Please read these three case histories: what is the diagnosis? Which are the differentiating diagnostic features?			
Provoking factors	Eating and brushing the teeth can make pain worse, touching the area can be painful	Prolonged chewing, yawning, tiredness	Eating, talking, shaving, washing face light touch
Relieving factors	Drugs help slightly	Massage	No activities
Associated factors	no other pain or disturbances	Often has migraine, back pain, fatigue, poor concentration, bruxist. occasional locking	Lost weight as cannot eat
Effect of pain on life style	Unable to socialise as much as would like, no anxiety or depression	Lost job recently, has had some impact on social life—going out to eat	considerable effect on quality of life, took a week of work as telephonist, mild depression
Examination	Very tender to touch in right mandibular alveolus area	Fully dentate,two tender points on muscles of mastication, good mouth opening but clicks	No cranial nerve abnormalities and fully dentate with no dental disease
Diagnosis			

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What's wrong with animal models of pain?

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Recent decades have seen an explosion in our understanding of the molecular and cellular underpinnings of pain, but virtually none of this knowledge has resulted in new clinical therapies. Many pain researchers believe that the problem may lie in the existing animal models of pain, which are reliable but much more complex and subtle than is commonly realized, and of questionable clinical relevance. Most basic science studies of pain continue to rely on the measurement of reflexive, evoked hypersensitivity responses after artificial neuropathic or inflammatory injuries, whereas clinical pain in humans features much spontaneous pain and an important cognitive and emotional overlay.

In addition to the disconnect between clinical symptoms and animal measures, there is a disconnect between the clinical epidemiology of pain and the types of pain being modeled in animals. We have recently attempted to develop an "ethological" approach to animal models of common pain pathologies, involving systematic and rigorous analysis of videotaped spontaneous mouse behaviors. I will talk about some recent successes in our laboratory, involving migraine, vestibulodynia, and the development of a facial expression-based pain scale for the mouse.

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Immunotherapy for neuroblastoma elicits a complement dependent whole body allodynia

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GD2 ganglioside is found on plasma membranes of tumor cells of neuroectodermal origin, including neuroblastoma cells. A chimeric antibody against GD2 (ch14.18) is currently being used as a treatment for pediatric neuroblastoma. Intravenous administration of the antibody induces severe whole body allodynia in patients which lasts from 24 to 48 h. Similar administration of antibody to rats produces tactile, but not thermal sensitivity, whole body touch evoked agitation as well as ectopic activation of identified C nociceptors in the sural nerve. Both the peripheral nerve firing and patient allodynia are sensitive to low dose systemic lidocaine. Pain behavior, in rats and children, is also sensitive to gabapentin.

We postulated that the mechanism of the anti-GD2-induced pain involved activation of the complement cascade resulting in a complement-dependent cytotoxicity (CDC). With this in mind we engineered a new form of the antibody (Hu14.18) with a point mutation within the C region that was intended to reduce complement fixation. In vitro experiments of the mutated antibody confirmed significantly diminished CDC, however, there was still a strong antibody-dependent cellular cytotoxicity (ADCC) involving natural killer cells. In rats, Hu14.18 results in a smaller magnitude of mechanical sensitization with a greatly shortened duration compared to ch14.18. Thus, ability to activate complement increases the antibody-elicited pain.

The two most likely complement factors to be involved in this process are C5a and membrane attack complex (MAC). Systemic pretreatment with a C5a receptor antagonist totally prevented ch14.18 elicited pain behavior. To look at the role of MAC, we utilized rats with deficient complement factor C6 as C6 is a necessary component of membrane attack complex. C6 deficient rats injected with ch14.18 showed greatly reduced tactile sensitivity. Injection of these animals with Hu14.18 resulted in pain behavior that was no different from animals injected with saline. We conclude that both C5a and MAC are necessary for full manifestation of the anti-GD2 induced pain behavior, although C5a appears to be playing a greater role. Reducing complement activity of immunotherapeutic agents may increase their utility by decreasing their side effects.

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Pain mechanisms in animal models of rheumatoid arthritis

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Rheumatoid arthritis (RA) is chronic disease affecting 1% of the population. It is characterized by infiltration of inflammatory cells into