Altmeppen J and May A 2006 Affective components and intensity of pain correlate with structural differences in grey matter in chronic back pain patients. *Pain 125*: 89-97

Schwab F, Smith VA, Biserni M, Gamez L, Farcy J-P and Pagala M 2002 Adult scoliosis: a quantitative radiographic and clinical analysis. *Spine 27*: 387-392

Schwimmer JB, Deutsh R, Rauch JB, Behling C, Newbury R and Lavine JE 2003 Obesity, insulin-resistance, and other clinicopathological correlates of pediatric non-alcoholic fatty liver disease. *Journal of Pediatrics, 143*: 500-505

Scuderi GJ, Brusovanik GV, Golish SR, DeMeo R, Hyde J, Hallab N and Vaccaro AR 2008 A critical evaluation of discography in patients with lumbar intervertebral disc disease. *Spine Journal 8*: 624-629

Şenocak O, Deðirmenci B, Özdoðan Ö, Akalia E, Arslam G, Kaner B, Taşci C and Peker Ö 2002 Technetium-99m human immunoglobulin scintigraphy in patients with adhesive capsulitis: a correlative study with bone scintigraphy. *Annals of Nuclear Medicine 16*: 243-248

Sharp RJ, Wade CM, Hennessey MS and Saxby TS 2003 The role of MRI and ultrasound imaging in Morton's neuroma and the effect of size of lesion on symptoms. *Bone and Joint Surgery 85B*: 999-1005

Shimada Y, Miyahoshi N, Kasukawa Y, Hongo M, Ando S and Itoi E 2006 Clinical features of cauda equine tumors requiring surgical treatment. *Tohoku Journal of Experimental Medicine 209*: 1-6

Sjöström M, Ängquist K-A and Rais O 1980 Intermittent claudication and muscle fiber fine structure: correlation between clinical and morphological data. *Ultrastructural Pathology 1*: 309-326

Song IH, Althoff CE, Hermann KG, Scheel AK, Knetsch T, Schoenharting M, Werner C, Burmester GR and Backhaus M 2008 Knee osteoarthritis. Efficacy of a new method of contrast-enhanced musculoskeletal ultrasonography in detection of synovitis in patients with knee osteoarthritis in comparison with magnetic resonance imaging. *Annals of Rheumatic Diseases 67*: 19-25

Song IH, Althoff CE, Hermann KG, Scheel AK, Knetsch T, Burmester GR and Backhaus M 2009 Contrast-enhanced ultrasound in monitoring the efficacy of a bradykinin receptor 2 antagonist in painful knee osteoarthritis compared with MRI. *Annals of Rheumatic Diseases 68*: 75-83.

Sonis ST, Eilers JP, Epstein JB, Le Veque FG, Liggett WH, Mulagha MT, Peterson DE, Rose AH, Schubert MM, Spijkervet FK and Wittes JP 1999 Validation of a new scoring system for the assessment of clinical trial research of oral mucositis induced by radiation or chemotherapy. *Cancer 85*: 2103-2113

Suenaga S, Abeyama K, Hamasaki A, Mimura T and Noikura T 2001 Temperomandibular disorders: relationship between joint pain and effusion and nitric oxide concentration in the joint fluid. *Dentomaxillofacial Radiology 30*: 214-218

Suzuki T, Segami N, Kaneyama K, Nishimura M and Nojima T 1999 Specific expression of interleukin-1β in temperomandibular joints with internal derangement. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology 88*: 413-417

Taljanovic M, Graham AR, Benjamin JB, Gmitro AF, Krupinski EA, Schwartz SA, Hunter TB and Resnick DL 2008 Bone marrow oedema pattern in advanced hip osteoarthritis: quantitative assessment with magnetic resonance imaging and correlation with clinical examination, radiographic findings, and histopathology. *Skeletal Radiology 37*: 423-431

https://doi.org/10.1017/S0962728600001925 Published online by Cambridge University Press

Tanigawa N, Komemushi A, Kariya H, Shomura Y, Ikeda K, Omura N, Murakami T and Sawada S 2006 Percutaneous vertebroplasty: relationship between vertebral body bone marrow oedema pattern on MR images and initial clinical response. *Radiology 239*: 195-200

Terslev L, Torp-Pedersen S, Qvistgaard E and Bliddal H 2003 Spectral Doppler and resistive index. A promising tool in ultrasonographic evaluation of inflammation in rheumatoid arthritis. *Acta Radiologica 44*: 645-652

Toffolo SR, Furtado RN, Klein A, Watanabe S, Andrade LE and Natour J 2008 Measurement of upper limb ulcers in patients with systematic sclerosis: reproducibility and correlation with pain, function, and quality of life. *Nursing Research 57*: 84-92

van de Sande MAJ, de Groot JH and Rozing PM 2008 Clinical implications of rotator cuff degeneration in the rheumatic shoulder. *Arthritis and Rheumatism 59*: 317-324

van Tulder MW, Assendelft WJJ, Koes BW and Bouter LM 1997 Spinal radiographic findings and nonspecific low back pain: a systematic review of observational studies. *Spine 22*: 427-434

Vassiliou V, Kalogeropoulou C, Petsas T, Leotsinidis M and Kardamakis D 2007 Clinical and radiological evaluation of patients with lytic, mixed and sclerotic bone metastases from solid tumors: is there a correlation between clinical status of patients and type of bone metastases? *Clinical and Experimental Metastasis 24*: 49-56

Vercellini P, Fedele L, Aimi G, Pietropaolo G, Consonni D and Crosignani PG 2007 Association between endometriosis stage, lesion type, patient characteristics and severity of pelvic pain symptoms: a multivariate analysis of over 1000 patients. *Human Reproduction 22*: 266-271

Vlčková-Moravcová E, Bednařík J, Dušek L, Toyka KV and Sommer C 2008 Diagnostic validity of epidermal nerve fiber densities in painful sensory neuropathies. *Muscle and Nerve 37*: 50-60

Wabnitz DAM, Nair S and Wormald PJ 2005 Correlation between preoperative symptom scores, quality-of-life questionnaires, and staging with computed tomography in patients with chronic rhinosinusitis. *American Journal of Rhinology 19*: 91-96

Wall PD, Melzack R and Bonica JJ 1994 *Textbook of Pain, Third Edition.* Churchill Livingstone: Edinburgh, UK

Wallny T, Lattaye L, Brackmann HH, Heß L, Seuser A and Kraft CN 2005 Clinical and radiographic scores in haemophilic arthropathies: how well do these correlate to subjective pain status and daily activities? *Haemophilia 8*: 802-818

Walther M, Radke S, Kirschner S, Ettl V and Gohlke F 2004 Power Doppler findings in plantar fasciitis. *Ultrasound in Medicine and Biology 30*: 435-440

Watanabe K, Hasegawa K, Hirano T, Uchiyama S and Endo N 2005 Use of scoliosis research society outcomes instrument to evaluate patient outcome in untreated idiopathic scoliosis patients in Japan. *Spine 30*: 1202-1205

Yilmaz Z, Renton T, Yiangou Y, Zakrzewska J, Chessell IP, Bountra C and Anand P 2007 Burning mouth syndrome as trigeminal small fibre neuropathy: increased heat and capsaicin receptor TRPV1 in nerve fibres correlates with pain score. *Journal of Clinical Neuroscience 14*: 64-871

Yun TJ, Lee HJ, Kim SH, Lee SE, Hong SK, Cho JY and Seong CK 2007 Prospective analysis on the relation between pain and prostate volume during transrectal prostate biopsy. *Korean Journal of Radiology 8*: 231-235

https://doi.org/10.1017/S0962728600001925 Published online by Cambridge University Press