CD4⁺ T cells may help initiate the skin lesions, CD8⁺ T cells that produce type 1 cytokines (IFN-gamma) are responsible for the persistence of the lesions. This may explain the paradox observed in HIV infected patients in whom psoriasis (and PsA/reactive arthritis) can worsen dramatically even as CD4⁺ T-cell counts fall. In PsA patients a predominantly TH1 cytokine response is observed (increased IL2, TNF-beta, and IFN-gamma), but there is also an increased IL-10 response. It has recently been proposed, based on MRI studies, that PsA is enthesitis based disease, and that it is distinct from RA, where synovitis is the primary pathological feature. Local treatment of psoriasis with psoralens plus ultraviolet A radiation (PUVA) often results in long-standing remissions by greatly reducing the number of activated T cells in psoriatic skin due to induction of T-cell apoptosis. Methotrexate, and DAB389-interleukin-2 preferentially induce apoptosis of activated T cells in skin and other sites. On the other hand, cyclosporine A and topical corticosteroids only inhibits the production of cytokines; and psoriasis often recurs soon after the cessation of this treatment. Likewise, TNF-alpha blockade therapy has been found to be very effective in treating patients with severe psoriasis and PsA (including SpA), but the benefit is relatively short-lived after the therapy is discontinued. Administration of CTLA4Ig fusion protein (that blockades the B7-CD28/CD152 pathway of T cell costimulation) has produced a marked improvement of psoriasis in a phase I trial.

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Pain and memory of pain – Thursday 14 June, 14.00-15.30/Forum Hall

SP0034 PLASTICITY OF PAIN MODULATION DUE TO CHRONIC PAIN

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10.1136/annrheumdis-2001.87

Descending, propriospinal, and segmental modulatory systems, tonically or phasically inhibit or facilitate the spinal transmission of nociceptive signals. Although it is widely accepted that these endogenous modulatory systems affect sensations of pain, the way in which they are brought into play and their consequences on nociceptive behaviour have rarely been addressed in the context of tissue injury. An increase of tonic descending modulation has been demonstrated during the acute stage of inflammation in both electrophysiological and behavioural experiments suggesting that this enhanced descending inhibition may limit hyperalgesia during acute inflammation.¹

To analyse further the changes of pain modulatory systems under pathological conditions and determine their potential role in the pathophysiology of pain syndromes, we investigated in a recent series of electrophysiological studies in the rat the modulation of the spinal transmission of nociceptive information during the course of inflammation.

In a first series of experiments,² diffuse noxious inhibitory controls (DNIC), which are supraspinally mediated inhibitory

controls triggered by the application of noxious stimuli, were investigated at different stages during the development of adjuvant-induced monoarthritis in the rat. In the acute stage of monoarthritis (i.e., 24-48 h), the DNIC-induced inhibitions of nociceptive neurons produced by mechanical or thermal stimulation of the arthritic joint were significantly increased at all intensities by comparison with the normal joint. In contrast, in the animals with a chronic monoarthritis (i.e., 3-4 weeks), the DNIC-induced inhibitions were not different from those observed in control animals. These data suggested that chronic inflammatory processes might have induced a reorganisation of the spinal transmission of nociceptive signals and/or modulatory systems, which could modify the recruitment of DNIC.

To test these hypotheses, other experiments were designed to analyse the changes of tonic modulation acting on the spinal transmission of nociceptive information in rats with acute or chronic monoarthritis.³ Tonic descending inhibitions were analysed by comparing the electrophysiological properties of spinal convergent neurons with ankle input before and after spinalization. Tonic descending inhibition of convergent neurons with input from the inflamed ankle was enhanced during the acute stage and then decreased during the chronic stage of monoarthritis. In addition, changes in the spinal transmission of nociceptive signals were unmasked by removing descending modulation in animals with monoarthritis: sensitisation of spinal neurons with input from the inflamed ankle was demonstrated during the acute stage of monoarthritis, while a crossed transmission between inflamed and normal sides was observed during the chronic stage of the disease.

In conclusion, these studies showed dynamic and stage-dependent modifications of the spinal transmission and modulation of nociceptive information during the course of inflammation. During both acute and chronic stages of inflammation, descending controls tended to dampen central changes at the spinal level. Such a functional plasticity might play a significant role in the pathophysiology of some acute or chronic pain syndromes observed in humans: an imbalance of descending controls could exacerbate the consequences of the central changes induced by the inflammatory processes and could result in increased and persistent pain.

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SP0035 SUPRA-SPINAL MECHANISMS OF PAIN AND NON-INVASIVE IMAGING IN THE STUDY OF CHRONIC PAIN IN HUMANS

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10.1136/annrheumdis-2001.88

Pain is a complex experience that includes sensory, emotional, autonomic and motoric components, and each of these components can differ among various pain states. Despite the many qualitative differences of clinical and experimental pain states, they all share a common aversive nature, leading us to characterise each as "pain." This talk will present evidence showing a

common cortical network that, when activated, leads to the perception of pain. Activation of this circuit can result from direct stimulation of peripheral nociceptors or from the disruption of endogenous modulatory circuits in the CNS that allows normally nonpainful stimuli to access the cortical pain system. Using positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), we find that a network of cortical regions is reliably activated by experimental pain and chronic clinical pain states, including the primary and secondary somatosensory cortices (S1 and S2), the anterior cingulate cortex (ACC) and the insular cortex (IC). This network is activated during pain produced by stimuli as divergent as cutaneous heat, visceral pain produced by esophageal distension, or tactile allodynia produced by capsaicin application. Our imaging data show that allodynia related to peripheral or CNS damage activates the same cortical pain system as that activated during acute pain states. Other experiments suggest that these various cortical regions have a differential role in processing the sensory and affective dimensions of pain. Experimental manipulations that selectively alter the affective component of pain predominantly modulate activity in ACC, whereas those that alter the sensory component of pain modulate activity in the other cortical regions, particularly S1 cortex. Finally, whether the cortical areas are activated by experimental pain or by aberrant chronic pain states, the pain-evoked activation can be modulated by cognitive factors, such as direction of attention.

Molecular genomics – Thursday 14 June, 14.00-15.30/South Hall

SP0037 WHAT HAS BEEN ACHIEVED AND WHAT CAN BE EXPECTED IN RHEUMATOLOGY?

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10.1136/annrheumdis-2001.89

Major advances have already been made in Rheumatology, many of which have translated into improved clinical care and management. These have largely centred around:

Descriptive studies. These have resulted in:

- a better classification/diagnosis and thus treatment of rheumatic conditions
- a clearer understanding of the natural history of diseases
- epidemiologically defined disease parameters (e.g. prevalence, incidence, geographical distribution, age at onset, gender ratios)

Imaging and definition of relevant laboratory tests

- higher resolution imaging of hard and soft tissues for appreciating both early disease processes and disease progression/severity.
- Laboratory investigations, as useful aids for diagnosis (autoantibody profiles, rheumatoid factor) and disease activity (e.g. CRP)

Treatments and interventions

- The development of effective and lasting joint replacement prostheses
- The introduction of better treatments (e.g. Cox2 inhibitors) and biological based therapies to antagonise inflammatory cytokines and processes (e.g. TNF-alpha antagonists)

What can be expected in the future for rheumatology remains speculation but exciting prospects are likely for clinical medicine in the post human genome sequencing era. A primary objective will be the identification of the genetic and environmental components to disease aetiopathogenesis. These should lead to:

- a better understanding of disease processes and classification resulting in more appropriate treatments.
- The identification of novel targets for pharmaceutical intervention.
- An ability to predict disease risk and disease outcome, permitting early screening and a more rapid or aggressive treatment plan.
- The characterisation of gene-environment interactions, resulting in health education and changes in life style or in possible prophylactic intervention.
- The identification of the pharmacogenetic basis for response to drugs and why there is variation in efficacy or adverse drug reactions. This should lead to personalised medicine.

New developments in molecular biology and cell biology are also likely to impinge on rheumatology in the areas of:

- Tissue Engineering
- Gene therapy
- Stem cell transplation

Genomics, genetics basis of disease and HLA/T cell recognition

AB0001 T-CELL IMMUNITY IN HLA-B27+ AND HLA-B27- PATIENTS WITH REACTIVE ARTHRITIS (ReA) OF DIFFERENT AETIOLOGY

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10.1136/annrheumdis-2001.90

Background

Objectives Estimation of T-cell immunity peculiarities in HLA B27+ and HLA B27- patients with reactive arthritis (ReA) of different aetiology.

Methods We observed 67 pts with ReA: male -62 pts., female 5 pts., mean age 27 ± 3 , 2 yrs., men duration of illness 24 ± 6 months. In all patients triggering infections were detected: in 36 pts. high levels of chlamydia trachomatis IgG and IgM together with HSV I IgG and IgM were observed, in 16 pts. serological activation of enterobacterial infection and in 10 pts. triggering agent was not found. Specific monoclonal antibodies were used to detect CD3⁺, CD4⁺, CD8⁺, CD16⁺, CD19⁺, CD22⁺ and presence of HLA-B27 antigen.

Results It was estimated that all patients with chlamydial infection were HLA-B27 positive. This pts had higher levels of CD4⁺ ($p < 0,001$), CD3⁺ ($p < 0,01$), CD22⁺ ($p < 0,01$), CD19⁺ ($p < 0,001$) and increased level of IgG ($p < 0,001$) and CIC ($p < 0,01$) in comparison to HLA-B27 negative pts. Presence of HLA-B27 correlated with duration and activity of ReA.

Conclusion Chlamydial infection often associates with presence of HLA-B27 antigen. This pts. have more expressed changes in T-cell immunity that leads to the longer duration and severe activity of the disease.