EDITORIALS

NOVEL TREATMENT FOR RHEUMATOID ARTHRITIS

After many years of frustrating dependence on non-specific anti-inflammatory and immunosuppressive agents for treating rheumatoid arthritis (RA), hopes are rising that a new phase of selective measures may have begun. These expectations are largely based on the current concept that RA is maintained by a predominantly T cell response to an antigenic peptide in the antigen-presenting groove of the class II HLA molecule [1]. This model suggests three basic means of suppressing disease activity, namely interdicting T cells, blocking peptide presentation and altering the class II sequences which confer susceptibility to RA. An associated theme is selectively to interdict the immunopharmacological events initiated by T cell activation.

The clinical implementation of this vision is furthest advanced in attempts to ablate T lymphocytes and so this subject merits particular attention. It is now clear that rheumatoid synovitis is suppressed by monoclonal antibodies directed at sub-populations of these cells, notably CD4 positive T cells [2-4]. The extent of this suppression is at least comparable with that achieved by conventional immunosuppressive methods and is the more impressive because the majority of the treated patients had failed to respond to established treatment. Nevertheless, while monoclonal antibodies of this kind are in theory and practice vastly more selective than cytotoxic drugs, they are still liable to paralyse the entire T cell repertoire, thereby risking all the consequences of long-term non-specific immunosuppression. This danger would not obtain if monoclonal antibodies to CD4 positive cells not only ablated the cells mediating synovitis but also restored or induced tolerance to the inciting antigens. These objectives have been achieved in experimental models of graft rejection [5] and there are hints that the same principles may obtain in the treatment of inflammatory diseases [6]. Such an outcome would obviate the need for long-term, non-specific immunosuppression. The current reality is that the outcome of controlled trials of the available agents is still awaited and their superiority over conventional drugs has still to be established.

In principle, the most specific means of suppressing rheumatoid synovitis would be to use monoclonal antibodies directed at the antigen receptors of the T cell clones reactive with the inciting antigenic peptides. This presupposes that dominant T cell clones can be identified in rheumatoid synovitis which ideally would be common to all patients with the disease. Two categories of T cells have been analysed. The first consists of cells with alpha/beta chain receptors which recognise peptides in the class II binding groove. The majority of studies indicate that T cells in rheumatoid synovial effusions and membranes are polyclonal, [7-9] although some Vbeta sequences are enriched in effusions compared with peripheral blood [10]. However, gene usage in these clones differs considerably among different patients. Clonal expansion is also more evident if the analysis is confined to activated T cells, defined as cells expressing interleukin (IL)-2 receptors [11, 12]. So-called superantigens may also account for this enrichment [13]. Superantigens, largely microbial in origin, engage virtually all T cells whose receptors express a given Vbeta chain and hence stimulate a wider range of cells than do conventional antigenic peptides which only stimulate T cells with complementary antigen receptors derived from all the gene families encoding the variable elements in these receptors. Obviously, reagents which suppressed T cells binding superantigens would be less selective.

The minority T cell population expressing gamma/delta chains in their antigen receptors also contribute to the synovial infiltrate and have been implicated in responses to mycobacterial antigens and heat shock proteins [14]. These cells engage antigenic peptides independent of presentation by class II antigens and their role in rheumatoid synovitis is controversial. There is some evidence for selective clonal expansion in this situation [15, 16].

It has long been appreciated that only a small percentage of the infiltrating T cells are specifically attracted to inflammatory lesions. The evidence to date indicates that such populations will not be easily isolated and characterized but do not exclude this possibility.

The practical problems associated with monoclonal antibody therapy are well known and mainly arise with repeated courses of treatment [1]. They have been largely overcome by administering engineered antibodies in which only the antigen-binding hypervariable regions are not of human origin. There is still concern that antibodies generated by the recipients to sequences present in the antigen combining sites of anti-lymphocyte monoclonal antibodies (anti-idiotypic antibodies) will interfere with binding to the target lymphocytes. However, there are indications that this will not be a major problem even with conventional monoclonal antibodies [17] and will be still less likely to arise in response to engineered antibodies. In the longer term, there are realistic prospects for generating antibody libraries of entirely human origin [18].

More serious reservations about the therapeutic prospects for selective T cell elimination centre on the true role of lymphocyte infiltration in rheumatoid synovitis [19]. It has long been clear that synovioocyte proliferation may be a primary event of great pathogenetic importance [20] and there are hints that cytokine production may be initiated in these cells independent of lymphocyte infiltration [21].
Other prospects for selective immunomodulation abound but are less advanced in terms of clinical trials. Vaccination with peptides has proved effective in preventing experimental autoimmune diseases such as diabetes mellitus [22] but the mechanisms involved are still uncertain and there is as yet no evidence that similar manoeuvres are effective in clinical practice. In principle, it is feasible to isolate and characterize the peptides occupying relevant sites on class II HLA molecules and other structures concerned with antigen presentation. This might help to identify pathogenetically relevant antigenic peptides but this will be no easy matter, given the range of oligopeptides already detected in the peptide binding groove of class I HLA molecules. Methods are available for generating awesome numbers of oligopeptides and testing their capacity to compete for these sites [23, 24] but systems for their therapeutic delivery are untried.

Similarly, it is feasible to characterize and block the sequences in class II HLA molecules which confer susceptibility to RA [25] but the practical application of these observations is also difficult. Moreover it is not clear that selective inhibition would interfere with disease induced by candidate microbial infections such as mycoplasma which are able to engage non-polymorphic HLA sequences [26].

The realization that cytokines account for many of the immunopathological consequences of inappropriate activation of the immune system has prompted great interest in their therapeutic manipulation. Unfortunately, the complexities of cytokine interactions ensured that the benefits would be scarcely dramatic and largely uninterpretable [27]. However there are now experimental systems which suggest that precise alterations in cytokine production, such as the constitutive production of tumour necrosis factor [28], can induce chronic arthritis. Among other methods, successful in vitro and in vivo experiments with precisely inhibitory antisense oligonucleotides [29] arouse expectations that therapeutic agents will eventually supersede corticosteroids on which rheumatologists are now experimental systems which suggest that pre-

The summit of the Delectable Mountains may still be enshrouded in mist but there is no lack of footpaths rising from the valleys.

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REFERENCES
19. Firestein GS, Zvaifler NJ. How important are T cells
The term whiplash describes the mechanism of acute flexion/hyperextension of the neck, a frequent feature of motor accidents. There is a spectrum of injury, ranging from minor tearing of muscle fibres to (rarely) vertebral fracture and spinal cord compression. Amongst the public whiplash injury has long been associated with chronic symptoms and financial compensation.

The problem for a variety of clinicians, including rheumatologists, lies in identifying, the influence on the clinical picture of three important factors—genuine injury, psychological factors and compensation 'neurosis'. Success to date in this regard has been hampered largely by inadequate trial data and a modern medico-legal epidemic continues unchecked.

Between 18 and 60 per cent of motor accidents (including front, side and rear impacts) give rise to whiplash injury [1, 2]. Common symptoms are neck pain, headache and upper limb paraesthesiae while dysphagia and visual or auditory symptoms occur infrequently. A number of noteworthy features in the history suggest more severe injury including high speed of impact, major damage to the vehicle, head injury and immediate onset [3] or intense initial neck pain [4].

Increasing age and radiographic evidence of cervical spondylosis are associated with the persistence of symptoms [4, 5] and along with the features of more severe injury may be useful in determining prognosis. Diffuse muscle tenderness and limitation of movement are the commonest clinical signs; neurological signs are rare, with root signs more frequent in those with cervical spondylosis. A review of cervical spine radiology in whiplash injury demonstrated prevertebral soft tissue swelling or angular deformity between vertebral bodies in 42 of 73 patients [5]. This high incidence of acute X-ray abnormalities has not been confirmed by others [6] while neither abnormality, surprisingly, was associated with the persistence of symptoms. The presence of neurological signs and cervical fracture or instability are indications for further investigation, particularly magnetic resonance imaging (MRI). This can demonstrate a range of injuries to bone, ligament or disc and indicate the degree, if any, of root or cord impingement [7].

Management of simple whiplash injury consists of rest and analgesics for 1 to 2 weeks. A collar may usefully be worn during this period but should be gradually discontinued thereafter. Moulded collars holding the neck in slight flexion appear better than the standard soft collar [8]. A number of trials suggest that outpatient physiotherapy is no more effective in relieving pain and improving movement than merely advice on home mobilization by a physiotherapist [8, 9]. Proper communication between doctor and patient is important. A common mistake in primary care is to assure patients of healing within a couple of months as this only creates anxiety and loss of confidence when it does not occur. While mobilizing it should be stressed that neck discomfort related to reasonable activities is not retarding healing or creating a risk of permanent damage.

Over 70% of patients settle in 2 to 3 months. Neurological symptoms and signs occasionally first develop some weeks after injury and are easily missed [3]. Judicious further physiotherapy may be useful for continuing symptoms, although clinical trials are lacking.

The major problem in whiplash injury is the assessment and management of those patients who remain symptomatic more than 6 months after injury. This may be a significant percentage of the total (26% in one large retrospective series [10] although others dispute such a high figure [11]. The term 'Late Whiplash Syndrome' (LWS) is useful to define this group who, in