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Rheumatoid inflammation and joint destruction: cause and effect or parallel phenomena?

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Summary

Joint damage is a characteristic and important consequence of rheumatoid arthritis; it is usually considered to be a direct result of the inflammatory synovitis. This view implies that by treating actively the synovial inflammation subsequent joint damage will be reduced and the long-term outlook of patients with rheumatoid arthritis thus improved. However, there is relatively little clinical evidence that suppressing inflammation reduces rheumatoid joint damage. An alternative view is that the mechanisms causing inflammation and those leading to joint destruction are parallel processes related only indirectly. Considerable evidence supports such a concept.

Clinical studies show radiological progression of the disease occurs despite improvements in measures of joint inflammation and a reduction in the levels of acute phase proteins. Damage can progress in either actively inflamed hot joints or cool swollen joints. Histopathologically the features of rheumatoid synovitis are non-specific, while the radiological pattern of joint damage is very characteristic. There is evidence that lymphocytic infiltration is not a poor prognostic finding, despite it being a typical feature of inflamed joints. Experimental studies also fail to show a close correlation between inflammation and cartilage damage: this is seen in experimental arthritis, co-culture *in vitro* systems, and the air pouch model of cartilage damage. We suggest that attempts to improve the outcome of rheumatoid arthritis should not merely concentrate on controlling inflammation but should also seek to modify the associated connective tissue changes of the disease.

Introduction

Joint damage is an important consequence of rheumatoid arthritis (RA) which accounts for considerable functional impairment and disability. The principal changes are cartilage loss and bony erosions which can be demonstrated radiologically. In the final stages there may be gross destruction or ankylosis. The suggested pathological mechanisms include: exogenous enzymes from synovial fluid cells [1], from inflammatory cells within the synovium [2], or from the macrophages and fibroblasts of the rheumatoid pannus [3]; endogenous enzymes produced by the chondrocytes and bone cells themselves [4]; free-radical induced toxic damage (5); dedifferentiation and remodelling of the cartilage and bone of the joint [6]. Whichever processes are involved, two crucial questions are the nature of the controlling factors and the sequence of events leading to destructive changes within rheumatoid joints.

The factors controlling articular inflammation and destruction have been the subject of intense investigation. Mediators such as histamine [7], prostaglandins [8], and the interleukins [9] are involved. However, in this article we wish to focus upon the sequence of events which, until now, has received less attention. Rheumatoid joints demonstrate inflammation and joint destruction. The traditional view is that inflammation leads to joint damage. For many years rheumatologists have therefore practised with the implicit assumption that inflammation within the joint is a harmful process. Inflammation, however, may often be protective, and it was described in the 18th century by John Hunter as a "salutory process". This paradox has led us to question the precise nature of the relationship between inflammation and joint damage.

Relationships between inflammation and joint damage

1. Cause and effect

This assumes that inflammatory synovitis is a direct cause of the cartilage loss and bony erosions of RA. This view is reasonable and is supported by findings such as joint damage being more severe in seropositive patients [10] and those with marked synovitis [11]. It gives a logical

sequence to the pathogenesis of RA. In this, initial synovial inflammation is mediated immunologically, involving mechanisms such as immune complex formation within the joint [12]. The inflammation persists due to factors such as the nature of the initiating agent or sequestration of antigen [13]. Continuing synovitis subsequently causes joing damage due to the enzymic or other processes outlined above. Such a scheme is simple, generally accepted, and appears to fit many of the available facts. Nevertheless, a number of difficulties remain.

2. A parallel mechanism

An alternative view is that inflammatory synovitis and joint damage in RA are not directly related. The inflammation does not cause joint damage and may even be a reaction by the body in an attempt to limit the amount of damage which occurs in the disease. In other words the inflammation may have a primarily protective role. The destructive component of RA results from another series of pathological changes involving proliferation and remodelling of synovium, cartilage and bone; these processes involve macrophages, endothelial cells, fibroblasts, chondrocytes, osteoblasts and osteoclasts. Such changes in mesenchymal tissues could be a characteristic reaction to the initiating factors of RA. Fassbender has developed this theme over many years [14] and recently concluded that there is no proportional correlation between the local inflammation and the destructive process in the life-long progressive course of RA [15]. If the joint damage in RA is more related to the degree of synovial hyperplasia than synovial inflammation it could be likened to a localised tumour, and Fassbender has even suggested that there is a degree of "mesenchymal transformation" involved in this process, with the development of tumour-like changes within the synovium.

Evidence for a dissociation between inflammation and joint damage

(i) Clinical studies

Non-steroidal anti-inflammatory drugs reduce some of the symptoms of inflammatory synovitis; but it is generally accepted that they have no effect on the progression of joint damage [16]. Slow-acting anti-rheumatic drugs such as gold and penicillamine work through different mechanisms. They reduce the amount of synovial inflammation and also improve the general indicators of inflammation such as reducing the raised ESR and acute phase protein levels [17]. The evidence that these drugs reduce the rate of radiological progression of RA, and thus have an influence on joint damage is weak [18]. A few studies show gold [19, 20] or cyclophosphamide [21] reduce radiological progression, but most do not [16]. Steroids do not have a more marked effect in reducing radiological progression [16].

The limitations of controlled clinical trials may be one reason for their failure to show reduction in the amount of radiological progression in RA [22, 23]. However, studies of the clinical course of RA over 1 and 10 years have also failed to show any evidence of significant reduction in the rate of radiological progression [24, 25]. A cohort of 56 patients with active RA treated continuously with slow-acting drugs for 12 months [24] showed significant falls in measures of inflammation (grip strength and articular index) and of the ESR and C-reactive protein, but radiological progression continued. The principal data is summarised in Table 1. Similarly a cohort of 112 RA patients [25], treated actively with steroids and slow-acting drugs, showed progression of X-ray damage (by a cruder radiological assessment) despite falls in the ESR. The main findings are shown in Table 2. The inevitable conclusion is that radiological progression is not altered to any great extent by treatment which reduces clinical and laboratory measures of inflammation within a joint. These arguments are strengthened by the observations of Young et al. [26] that progressive joint damage occurs equally

Table 1

Comparison of clinical, laboratory and radiological changes in 56 RA patients given 12 months continuous therapy with gold, penicillamine and other slow-acting drugs. The results are shown as percent of initial (pretreatment) values. Radiological damage was assessed in the hands and wrists by Larsen's method. Significant changes ($p = 0.05$ or less) at 0–6 months are shown as *, and at 6–12 months as +. The data is derived from reference [24].

	6 months therapy	12 months therapy
Grip strength	124%*	125%
Articular index (Ritchie)	57%*	45%
ESR	57%*	58%
C-reactive protein	41%*	40%
Radiological damage (Larsen score)	109%*	117% +

Table 2
10 year follow-up of a cohort of 112 RA patients treated intensively with slow-acting drugs and steroids. There were 90 cases alive and available for reassessment at 10 years. Radiographs of the hands and wrists were assessed to determine the number of severely damaged joints. The data is derived from reference [25]. The percent of cases in each category is shown.

Variable	Category	Initial results (n = 112)	10 year results (n = 90)
ESR	0–20 mm/h	23%	45%
	21–49 mm/h	44%	43%
	50 mm/h	33%	12%
Rose-Waaler titre	0	26%	26%
	1/4–1/32	8%	23%
	⩾1/64	66%	51%
X-ray grading	0–10	89%	56%
(number of damaged	11–15	5%	22%
joints	⩾16	6%	22%

in cool swollen joints as in those which are actively inflamed.

(ii) Histopathological studies

Histopathologically the inflammatory synovitis of RA is very similar to most other forms of active inflammatory synovitis [27, 28]. By contrast the overall pattern of joint destruction is rather specific for RA [29, 30]. Inflammatory synovitis therefore does not necessarily cause RA joint damage. If lymphocytes and chonic inflammation are directly responsible for joint destruction these should show some relationship to each other. Yet one careful histopathological study showed that lymphocytic infiltration is not a poor prognostic finding in RA. Muirden and Mills [31] found an inverse correlation between the degree of lymphocytic infiltration and joint damage, and thought that lymphocytes may play a helpful role in protecting the joints against rheumatoid damage rather than being a direct cause of destruction. These findings need to be interpreted with some care in view of current knowledge concerning lymphocyte sub-populations; nevertheless the observation is consistent with the view that inflammation and joint destruction are dissociated. Some forms of arthropathy, such as villonodular synovitis, show synovial proliferation with little inflammation, yet can cause bony erosions [32]. This provides additional evidence that the development of erosive damage is not restricted to arthropathies with a marked inflammatory reaction in the synovium.

(iii) Experimental models

There are no ideal animal models of RA. All have drawbacks. Nonetheless, there are indications from experimental models that in inflammatory synovitis there is no direct relationship between the inflammation and joint destruction. Descriptions of the rheumatoid-arthritis like disease of MRL/1 mice strongly support the concept of this dissociation. MRL/1 mice spontaneously develop hindlimb arthropathy as well as a number of immunological abnormalities, including circulating rheumatoid factors. O'Sullivan et al. [33] recently showed that throughout the disease progression there is a striking dissociation between inflammatory cell infiltration and exudation on the one hand and tissue destruction on the other. A slightly different experimental arthritic model is carrageenin induced arthritis. The data here is open to a considerable number of interpretations. However, Santer et al. [34] have shown that the increase and decline in polymorphs which indicate an acute inflammatory reaction following a single injection of carrageenin to a rabbit knee joint is dissociated from cartilage damage which can be measured by proteoglycan loss and synthesis. This also supports the concept of a dissociation between inflammation and cartilage damage.

Given the drawbacks of direct arthritic models, further evidence can be gained from alternative models. The co-culture system of Fell and Jubb [35] shows that inflammation is not needed to induce cartilage proteoglycan loss in their *in vitro* system. Indeed, Jubb has shown that only vascular tissue alone is needed when cartilage is co-cultured *in vitro* [36]. The mechanism of cartilage proteoglycan loss in the experimental system, is thought to be due to the effect of

Table 3
Effect of inflammatory change on cartilage proteoglycan loss after 10 days in the rat subcutaneous air pouch system. Results are expressed as percent of non-implanted control values (SEM). In each experiment n = 6. Methodology as for reference [40].

	Rat femoral head cartilage	Bovine nasal disc cartilage
Subcutaneous inplantation	56% (4)	158% (30)
Inplantation into a non-inflammed air pouch	41% (3)	150% (27)
Inplantation into an air pouch inflammed by carrageenin	70% (5)	162% (18)

catabolin [37] which is now considered to be one component of the activity of Interleukin-1 [38].

Another approach is the use of subcutaneous air pouches in rats to study the development of cartilage proteoglycan loss. The air pouch develops a lining which is very similar to the synovium [39] and it can be inflamed by local irritants such as carageenin. Implantation of cartilage into the air pouch then allows the examination of possible mechanisms. Cartilage proteoglycan loss occurs over 1–3 weeks in the air pouch [40]. There is no evidence that this is exacerbated by inflammation. Recent experimental studies supporting this are summarised in Table 3 [41]. The type of cartilage inplanted is important, with only femoral head cartilage from rats showing degradation. However, there was no evidence in studies using femoral head cartilage or implantation of bovine nasal cartilage discs that inflammation caused more proteoglycan loss. If anything, its effect is protective.

Practical consequences of a dissociation between synovial inflammation and joint damage

If the hypothesis which we have submitted is broadly correct, are there significant implications for the practice of rheumatology and for related research, or are such considerations of merely theoretical interest? A number of practical inferences may be drawn:

(1) NSAID's may exacerbate the destructive process in RA if the inflammatory aspect of the disease does represent an attempt at tissue protection. There is a little experimental evidence for this, albeit mainly in animal models [42, 43]. The removal of prostaglandin-mediated negative feedback on cytokine production is one possible mechanism whereby this could occur [43, 44]. There is the additional possibility of directly deleterious effects on the metabolism of connective tissue cells. It may be appropriate for rheumatologists to be more sparing in the use of these drugs, particularly in chronic joint disease where analgesia is often the principal requirement.

(2) Currently available slow-acting antirheumatic drugs used singly may have little influence on the progression of joint damage. Combinations of such agents with anti-proliferative drugs or with cortico-steroids may be more effective in this regard, but the increased risk of serious side effects limits the use of such an approach [45].

(3) A new class of drug is needed in RA which will specifically influence connective tissue cells in situations of increased turnover, as occurs in the disease. A drug which antagonised the actions of Interleukin-1 might fulfil this function. Unfortunately such an agent would probably also gravely impair the ability of the body defences to deal with infections, and seriously interfere with normal wound healing. The search for the 'ideal' drug in RA may thus be an impossible task, unless perhaps the main target cells have receptors which are sufficiently different from those of normal cells to render pharmacological exploitation feasible.

(4) In view of earlier observations regarding NSAID's it would seem inappropriate for the pharmaceutical industry to invest large sums of money and much research effort in a search for more similar drugs. Moreover, since most of the traditional models used for drug screening were chosen for their ability to discern agents with anti-inflammatory properties, and as none of them are good models of rheumatoid disease there is an urgent need for a reappraisal of methodology in

the field of drug research. There are some signs that this is beginning to happen.

Conclusion

The concept that synovial inflammation is not directly related to joint damage must remain contentious. We have presented evidence to support our hypothesis that inflammation and joint destruction are parallel phenomena in RA. Many rheumatologists will disagree with our view, and especially with the implication that non-steroidal anti-inflammatory drugs may be deleterious in their effects. We know there is a considerable body of evidence from other studies which does not support our hypothesis and inevitably we have been selective in the references we have quoted.

One relevant question is the definition of inflammation. We would put forward the view that for the arguments we have made, acute inflammation is related to polymorph infiltration and chronic inflammation is related to lymphocyte infiltration. If one took a broader view of the inflammatory process one could argue that synovial proliferation, which we consider is related to joint damage, is in fact no more than another facet of the inflammatory reaction.

We suggest our hypothesis merits further examination. In view of the enormous expenditure on anti-inflammatory drugs it seems to us worthwhile to try to establish the precise course of events in the destruction of rheumatoid joints in an attempt to find new approaches to preventing this longstanding problem.

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