EDITRORIALS

THE RESPECTABLE ART OF MODELLING

The study of animals offers opportunities to dissect the aetiology, pathology and therapeutic control of arthritic disease, and allows models to be built for subsequent testing in human disease processes. The great spectrum of symptoms seen in rheumatoid arthritis (RA) tells us that no one animal model and indeed no one case can offer credible models for the rest. Good modelling deals with narrow issues. A recent workshop organized by Dorian Haskard discussed many of the ideas considered below.

Activation of lymphocytes is a cardinal event in rheumatic diseases but identification of the activating signals and their immunological specificity is far from complete. Mycobacteria and type II collagen induce arthritis in rodents when administered in Freund's adjuvants, implying a role for these antigens, but the mineral oil Pristane used alone, will also induce arthritis in mice, emphasizing the complexity of apparently simple experimental systems. Pristane-induced arthritis involves lymphocyte activation, depends upon a radiation resistant cell population, and is genetically linked to the Ig-1 allotype [1]. Whether this is a non-specific response as are the activation signals probably involved in zymosan arthritis in rats [2] is not yet clear. In both models, analysis of the specificity of autoreactive lymphocytes might be revealing—non-specific activation may also include the activation of specific autoreactive cells.

Intra-articular injection of a protein antigen into an animal sensitized to the same antigen injected intradermally in Freund's complete adjuvant induces a monoarthritis. Here, the activating signal is immunologically specific although the antigen is irrelevant as a target of any ensuing autoimmune process. It may be that the triggering of CD4+ T-cells in the joint leads inevitably to an inflammatory arthritis. This could be relevant to human reactive arthritis and, in modelling this in rats, Toivanen recently reported how the intravenous injection of live Yersinia enterocolitica into specifically hypersensitive rats induces a resolving polyarthritis similar to adjuvant arthritis. No live bacteria could be found in the joints but it may be that antigen becomes trapped in synovial tissue in some way. This is reminiscent of earlier observations that antigen administered either intravenously or orally will cause a flare in antigen-induced arthritis [3,4].

Why and how antigens become trapped or captured in joints and the nature of the subsequent pathlogy they initiate are important issues. Different components of the arthritic process in guinea-pigs with monoarticular arthritis can be quantitated and may model the erosive processes, but not the synovitis, of human arthritis. The reaction in the guinea-pig differs from the reaction in the rabbit knee; the latter may be accompanied by lymphoid foci [5]. In the mouse, synovitis and erosions progress in parallel, illustrating another species difference that must be accommodated in relevant modelling [6,7]. The physicochemical properties of the antigens influence the nature and duration of the pathology. Cationic antigens, especially those with a pI greater than 9, are active in inducing chronic monoarticular arthritis [8] and parallels have been drawn between their causing glomerulonephritis in mice and arthritis in rats, depending upon their route of administration [9]. The antigens probably anchor to proteoglycans in the extracellular matrix and though the joint has no obvious drainage of sequestered antigens, the size of the antigen is critical. Those of less than 50 kDa are not readily retained, and cause only transient inflammation.

Trapped antigens are not sufficient to cause inflammation and a lymphocyte response appears essential. The role of antibodies is undefined. From studies [10] on the air pouch model Edwards [11] concluded that lymphocytes in the effusion may not be the direct agents of damage, but rather that they secrete suppressive or aggravating factors involved in inflammation. In most, if not all arthritides, persistence of the 'irritating' antigen is the key to chronicity and erosion [12,13]. Current hypotheses on the necessity for continued antigenic stimulation for the survival of memory lymphocytes support this model.

A viral aetiology can be seen in the effects of lentivirus infections in sheep and goats. As retroviruses, they are relevant to understanding HIV infection: the lentiviruses cause effects that include lymphoid disturbance, arthritis, enceph-
exposed to CII influences the development of
mentation of IL-1 [22]. MHC class II antibodies despite persistent ele-

showed that CD4 monoclonal antibodies sup-
press rat adjuvant arthritis transiently as do anti-
pathology of the disease is uncertain. It has been
activated by CII their relative importance in the
it is clear that both T- and B-cells are specifically
induced by soluble collagen type II (CH). Whilst
prompted extensive study of arthritis in rodents

The route by which the immune system is
exposed to CII influences the development of
CII arthritis. Soluble CII administered by per-
gastric gavage has prevented the induction of ar-
thritis [23-25] or ameliorated established disease
when introduced after disease induction. The or-
als tolerance effect can be adoptively transferred
to normal rats by enriched splenic T-cells but not
B-cells [26]. A contributory role for B-cells was
implied by the association with arthritis of anti-
odies of relatively low functional affinity in both
both the rat and the mouse [27]. The histological
changes seen in arthritic mouse joints following
jection of homologous murine CII in DBA/1 mice have been documented [28]. Autologous
CII will induce disease and this indicates a more
credible role for true autoimmunity against en-
dogenous joint antigens in both the initiation
and progression of arthritis. As in other studies,
the presence of relatively high levels of antibo-
dies of the IgG2a subclass in arthritic animals is
reported [29].

Type II collagen, the major collagen of arti-
cular cartilage, is not the only arthritogenic col-
lagen; CIX (glycosylated and with helical and
non-helical tracts, unlike CII) and CXI (struct-
urally and antigenically related to CII) may also
 induce arthritic disease in mice [30]. However,
it has been shown that CIX is not arthritogenic in
rats although CXI is. The antibody response to
CXI was analysed using separated alpha chains:
the appearance of antibodies against a2XI chains
preceeding those against the a2XI and a2XI chains.
The specificity of antibodies reactive with CNBr peptides of CII were similar in
arthritic and non-arthritic mouse, but in sera from
human RA patients antibodies against peptides
8 and 11 are especially frequent [31]. In this
issue, anti-native CII antibodies are described in
miscellaneous, naturally occurring canine ar-
thropathies, raising questions about the path-
ological role of these, at least in a spontaneous
animal model [32].

None of the models is sufficient to explain
human RA, but together they allow certain con-
clusions to be drawn. First, antigens of different
endogenous and exogenous types initiate the im-
mune reactions (almost certainly under the guid-
ance of the MHC) that lead to arthritis. Second,
antigen persistence, probably in the joint itself,
is necessary for chronic pathology. Third,
specifically activated T-cells and B-cells act in
concert to cause lesions. Fourth, immunolog-
ically non-specific factors such as cytokines and
eicosanoids cause the tissue changes. Fifth, syn-
ovitis, cellular infiltration, erosions and algetic
stimuli are under separate but interlinked con-
trol. As far as the aetiology of RA is concerned, these models should warn that the search for a universal and unspecific immunological stimulus is illusory.

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AN INNOCENT ABROAD

The broad leaved coconut palms reflected the glow of a tropical dawn as Jim’s plane pitched gently and stopped. For the tenth time he examined his slides then carefully replaced them in his hand baggage. Emerging from the airport he sniffed the stale aroma of diesel oil and sweat which he associated with the Third World. An agent from a pharmaceutical company held out a hand of welcome.

Outside his hotel, dark skinned men and boys in soiled, threadbare clothes offered him T-shirts, towels, balloons and beads. Within, the air conditioning blew luxurious draughts of scented air. From his room he could view a long arc of white beach, conical mountains and tumbling foam. He soon located the hotel pool and restaurants where he scrutinized the menus with anticipation. True, he had eaten and drunk regularly during the business class flight and the flavour of dry champagne lingered on his palate. It is strange how a man may quickly accept as customary that which was previously rare or remote.

He looked forward to the meeting, displaying genuine enthusiasm for exchanges with overseas friends and the serendipitous opportunities for learning. The halls bustled and speakers performed to large audiences. The organization worked well. Around the exhibition stands, throngs moved and paused, some delegates carrying plastic bags bearing the names of drug companies.

On that first day, Jim attended many sessions but his concentration was ordinary. By mid-afternoon he was becoming more reflective than receptive, isolated from the world by the hesitant transmission through his headphones of what he thought might be a Portuguese translation. A spontaneous doubt troubled him. He could not define it or even call it a thought. His reverie disturbed, he left the auditorium. A doctor hurried past in apparent consternation muttering ‘I’ve had enough’. The man rushed through the door and into a taxi. He was not seen again until the last evening of the meeting when he was smiling, perhaps a little fatter and certainly more tanned.

On the second day Jim found that there was no difficulty at all in finding a seat. He listened patiently to the tedious argot of ‘deemards’ and ‘enseds’. He was much relieved not to hear ‘paradigm’ more than twice. Some presentations were patronizing and they bored him. These talks were usually given by famous guest speakers who graced the meeting for not much longer than their lectures. Mainly, they flew directly northward on the same day.

There was conversation about robbery and mayhem in the streets but Jim, like many of his countrymen, secretly revelled in these hazards, often to the point of recklessness. There were other distractions. Jim received many dinner invitations and accepted them all. Sometimes, after a meal, he was taken to a show or discotheque. He was surprised that despite these lavish nocturnal activities he seemed to spend little money.

The daily bus route to the congress was long but scenic. Jim, romantic by disposition, wondered whether he was passing the hills and islands where the fictitious Nostromo secreted his silver. Jim wished he could write like Conrad and often tried to do so. On these journeys he talked to colleagues about the congress and the country. Occasionally there was serious discussion. He enquired, ‘Do you think that we need large international meetings when two excellent gatherings occur in America and Europe annually?’