Current perspectives on the clinical presentation of joint pain in human OA

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Abstract. Pain is the commonest symptom of osteoarthritis (OA), the principal reason why individuals seek medical care and a major determinant of other outcomes such as disability and joint replacement. Most studies have examined knee OA: little is known about other sites. Community studies indicate only a modest relationship between structural change on X-ray and reporting of pain. Many community subjects, for example, fail to complain of pain despite extensive X-ray change, while others report pain with normal X-rays. Pain severity of patients attending hospital is even less related to X-ray change, being more dependent on body mass index (BMI), coping strategies and psychosocial variables. Many patients can identify more than one type of pain. It is increasingly clear that OA pain is heterogeneous, being classifiable on the basis of location, precipitating factors, response to anti-inflammatory and steroid medication and the effects of local anaesthetic. This potential to classify OA pain represents a useful tool with which to test hypotheses regarding structural origin of pain.

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Osteoarthritis (OA) is a disorder of synovial joints characterized by destruction of articular cartilage and overgrowth of marginal and subchondral bone. Pain is the principal symptom of OA and the major reason why subjects seek medical attention, which may include costly interventions such as joint replacement. Pain is also the most significant determinant of disability. Given the current lack of disease modifying drugs in OA, the treatment of OA is essentially the treatment of OA pain.

Although OA may affect many peripheral joints (knees, hands, hips, feet) most of our knowledge of pain in OA derives from the knee. It is important to note that mechanisms may vary from joint to joint and data from the knee may not necessarily be transferable to other joints.

Knee pain in the community

Knee pain is usually assessed as a dichotomous variable (present or absent) using, for example, the NHANES-1 screening question: 'Have you ever had pain in or around the knee on most days for at least one month?' Subtle changes in the phrasing of the question can result in large differences in the apparent prevalence of pain but in general about 24–28% of community dwellers aged 40–70 respond positively to such a question (O'Reilly et al 1996). Prevalence of knee pain increases with radiographic severity of OA (Felson et al 1987, Hochberg et al 1989, Carman 1989, Spector et al 1993, Lethbridge-Cejku et al 1995). In the NHANES-I study, for example, among subjects aged 65–74 knee pain was reported by 8.8% of subjects with normal X-rays, 20.4% with Kellgren and Lawrence (K+L) grade 1 OA, 36.9% with grade 2 and 60.4% with grades 3–4 (Davis et al 1992). Similar findings of a progressive increase in the risk of pain reporting with worsening radiographic change have been reported at other joint sites (Table 1).

It is, however, clear that there are many subjects in whom X-ray changes and reported pain are discordant. Pain may be reported in the absence of X-ray changes — the prevalence of self-reported knee pain with normal X-rays is about 10.0%. There are several potential reasons for this. First, most studies utilize only supine or weight-bearing views of the tibio-femoral joint; failure to assess the patellofemoral joint could result in a subject being classified as 'X-ray negative' when in fact changes were present but not seen. Indeed, up to 24% of females reporting knee pain have isolated patellofemoral disease and if lateral views are included the predictive value of pain for radiographic change increases (McAlinden et al 1993). Second, a positive response to the NHANES-I knee question does not differentiate between isolated knee pain and widespread pain of which the knee is but a part. The prevalence of 'widespread chronic pain' is about

TABLE 1 Prevalence (%) of reported pain by radiographic severity at 1st carpometacarpal (ICMC), distal (DIP) and proximal (PIP) interphalangeal, and hip joints

Radiographic severity (KL grade)	*Joint site*		
	ICMC[a]	*DIP/PIP*[a]	*Hip*[b]
0/1	10.6	15.2	8.0 (M) 12.0 (F)
2	34.2	48.7	10.0 (M) 14.0 (F)
3/4	65.1	80.9	44.0 (M) 86.0 (F)

[a]Hart et al 1994.
[b]Lawrence 1997.

11% (Croft et al 1993). Such patients may answer affirmatively about knee pain but this would not necessarily imply local pathology. Third, X-rays are relatively insensitive: they may be normal when other diagnostic studies such as arthroscopy show clear evidence of OA (Fife et al 1991). X-rays do not allow visualization of non-bony sources of pain, such as capsule, synovium or ligaments. Finally, not all knee pain is due to OA: causes such as anserine bursitis, internal derangements and referred pain from hip or spine would not be identified on X-rays of the knees.

The second group (X-ray positive, pain negative) is larger. Pain reporting in grade 3–4 OA ranges from 40–79%: thus, up to half the patients in the community with, by any standard, established radiographic OA deny pain. The relationship improves if osteophytes rather than global change are used (Spector et al 1993, Lethbridge-Cejku et al 1995, Cicuttini et al 1996). The precise question that is asked may affect the response in terms of pain reporting. The NHANES-I question may underestimate prevalence: patients may have had pain but not on 'most days of a month' or they may simply fail to recall previous episodes of pain. Further, OA may be a phasic condition with episodes of pain separated by remissions: the question may fail to capture the painful episode.

Another approach to examining the relationship between structural change and pain is to consider the prevalence of X-ray change in those presenting with joint pain. A community survey of 4057 subjects aged 40–70 found a prevalence of knee pain of 28.3%. Of these, 74% had at least grade 1 osteophyte and 40.9% had at least grade 2 (O'Reilly et al 1996). In 195 subjects aged over 40 presenting to their GP with a first episode of hip pain, Birrel et al (2000) found 44% had a KL grade $\geqslant 2$ and 34% had KL $\geqslant 3$. A minimum joint space of $\leqslant 2.5$ mm was seen in 30%. By the time subjects present to primary care with hip pain, therefore, a significant number will already have established OA change on X-ray.

The risk factors for radiographic knee OA (age, sex, race, obesity) are different from those for knee pain reporting in the community. In addition to X-ray change, psychological well-being and health status (Davis et al 1992), anxiety (in women only) (Creamer et al 1999a), feeling 'low' or 'very low' in spirits (Hochberg et al 1989), hypochondriasis (Lichtenberg et al 1986) and 'negative affect' (Dekker 1993) have all been associated with higher levels of knee pain reporting. Lower educational level is an independent risk factor for pain reporting (Hannan et al 1992).

OA pain in the clinic

Some individuals with knee or hip pain elect to present to medical care. The reasons for this choice are unclear but co-morbidity (especially psychosocial), coping beliefs, social support, availability of services and degree of empowerment are all

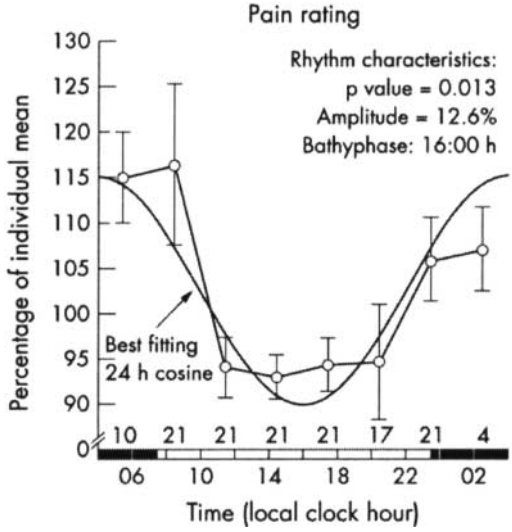

FIG. 1. Circadian rhythm for pain in patients with OA of the hand. Self measurements/ratings were made by 20 or 21 patients every 24 hours during waking for 10 days. Individual values had trends removed and were converted to a percentage of the mean before combining for group analysis by population mean cosinor. For rhythm characteristics *P* value is from the zero amplitude test; amplitude = half peak trough difference of cosine; bathyphase = lowest point of cosine (referenced from 0000). $P < 0.001$ for each variable from ANOVA for time effect. Reproduced with permission from Bellamy et al (2002).

likely to be more important than pain severity, radiographic change, age or functional limitation. A community study of subjects with hip or knee pain found that depression scores were significantly higher in those that had elected to seek medical care (Dexter & Brandt 1994). A similar role for psychological factors in the promotion of healthcare seeking behaviour has been suggested in other conditions such as fibromyalgia.

It is safe to assume that almost all individuals with OA presenting to healthcare will have pain. Although pain is clearly important to patients and is discussed at 98% consultations, potential causes are discussed minimally or not at all in up to 46% cases (Bellamy & Bradley 1996). Furthermore, physicians and patients may disagree about the severity of their pain and effect on life (Hogkins et al 1985). Suarez-Almazor et al (2001) in a study of 105 patients with musculoskeletal disease found that intraclass correlation coefficients (ICCs) were only 0.42 for pain. Physicians tended to rate their patients' health status higher than the patients themselves and were less willing to gamble on the risk of death versus perfect health. The *importance* of pain to patients with OA and the relationship

between *pain severity and its importance* has been little studied but clearly has great relevance.

For patients presenting to healthcare, pain becomes a continuous variable—pain severity. A major advance in OA pain research has been the adoption of standardized, validated questionnaires such as the WOMAC, Lequesne, McGill Pain Questionnaire (MPQ) or a simple VAS. The WOMAC has recently been shown to be more sensitive than the SF-36 (Davies et al 1999) and the Lequesne Index (Theiler et al 1999) and appears not to be influenced by anxiety and depression as much as the MPQ (Creamer et al 1999b). It also allows pain occurring in different situations to be separately assessed. The risk factors for pain severity reporting are different from those for pain as a dichotomous variable. In a group of hospital outpatients with knee OA (Creamer et al 1999b) risk factors for pain severity reporting differed slightly according to the scale used though obesity, helplessness and education remained associated with pain severity after adjustment for confounding variables. Age, disease duration and quality of life were not related to severity of pain. Others have reported links between pain severity and psychological factors: Summers et al (1988) reporting on 65 patients with OA of hip or knee found that depression (as measured by the Beck Depression Inventory) and anxiety correlated with some measures of the MPQ. Another study of 61 patients with knee OA found significant correlations between MPQ and Zung Anxiety and Depression Inventory scores (Salaffi et al 1991). In the community chronicity and severity of knee pain were associated with higher psychosocial disability (as measured by subscales of the Sickness Impact Profile) compared to age- and sex-matched controls from the same community (Hopman-Rock et al 1996).

A number of studies have shown that, in hospital patients, radiographic change is not related to pain severity (Creamer et al 1999b, Bruyere et al 2002). It may be that a threshold needs to be reached for joints to become painful but beyond that, other factors (coping strategies, depression, co-morbidity, BMI) determine the perceived severity for an individual.

The nature of OA pain

Generally quoted descriptions of OA pain are largely anecdotal, supported by surprisingly little patient-based evidence. 'Typical' OA pain is said to be insidious, variable and intermittent ('good days and bad days'); mainly occurring on use, movement or weight bearing and later in the day. Nearly all symptomatic patients have use-related pain but many also have rest or night pain. Knee pain is generally anterior or medial; hip pain classically is felt in the groin but may radiate to the knee. Thumb base OA is more likely to cause pain than interphalangeal OA and may be felt diffusely 'around the wrist'. A diurnal variation has been described

at both the knee (Bellamy et al 1990; see Fig. 1) and the hand (Bellamy et al 2002) with pain worse in the evenings and easier in mornings. The reason for good and bad days is unclear: influences of weather or barometric pressure are often cited by patients and may have some validity. Strusberg et al (2002) found that in OA, pain correlated with low temperature ($r=-0.23$, $P<0.001$) and high humidity ($r=0.24$, $P<0.001$). Seasonal variation (worse in winter) is often reported but this may be more due to perception than reality since reported symptoms do not necessarily agree with measured clinical scores (Hawley et al 2001). Pain may also be reported more strongly at weekends (Bellamy et al 1990).

Although the cause remains uncertain it is increasingly clear that pain in OA is heterogeneous, varying between individuals and with different phases of the disease. Recently efforts have been made to identify different patterns of pain, in the hope that they may indicate different pathological or anatomical processes. The location of pain at the knee, for example, is not random, but falls into two well defined groups: generalized anterior pain and localized inferomedial pain. These differences are not explicable by radiographic change and may represent local bony or soft tissue sources (Creamer et al 1998a). Another example is the response to local anaesthetic (Creamer et al 1996, Hassan et al 2002): in many patients this will abolish pain temporarily whilst in others no effect is seen. In simple terms, some patients may have local sources of pain whilst in others the pain is centrally driven. The complexity of pain mechanisms is further emphasised by the fact that intra-articular anaesthetic can also abolish pain in contralateral, untreated joints, implying central or spinal mechanisms (Creamer et al 1996).

Finally, the effect of intra-articular steroids overall is short lived, but individual patients derive sustained benefit — do they have a more inflammatory cause for their pain?

Night pain (often used by orthopaedic surgeons as an indicator of the need for joint surgery) is said to be an unusual feature, limited to advanced disease. We found (Creamer et al 1998b) that 43% subjects with knee OA reported pain of $\geqslant 30$ mm on a VAS for night pain and 14.7% actually felt the night to be the most painful time. 27.9% felt that resting in bed made their pain worse. Using the latter definition, we were unable to confirm a relationship between night pain and disease severity as assessed by pain severity, disability, examination findings or radiographic change. A modest relationship with disease duration was seen, but most significantly, night pain was associated with high levels of helplessness and worse perceived quality of life, perhaps due to underlying fatigue.

Such clinical observations allow testable hypotheses to be generated. Night pain, for example is often thought to be due to raised intraosseous pressure: the ability of MRI to detect focal changes in subchondral bone linked with pain (Felson et al 2001) allows this to be investigated further. If inferomedial knee

pain is due to collateral ligament pathology, again this may be detected by magnetic resonance imaging (MRI). If failure of intra-articular anaesthetic to abolish pain indicates a central source this may be associated with higher depression or helplessness. Such studies have the potential to allow a more tailored, individual approach to pain treatment.

Longitudinal studies show that most patients feel that their pain gets worse with time though there is considerable variability. In the Bristol OA 500 study (Dieppe et al 2000), for example, the proportion of subjects with knee OA reporting their pain to be 'severe' was 25% at baseline, 17% at 3 years and 27% at 8 years. However, 80% of patients felt they had worsened overall.

Effect of pain in disease

We have considered the risk factors for pain reporting but what about the effect pain may have on the underlying disease? Reduction in pain, for example by intra-articular local anaesthetic, results in increased maximum voluntary contraction (MVC) of quadriceps (Hassan et al 2002). The influence of pain on other potential risk factors such as proprioception and balance is unclear: Hassan et al (2002) reported that pain reduction did not result in improvements in proprioception or static postural stability. Jadelis et al (2001), examined dynamic balance in a cross sectional study of older patients with knee OA. Balance was most strongly related to quadriceps strength, but in those subjects with weak quadriceps pain severity became an independent predictor of poor balance.

We do not know if long term pain reduction can reduce progression of disease but there is some evidence that pain predicts incident knee OA and that subjects with pain progress faster than those with similar radiographic change without pain. Hart (Hart et al 1999) found odds ratios of 1.91 (95% confidence interval 1.18–3.09) for knee pain predicting development of osteophyte at follow up. Cooper et al (2000) in a follow up study of 354 community subjects found that baseline knee pain predicted incident knee OA at 5 years (odds ratio 2.9 [1.2–6.7] for KL $\geqslant$1; odds ratio 1.3 [0.6–2.7] for KL $\geqslant$2). Knee pain also predicted progression over 5 years.

Causes of pain in OA

The anatomic cause of pain in OA remains unknown. Any theory has to consider that the principal structure involved (cartilage) possesses few pain-sensitive fibres. Bone pain may be a factor in many subjects: perhaps via osteophyte growth with stretching of periosteum, raised intraosseous pressure or microfractures. Felson et al (2001) examined the relationship between 'bone marrow lesions' (thought to represent oedema) on MRI and knee pain. Lesions were found in 77.5% persons

with painful knees compared with 30% with no knee pain ($P < 0.001$). 'Large' lesions were present almost exclusively in persons with knee pain (35.9% vs. 2%; $P < 0.001$). Although lesions were associated with more severe radiographic change in general, the relation with pain persisted even after adjustment for severity of radiographic disease, effusion, age and sex. No relation was seen with pain severity.

Other sources of pain include ligament damage, capsular tension, meniscal injury and synovitis. Inflammation may be present in OA and may cause pain either by direct stimulation of primary afferent peripheral afferent nociceptive fibres (PANs) or by sensitizing PANs to mechanical or other stimuli. Systemic markers of inflammation such as C reactive protein (CRP) are raised in many patients with OA and may predict future progression of disease (Spector et al 1997). In addition there is a central component to pain and influences such as anxiety, depression and comorbidity are likely to operate in some patients as described above.

Conclusions

Many questions remain about OA pain. What makes a person with OA pain seek medical attention? Is it worsening of the disease (little evidence for this)? Loss of coping skills? Socioeconomic or financial factors? What would be the effect of early aggressive pain control in reducing intensity or duration of chronic pain? In other words, does control of pain affect the natural history of the disease? To what extent is pain protective and to what extent does it reduce function and result in physical deconditioning? How can we improve our understanding of our patients' health perceptions and risk-benefit preferences so that we may suggest more appropriate interventions?

Many individuals with radiographic OA do not report pain and perhaps we should ask not 'why is OA painful?' but 'why is it so often pain free?'

Much effort is being expended on finding drugs capable of modifying the disease process, notably on cartilage loss. We would expect an effective disease-modifying drug to also have an effect on pain but, given the poor correlation currently seen between structural change (at least on X-ray) and symptoms, a word of caution might reasonably be sounded. There are grounds to at least consider the wisdom of investing large resources in expensive technologies designed to reduce structural change when this may not, in fact, affect the problems that are important for the patient.

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DISCUSSION

Bradley: I want to comment on your data on anxiety. The role of anxiety in pain reporting is greatly underestimated. With regard to the McGill Pain Questionnaire, one reason why you find low correlations between the WOMAC and the visual analogue scale from the McGill is that, unlike the WOMAC pain scale, the McGill is multidimensional and contains a large subgroup of words dealing with affect and emotion. When you look at ethnic group differences on the McGill, do you find variation as a function of the types of words chosen to describe pain? My reason for asking this is that when we apply quantified stimuli in the laboratory to patients, we find that African–Americans tend to use higher intensity affective words compared with Caucasians, even if their sensory intensity responses are the same. Do you find similar phenomena in your larger population studies?

Creamer: There are differences between English English and American English. In the more detailed study we didn't have enough African Americans to really address this. They did report higher McGill pain scores, but most of this effect disappeared when we adjusted for BMI. There was a sense that the words chosen might have been different. And with the McGill we have a sense that it isn't really measuring what I want it to measure. On the McGill I also looked at whether there were words people would choose given the opportunity that aren't on the McGill. There aren't many, because the McGill has 76 words, but there were a few. There are some words that are never chosen by people. McGill was developed for all sorts of pain, including cancer and dental pain. It may not be the best tool to look at some of these issues in OA.

Schaible: What is the minimum set of symptoms that you need to diagnose OA? In effect, one could ask if someone reports pain but you don't find anything in the joint, why do we call it OA pain? And if someone has joint changes visible by X-ray but the pain doesn't correlate, is this OA?

Creamer: It depends on how you define OA. OA can be defined pathologically, radiographically or clinically. There is some overlap, but there are also some differences. In the community, pain is defined as 'yes' or 'no'. Patients are asked a question about whether they have pain, and we try to define this on the basis of it being experienced on most days for at least a month. When we are looking at pain severity then it is much more arbitrary, but sometimes people try to develop

cut-offs for studies to ensure that they have people in the study with adequate pain, so a benefit can be shown for whatever intervention is used.

Schaible: For a clinician, if someone reports joint pain, is this sufficient to make the diagnosis of OA in the absence of any visible inflammation?

Creamer: Not all knee pain is due to OA. One of the explanations for the knee-pain-positive people who are X-ray negative is that they have another pathology in the knee joint. The other thing is that X-rays are relatively insensitive. Arthroscopy may well reveal cartilage changes long before the X-ray has changed. Some people propose that we should talk less about knee OA and more about knee pain.

Dieppe: I think the sub-setting of pain is a very important concept. I think we are not getting this sorted because we don't know what hypotheses to test and we don't know what questions to ask. We have got into this habit of thinking about night pain, rest pain and walking pain as being entities. I think this is based on nothing. Similarly, the other methods of subtyping that are being attempted are potentially unhelpful. I have been rather impressed by what the social scientists can offer fields like this. We should be doing qualitative research before we do quantitative research. We should be doing in-depth, unstructured interviews with people with OA, however defined, trying to take out themes from this sort of qualitative research as to what the issues are, and then derive the hypotheses and do the sorts of studies you have done having first got some hypotheses about pain subgroups.

Creamer: I agree with you. Qualitative research is fiendishly difficult, so it is much easier to go for the tools that have already been developed. But at least this sort of work shows that potentially there are differences.

Dieppe: Yes, your sort of work stimulates me to think we really should go for this.

Kuettner: We are mixing the different forms of OA. Aren't knee and hip OA totally different in their aetiology, and don't they require different clinical approaches?

Felson: There is no clear cut answer to this.

Pisetsky: There is another way you could subset: those patients who have surgery and those who don't. If you look at the people who have operations, how are they describing their pain as opposed to those who don't? Do you get any insight by dividing the patients up in this way?

Dieppe: We have been looking at those issues. We have been studying the barriers and facilitators to people seeking medical help in the first place, and we have been trying to take this through to referrals and surgery. A lot of this is being done with qualitative research, so the numbers of people we have information on is small. Where we are so far suggests to me that healthcare utilization for OA has little to do with pain or disease severity, but that other sociocultural factors are determining it. Some of my social scientist colleagues

go as far as saying that there is no disease here, and that it is all purely a sociocultural phenomenon!

Brandt: With respect to the issue of OA pain and progression, there was some nice work from Hurwitz et al (2000) measuring gait and pain in patients with arthritic medial compartment knee OA. They showed that when the patients were taking pain medication they increased the loading of the medial compartment. When the pain medication was washed out and joint pain became more severe, the subjects changed their gait so as to protect the damaged cartilage. However, long-term data are not available to show whether this results in analgesic arthropathy. But this also relates to Leena's study (Sharma et al 2003), because she didn't measure joint pain. One of the possibilities that needs to be considered is whether those people who were stronger had less pain and therefore loaded their knee more than others.

Felson: Pain is a protective mechanism. I'd like to ask an almost rhetorical question. In RA, it is my understanding that anxiety and depressive symptoms contribute to pain severity also. Yet therapies for RA seem to have terrific effects on pain. Does this mean that we can address pain anyway without grappling with this concern? In RA, a third of the patients don't have morning stiffness, for example, so there is the same variability in pain description and reporting that you have described in OA. Yet we don't seem to have too much trouble in developing therapies for RA while we ignore the qualitative aspects of pain. Will this be true for OA also?

Creamer: Do you think that in RA we have a more defined pathology and site of origin of pain? There is synovitis and inflammation.

Felson: Is that where the pain comes from in RA?

Creamer: Treatments such as a steroid injection into an inflamed knee are highly effective ways of reducing pain in RA. I have a better feel for the pathology of RA than OA, and inflammation seems to be what is driving most of the pain in RA. But your point is well made.

Grubb: A number of us are interested in the development of animal models for the study of OA, and what worries me is that we have this clear lack of correlation between the radiological scores of the disease and pain. How can we develop a model if we don't have a clear idea of what typical OA is? What features should we be looking for in an animal model that would well represent human OA? We can't develop a good animal model of human OA without that correlation.

Brandt: It also depends on what you want to use the model for. If you want to use it to study a drug that might inhibit cartilage loss, then you want a model that demonstrates a certain rate of cartilage loss. If you want a model to evaluate pain, this imposes an entirely different set of requirements. This is challenging.

Grubb: That is what many of us here are interested in — the pain aspect. It is not clear to me what we should be doing here.

Brandt: There is an obvious difficulty in evaluating OA pain. It is, however, no easier to assess structural damage. While there are similarities in pathology, no animal models have been clearly shown to predict the effects of 'chondroprotective' drugs in humans.

Schaible: This comes down to the question of nociception and pain. A model is urgently required to find out whether there is any change in nociception, or whether there is nociception at all in degenerative processes in a joint. Then there is a discussion about what this means for pain. I wouldn't be too negative about this.

Grubb: I am not being negative. Complete Freund's adjuvant (CFA) polyarthritis is a very good animal model with a lot of joint pathology in which changes in nociception are seen. It is not, however, a model of OA.

Schaible: I am biased. We should say that there is a defined process in the joint, and we should answer the question about whether this evokes nociception. This is something we could answer and should answer.

Henry: The idea of subgroupings raises a lot of issues. The people looking for biomarkers must feel lost as well. The real answer lies in making a stab at developing animal models. When we develop an animal model, what can we learn about the process? From this we might stumble across one model that will be particularly useful in terms of understanding nociception. Even humans don't have a good model of OA. Some have pain without clinical signs, and some have clinical signs without pain. What are the basic scientists trying to model? It is not as simple as it was a few years ago when we had OA and models.

Pisetsky: I have a question about the value of pathology. There are many operative specimens in OA. Are we getting the most information out of them? Given the heterogeneity of the disease, should we be doing more pathology? In the RA world where there is not much surgery any more, when people did pathological studies, different forms of RA were histologically distinguishable. Not all people are alike, and subsets that were informative could be identified.

Kuettner: If you explant the cartilage from different animals, you get distinctive responses to different mediators. It becomes very difficult to say, for example, that the rabbit is a good model for the human disease. Even within the human, the different cartilages from different joints respond quite differently.

Pisetsky: I am asking, for example, should I be looking at nerve fibres in capsules?

Lohmander: The problem with surgical specimens in OA is that they represent end-stage disease in most cases, and also that the patients receiving surgery have been filtered through the filters we have heard about here, so they might not be representative.

Pisetsky: But, even bearing these limitations in mind, we have the opportunity to get pathological tissue.

Kuettner: You can also get normal tissue from tissue donor banks.

Hunter: I'd like to address the qualitative research issues. You presented some nice data from Nick Bellamy showing huge diurnal changes within subjects. There is also that huge dichotomy between people who have structural OA and those people who are symptomatic. Surely there is room for research into those particular subjects who are asymptomatic with structural changes and those people who have big diurnal changes, to try to explore what is going on there. Do you have any ideas what this may be?

Dieppe: I agree with you. Unfortunately qualitative research is difficult, expensive and time-consuming. The only data we have are more to do with accessing healthcare utilization, so I don't have any useful qualitative data on pain.

Mackenzie: You tried to control for pain threshold differences in a structured way. How clear are you that this really reflects the ability of different patients to tolerate pain in the real world in very different ways?

Creamer: It can only ever be a surrogate. It is coming from the fibromyalgia literature where there has been some work on the pain threshold in general. This was just an attempt to get a bit of a handle on this.

Mackenzie: You can perhaps get a handle on this by trying to understand the differences in the way in which people deal with pain.

Creamer: Some of the brain imaging studies might be relevant here.

Bradley: One thing that comes out from the imaging literature is that we haven't paid as much attention as we should to the emotional/affective dimension of pain. This affective dimension is very important in the way patients present in the clinic. However, even in the laboratory, psychological factors have a much greater association with pain tolerance tasks as compared to pain threshold tasks. In the imaging world, where people are only just beginning to study pain through neuroimaging, most of the effort is focused on mapping the neural correlates of intensity, and much less attention is paid to the neural correlates of affect. So, neuroimaging of pain affect responses is a very important question.

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