What's special about pain?

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The purpose of this paper is to present a range of perspectives on pain and to provide an overview for the other papers in Session 1 that review invertebrates, fish, birds, ruminants and the human fetus.

A widely accepted definition of pain is the one used by The International Association for the Study of Pain. It defines pain as:

> *An unpleasant sensory and emotional experience arising from actual or potential tissue damage or described in terms of such damage.*

We tend to use the word "pain" in a pejorative sense, for there is nothing warm and friendly about pain. Pain generally indicates adverse or noxious clinical conditions. And so in the English language we use phrases such as 'a pain in the neck' or 'a pain in the arse'. There are equivalents in other languages; for example, in Dutch, 'Blok aan mijn been'; in Spanish, 'Es un dolor de cabeza'; and in German, 'Es geht mir auf die Nerven'.

Working with experimental animals always demands careful consideration of the legal and ethical obligations all personnel have to minimise pain and suffering. Animal Ethics Committees (AEC) must determine whether the impact on the animal is outweighed by the potential benefits to be obtained. And in making such judgements, I believe that it is important to remember that the experimental animal was not consulted on its recruitment, nor did it sign the consent form. Furthermore, the animal will not benefit from the procedures performed on it. In comparison, humans will generally manage to tolerate significant pain in the hope of a good recovery.

Because of advances in public health, we seldom come into contact with people suffering from polio, diphtheria, tuberculosis or leprosy. Therefore I would argue, most of us fortunately have minimal exposure to pain, and I question whether this lack can lead to desensitisation. I believe that we may underrate the impact of pain on experimental animals. From personal experience, I recall that undergoing hand surgery to correct a Dupuytren's contracture reacquainted me with pain following the surgery. In this context there is an aphorism which states *'all orthopaedic registrars should have a bone fracture repair surgery performed on themselves, to fully appreciate what their patients actually experience.'*

The good the bad and the ugly of pain might be described as follows. The good: pain is protective, for example, the immediate withdrawal of the hand or foot from a noxious stimulus which would cause tissue damage. Clearly pain indicates a problem, which should be evaluated by a health professional. The bad: pain hurts and changes physiological functions and the quality of life can be compromised. In 2003 in the USA it was estimated that $US 61 billon worth of productive time was lost due to personnel experiencing pain in the workplace. This figure did not cover loss of productivity due to sick leave.

The ugliest form of pain was first described during the American Civil War in 1864 by Dr Silas Weir Mitchell, who was a neurologist attending soldiers recovering from limb amputations. Many of these amputees experienced long-lasting burning pain and Mitchell defined the term "causalgia" to describe their suffering. This early medical opinion has since developed and is now referred to as the 'Complex Regional Pain Syndrome'. It is characterised by an

intense, burning pain, much stronger than would be expected for the type of injury that occurred. The pain gets worse, rather than better over time. The pain begins at the point of injury, but often spreads to the whole limb, or to the arm or leg on the opposite side of the body. On the McGill pain scale, this syndrome rates as one of the most severe conditions which humans can experience. There are changes in skin temperature, switching between warm or cold, faster growth of nails and hair, muscle spasms and joint pain with a severe burning, aching pain that worsens with the slightest touch or breeze. The skin slowly becomes blotchy, purple, pale, or red; thin and shiny and swollen. The Complex Regional Pain Syndrome has been described in these terms: *"The elongated history, unbearable symptoms, and lack of a sufficient antidote for CRPS support the notion that it is the most agonizing and detrimental disorder ever experienced by mankind."*

A brief and simplified review of pain is presented below, to set the scene for the specialists' papers that follow. The concept of a basic wiring diagram of pain is a useful strategy, given the complexity and range of the species with which we work.

Pain starts after tissue is damaged. These damaged tissues release what is described as 'a *biological soup of molecules'*. These molecules stimulate pain receptors. And the soup diffuses to adjacent areas, thereby increasing pain. The soup contains a range of cell-signalling protein molecules produced by cells of the nervous system and the immune system. These cytokines are classified as peptides, proteins or glycoproteins, and are further classified as interferons or interleukins.

It is useful to consider a basic wiring diagram of pain, presented in Figure 1.

The arrangement of receptors in the body has been mapped onto the brain to illustrate their relative distribution. Such a map is called an Homunculus (literally 'little human'). Figure 2 illustrates a typical map of somatosensory and motor cortices and Figure 3 provides a three dimensional image of the same concept. These maps clearly illustrate the predominance of receptors in the face and hands.

It is interesting to note the variation in pain responses amongst individuals in a population. This variation is taken into account when evaluating the potency of gaseous anaesthetics. The minimum alveolar concentration (MAC) is defined as: '*the concentration of gas which will prevent movement (in response to stimulation) under anaesthesia in 50% of the population'*. Dr Rene Leriche was a French military surgeon operating on wounded soldiers in World War 1 on the Russian front. He was persuaded by his Russian medical colleagues to amputate fingers and a foot without using any anaesthetic – presumably anaesthetics were in short supply. Leriche reports that the justification he was given was: *"useless to give anaesthetics to Cossacks because they felt nothing"*. He was most surprised at the lack of pain response in these Russian soldiers.

Clearly the Cossack account is an extreme example. However, individuals with cerebral palsy can show significant differences in their response to pain, apparently unaffected by some noxious stimuli which would cause major suffering in others not afflicted with this condition. Given the range of pain responses in humans, it is reasonable to assume that

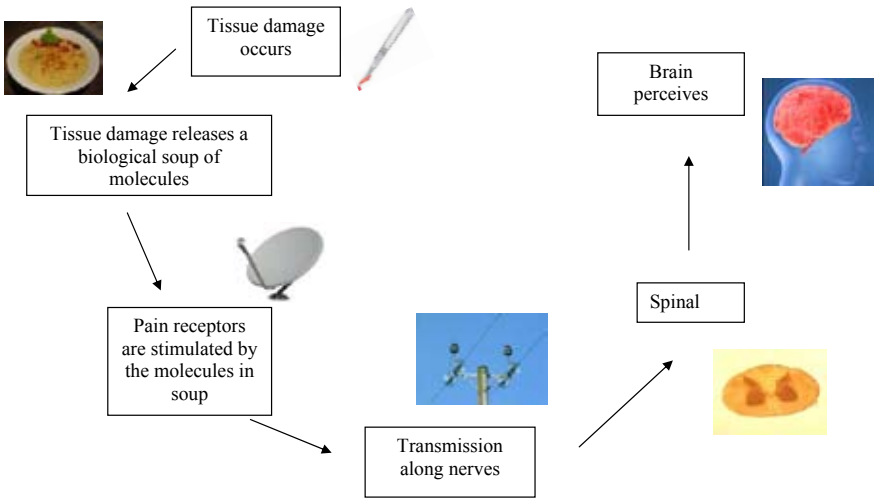

Fig. 1 The basic wiring diagram of pain.

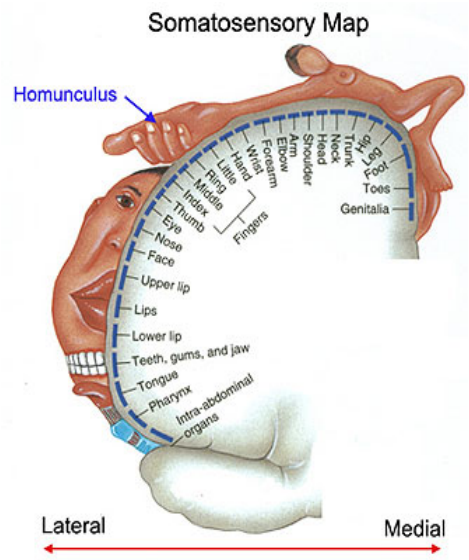

Fig. 2 Homunculus.

Fig. 3 Homuculus in 3D.

a similar variation occurs within different species and between different species. With reference to Figure 1, the wiring diagram, we can ask the question: do all species have the same components in their pain perception pathways? The specialist papers following provide some insights into such variation.

The wiring diagram in Figure 1 is an over-simplification. There are many different receptor types. For example, the three basic opioid receptors called mu, delta and kappa are located throughout the body, namely in the brain, the spinal cord and the intestinal tract. In addition, there are other kinds of receptors identified. When morphine is administered to a patient to control pain, the morphine binds to these receptors. Although drugs can control pain, sometimes there are adverse side-effects. For example, opioid-induced constipation (OIC) is a well recognised complication in humans. In laboratory rats, opioid treatment can sometimes cause animals to eat their bedding. This behaviour, called pica, can compromise their welfare. It has been suggested that because rats are unable to vomit, they may instead experience nausea (another side effect of opioids in humans) which may cause this bizarre behaviour.

In conclusion, a review of pain control in different species should include questions regarding the presence or absence of opioid or other receptors, evaluation of analgesic dose rates and an appreciation of the wide variability in anatomical pathways which enable animals to perceive painful stimuli. I am sure we would all prefer an existence without pain; however, we could not function safely without the ability to detect pain.