Understanding pain

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This essay forms a report of a conference held at the Royal College of Physicians on 5 July 2000, entitled 'Understanding Pain'. Its aim was to explore new concepts relating to the understanding of pain, ranging from new treatment strategies derived from knowledge of the cellular mechanisms of peripheral pain processing, to psychosocial issues pertinent to chronic pain syndromes. New ideas relating to the development and persistence of chronic musculoskeletal pain were also raised.

In its definition of pain as 'An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage', the International Association for the Study of Pain (IASP) does not associate the perception of pain with a stimulus, but emphasises the multidimensional nature of pain, with its emotional, conceptual, judgmental and motivational components[1]. However, the 'Irish Ode'

There was a faith-healer from Deal
Who said, 'Although pain isn't real
If I sit on a pin
And it punctures my skin
I dislike what I fancy I feel.'

The weekend book, 1925

embraces the concept of a stimulus and the multidimensional nature of pain rather better! Pain can be good or bad, necessary or unnecessary, and its presence relies on self-report of the experience, making pain entirely subjective. To understand pain, we have to explain why a similar pain can be experienced both in the presence and absence of peripheral tissue damage, the most extreme example being that of phantom pains in a missing limb[2]. Equally, we must explain why pain symptoms for a given pathology vary greatly in intensity, site and duration.

The complex biological relationship between disease (inflammation, tissue damage, nerve damage) and nervous system (NS) processing determines a varied range of pain symptoms. Nervous pathways involved in pain processing are inherently plastic and can be modified both functionally and structurally. This concept of neuroplasticity allows functional change within the NS to persist long after the initial stimulus has resolved – a hypersensitive pain pathway[3]. However, these adaptations can also be transient and reversible, opening up new routes for therapeutic intervention.

Disturbing nociceptive pathways (see Table 1)

Peripheral and central sensitisation

Changes to the sensitivity of individual nerve fibres both peripherally and centrally are thought to be key to the concept of neuroplasticity[4]. Molecules released in the periphery can directly stimulate pain fibres and activate previously silent sensory neurons. Certain neurons can not only signal tissue damage but can also play an active role in inflammation, mediated by neuropeptides such as substance P, neurokinin A, and calcitonin-gene related peptide (CGRP). Sustained peripheral activity can also induce significant changes in the CNS. In particular, the involvement of certain receptors on spinal neurons – N-methyl-D-aspartate (NMDA) and neurokinin receptors – is integral to this plasticity. Changes in the activity of the NMDA receptor, mediated by neurokinin release and ion channel coupling, can lead to the phenomenon of spinal 'wind up' – where sustained peripheral input leads to a progressive increase in discharge with further stimuli[5].

Structural changes may also occur in the CNS, in addition to the functional alterations described above, in response to persistent peripheral nociceptor activation. For example, constant firing of A-beta fibres can lead to the reorganisation of A-beta terminals in the dorsal horn of the spinal cord (SC).

Table 1. Disturbing nociceptive pathways

Target	*Example*
Interfere with peripheral mediators/sensitisation	anti-TNF and anti-cytokines therapy, bradykinin antagonists, $5HT_3$ antagonists NSAIDs, cannabinoids
Interfere with ion channels	Ca^{++} channels, Na^{+} channels (anticonvulsants, lignocaine)
Target central receptors	SP receptor cell NK1, NMDA receptor antagonists (NR2B)
Block disease specific messengers	e.g. osteoprotegerin (OPG)

The fibre terminals can grow from deeper to more superficial laminae, normally areas of C fibre termination. These changes are thought to contribute to the phenomenon of central sensitisation and have been proposed as a mechanism for the symptom of allodynia. It is thought unlikely that drugs can reverse this structural change. The argument is further complicated by the observation in experimental animal models that these anatomic changes are seen after allodynia is clinically evident. Which particular group of neuron(s) is responsible for allodynia is controversial and, due to the multiplicity of mechanisms, it is unlikely that neuropathic pain corresponds to a unique entity – the story is far from complete. These observations, in addition to evidence relating to a host of other excitatory and inhibitory convergences in the SC, begin to explain varied pain symptoms and phenomena such as primary and secondary hyperalgesia, allodynia and referred pains.

Care should be taken when using pain terminology (Table 2) in the context of inflammatory diseases such as rheumatoid arthritis, as the meaning can be confusing. For example, is pain on movement of a joint (which is pain-free at rest) termed allodynia or hyperalgesia – or should there be other terms and descriptions?

Routes to disturbing nociceptor pathways

Tissue injury results in activation and sensitisation of peripheral nociceptor fibres, and there is a plethora of mediators of nociceptor function. Interference with these mediators is difficult because they are so numerous and are derived from varied sources. If one mediator is blocked, it is likely that others will upregulate and continue to promote nociceptor activation and pain. Blocking the receptors of pain mediators is an attractive option, but few compounds are available, and unfortunately those that are, are often pharmacologically 'dirty' drugs.

As well as unidirectional pathways running from injury to pain, there are also numerous descending excitatory and inhibitory mechanisms that interfere with afferent function and further sequences of complicated higher processes that result in the perception and experience of a pain. This complex picture makes interference with single mediators of the nociceptive pathway a difficult task. Some examples of such attempts are given below.

Tumour necrosis factor (TNFα)

TNFα has a pivotal role in inflammatory hyperalgesia, with bradykinins (BK) acting as potent drivers of TNFα production. There is a whole range of pro-inflammatory mediators and peripheral nociceptor sensitisors (e.g. Il-1, Il-8, Il-1b, COX 2 products) induced by TNFα itself. Experimental BK antagonists can block TNFα production, and may be developed for use in chronic painful inflammatory diseases such as rheumatoid arthritis (RA)[6]. Exciting advances in anti-TNF therapy in RA have been made recently, with the launch this year of two compounds, Etanercept (Wyeth) and Infliximab (Schering-Plough), both of which are effective in RA[7].

Calcium and sodium ion channels

Studies on ion channel properties have led to new concepts of how peripheral nerves become sensitised following nerve injury[8]. This has also allowed alternative proposals regarding the mechanism of action of new and established pain modifying drugs. Work on calcium (Ca^{++}) channels involved in the release of SP and glutamate from C fibre terminals in the dorsal horn was described by several speakers. The drug gabapentin, despite its misleading name (suggesting a GABAinergic mechanism of action), is able to bind to a subunit of the calcium channel and interfere with its function. This may explain its action in neuropathic pain. Morphine also has an action on peripheral N-type calcium channels via the coupling of opioid receptors and its peripheral action could be explained by these observations.

Tetrodotoxin-resistant (TTX R) Na^+ channel activity increases following nerve (and tissue) damage. Adenosine may play a role in the differential expression of ion channels. Increased spontaneous activity in nerve fibres adjacent to damaged tissue spreads into SC neurons and leads to central sensitisation and 'wind up' of the pain pathway. Blocking these channels is therefore an attractive idea, particularly to treat neuropathic pain. Unfortunately, in clinical practice side effects limit the use of sodium channel blocking drugs – local anaesthetics and anticonvulsants[9]. It is believed that specific Na^+ channel blockade of this 'final common pathway of peripheral transmission to CNS' will lead to effective analgesics, bypassing the whole range of molecules that are released during tissue and nerve damage, so contributing to peripheral sensitisation.

Spinal neurokinin receptors

In neuropathic pain models, glutamate and substance P (SP) are released in lamina 1 of the SC and interact with neurokinin 1 (NK1) receptors[10]. These cells project to parabrachial nuclei and then link to the hypothalamus and amygdala, centres known to be involved in pain processing. The ligand and receptor are internalised when they meet at the cell surface. Pharmacologists now have a route by which a drug can be delivered into the cell.

Table 2. Pain terminology – definitions

Referred pain:	Pain in an area far removed from site of tissue injury
Phantom pain:	Pain in a part of the body that has been surgically removed or is congenitally absent
Allodynia:	A non-noxious stimulus is perceived as painful
Sensitisation:	Receptor responds to a stimulus in a more intense fashion, or to a stimulus that it would not normally respond to
Hyperalgesia:	Exacerbated pain produced by a noxious stimulus
Hyperpathia:	Intense pain with repetitive stimuli
Nocioceptor:	Nervous system receptor capable of distinguishing between a noxious and an innocuous stimulus

Professor Stephen Hunt described animal studies in which NK1 receptor specific molecules are attached to a poison (saporin) that kills SP receptor cells[11]. Subsequent observations of animal behaviour and paw withdrawal thresholds suggested a significant analgesic effect. Studies on the role of SP in determining morphine 'addiction'[12] were also described by Professor Hunt. Using a conditioned place preference method, his group has shown that SP knock out (SPKO) mice experience no reward behaviour from opiates although the analgesic effect remains. This effect is opiate specific, as the SPKO mice continue reward behaviour from cocaine in this experimental model. Although therapeutic morphine 'addiction' is a controversial topic, this research may lead to the development of treatments to combat possible addiction.

Cannabinoids

In 1964 tetrahydrocannabinol was identified as the main psychoactive ingredient of cannabis. Since then the role of cannabinoids in both the peripheral and central pain systems has been clarified, in particular the fact that endogenous cannabinoid ligands are analgesic. In the periphery, cannabinoids have a possible role in down-regulating the effects of nerve growth factor mediated, mast cell induced, inflammation and sensitisation of primary afferent nociceptors[13]. This action is via CB_2 receptors, expressed on immune cells. They also attenuate noxious heat-evoked activity in spinal Wide-Dynamic-Range neurons, possibly via inhibition of C-GRP. There is also evidence for cannabinoid analgesia in visceral and neuropathic pain models[14]. In the CNS, the endogenous cannabinoid anandamide plays a role in a cannabinergic pain-suppression system existing within the dorsal and lateral periaqueductal gray (PAG)[15]. Cannabinoid receptors in the brain interact with noradrenergic and kappa opioid systems in the spinal cord to modulate the perception of painful stimuli. Cannabinoid research is set to play a significant role in the development of new analgesics in the next few years.

Bone pain and molecular signals

Neurohumoral signals of bone cancer pain differ from those that occur in persistent inflammatory or neuropathic pain states. Interference with these mechanisms may lead to therapies that can reduce bone destruction and alleviate bone pain[16]. Bone destruction is common, both in cancer medicine and musculoskeletal disease.

Osteoprotegerin (OPG) is a novel, naturally occurring protein that inhibits osteoclast formation[17]. Animals with an experimental femoral injury induced with sarcoma cells were treated with OPG. The animals given OPG had less bone destruction and less pain behaviour than those given control treatments. This new understanding has opened new avenues for developing possible treatments for diseases characterised by excessive bone resorption[18]. OPG may have a role in the treatment of arthritis, and recent trials with OPG supported its potential as a therapeutic agent for osteoporosis.

5-HT antagonists and irritable bowel syndrome

One theory explaining pain symptoms in irritable bowel syndrome (IBS) proposes that subliminal damage to colonic mucosa is triggered by local trauma or infection. This putative low grade inflammation can lead to sensitisation of colorectal nerves and subsequent release of neuropeptide mediators. New treatments have been developed by inhibiting this process[19]. Dr Chas Bountra described an animal model in which noxious intestinal distension was used as an index of visceral nociception, the rat colorectal distension model (CRD)[20]. The $5\text{-}HT_3$ receptor antagonist alosetron inhibits responses to CRD in a potent and dose dependent manner. These experiments suggest that $5\text{-}HT_3$ receptors are involved in visceral nociceptive transmission, perhaps located on primary afferent or spinal neurons. Inducible nitric oxide synthase (iNOS) is almost certainly involved in this process, as it is found to be upregulated in dorsal root ganglia and the SC in the CRD model, is present in bowel mucosa cells, and probably plays a role in mediating the peripheral sensitisation of the visceral afferents.

Relevance of experimental models to clinical observation and practice

By understanding pain mechanisms we may be able to reach a mechanism-based classification and treatment approach to pain, and therefore be able to develop new treatments[21]. Models of either diseases or symptoms can be used.

When using models of symptoms, such as ongoing stimulus independent pain (i.e. neuropathic pain), animal studies use hyperalgesia and paw withdrawal thresholds. These studies may not be relevant to clinical practice, as heat hyperalgesia is a rare symptom of neuropathic pain in man. Furthermore, carbamazepine is helpful in clinical practice, but has little therapeutic effect in the animal chronic nerve constriction model.

In stimulus dependent pain models it is difficult to produce a stimulus (in animals or a human surrogate procedure) that accurately reflects the insult seen in the clinical condition. Also, it is likely that the mechanisms involved in mechanical, chemical and thermal hyperalgesia are different, as are the pathological processes involved in acute, transient pain and chronic pain. Therefore, chronic pain cannot be regarded merely as a temporal prolongation of acute pain. These considerations have implications when extrapolating experimental findings in pain models into clinical conditions in man. However, the mechanistic symptom based approach seems more likely to lead to the development of new symptom specific therapies than disease model led research.

Chronic pain syndromes: fact or fantasy?

It is difficult to distinguish between pain that has a 'somatic' basis and pain with a 'psychogenic' basis, and there are no tests available to establish one or the other (if such a distinction exists). However, it is possible to assess the degree of distress related to

the pain experience and to make sensible judgements about the relative contributions of anxiety, depression, beliefs and illness behaviour. The existence of psychological disturbance in patients with chronic pain is not in doubt[22]: depending on the definition used to identify widespread pain, between 1 in 4 and 1 in 6 patients have 'psychopathology'. The debate continues about the relative importance of the psychosocial risk factors for the development of chronic pain and the psychological sequelae of the syndrome.

Patients with chronic widespread pain (CWP) have a 'somatic focus'[23]. They perceive an increased threat of pain and experience an increased interruption of pain related thoughts with poor general attentional function[24]. They also seem to have lost the 'idea' of normal sensation and seem distressed by many 'normal' bodily sensations.

Iatrogenesis and the maintenance of CWP

The controversy surrounding the fibromyalgia construct (aka CWP) continues, although the syndrome is common and there are more similarities than differences between CWP sufferers. Such controversy about diagnosis, and the very existence of the syndrome, can contribute to the development of a chronic pain syndrome by adding to the distress and anxiety already experienced by the pain sufferer[25].

With an uncertain diagnosis, an uncertain prognosis and a controversial label, glib reassurances are unhelpful, and patients search for alternative sources of knowledge. CWP sufferers, in addition to having a 'somatic focus', are often fearful of activity and avoid all possible pain related situations, further reinforcing their illness behaviour and beliefs. It is a mammoth task to unravel these complex situations, some of which could be prevented by physicians refraining from giving the message that 'pain is simple and can be cured'. In many cases, change is only possible through the cognitive-behavioural approach of a formal pain management programme. Our experience managing patients with 'bizarre' musculoskeletal pain phenomena has led David Blake's group at the Royal National Hospital for Rheumatic Diseases, Bath, to question some of the accepted mechanisms of joint and muscle pain, and has also led to novel treatment concepts.

Pain phenomena in arthritis

Nervous system and arthritis

Clinical observations and evidence from animal studies point to a significant neurogenic component in the development, distribution and severity of inflammatory arthritis[26]. RA is a symmetric disease, with immune and systemic mechanisms not solely responsible for this. Examination of patients with central and peripheral nervous system lesions shows relative sparing of the denervated or paralysed joints. Synovial damage results in acute inflammation in the damaged joint and a neurogenically mediated neuropeptide release and infiltrate of inflammatory cells in the contralateral joint[27,28]. This contralateral mirroring phenomenon may be important in arthritis, and we are currently testing this hypothesis in man, supported by the Arthritis Research Campaign.

Phantom joint pain

We have recently seen a lower limb amputee with RA who clearly describes a diurnal variation of pain and stiffness in her phantom lower limb. In association with the observation that RA joints are relatively denervated of C fibres (in the superficial synovial layer) by the chronic inflammatory process, other (central) pain mechanisms must be considered[29]. We have also recently recognised a subset of RA patients who perceive their joints to be swollen and tight (especially with their eyes closed), but when they look at their joints are aware that, paradoxically, they are of normal appearance[30]. This 'phantom swelling' phenomenon is also reported by patients with fibromyalgia syndrome and by patients with complex regional pain syndrome (CRPS). The mechanism of the pain phenomenon is not clear, but may be determined by a subtle incongruence between vision, proprioception and movement, mediated by a centre in the prefrontal cortex. These changes in cortical representation may generate pain responses[31].

Mirror, mirror on the wall

A visual feedback system used to treat phantom limb pain allows patients to see a reflection of their intact limb in a body space that the phantom limb occupied[32]. Pain was relieved whilst the mirror visual feedback system was used. Harris has subsequently postulated that other painful disorders could be generated because 'disorganised or inappropriate cortical representation of proprioception may falsely signal incongruence between motor intention and movement, which results in pathological pain'[32].

We have postulated that CRPS could be driven by such an incongruence based mechanism. Therefore, we have used a 'virtual visual feedback system' in which patients observe a mirror reflection of their normal limb in place of attending to their painful limb, and undertaking a series of congruent exercises. This has led to a remarkable reduction in pain while the mirror is in use, and for long periods afterwards.

Conclusion

Our understanding of pain mechanisms continues to expand, and new pharmaceutical tools that selectively influence pain pathways are in development. In addition to intervention with drugs, the review of clinical observations from an alternative perspective can also lead to novel therapies. However, too many patients live in a vicious cycle of pain and disability, unable to gain relief with any therapeutic manoeuvres. Therapy aimed at coping with chronic pain using psychological interventions, as part of pain management programmes, is an effective, though challenging, option[33].

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