MATTERS ARISING

Epidemiology of whiplash

Space restrictions prohibit a comprehensive refutation of the uneven treatment of the whiplash literature presented by Ferrari and Russell.1 They fiercely interrogate research that does not support their view, yet uncritically embrace literature favouring their pre-conceptions. Central to their argument is the assertion that there are different rates of chronic whiplash in different countries, and that the unrepresentative way in which this data is reported cannot account for the wide differences.2

A valid comparison between the prevalence of any condition in two places would require that it is measured in the same way. Balla’s study comparing Singapore and Australia was little more than anecdotal from interviews of selected Singaporean doctors compared with the data from Australia.3 Such data may be fatally corrupted by recall, case selection, sampling, and expectation bias.

Caution should be observed in comparing insurance claim rates between countries. There is no international consistency in notification of accidents or insurance or compensation procedures. Conclusions drawn from such comparisons are unsustainable and subject to the ecological fallacy. The frailty of using insurance claims as a surrogate for the incidence of injury does not seem to have been acknowledged by Ferrari and Russell. A claim is a behaviour arising from a combination of motivation, enabling circumstances, perceived benefits, costs, social norms, peer and family pressure, and fear of current or future pain and disability—all factors excessive to the injury itself. The Victorian experience in Australia is particularly pertinent. Fewer claims for whiplash were noted after the introduction of legislation creating bureaucratic barriers, disincentives, and up-front costs for potential claimants. Some then fibre their advertisements if they had whiplash, producing a biased sample. However, the advertisement was in a medical journal, seeking doctors to enrol participants, producing a representative sample. Ferrari and Russell have used these studies in a previous article, apparently accepting the methodology then.6 These flaws alone raise grounds for concern that the opinions of Ferrari and Russell are not responsibly based on an appraisal of the literature and will raise alarm and reinforce prejudice against genuinely afflicted patients.

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6 Fletcher G, Haughton VM, Khor K, Alves W, Orr AJ. Zygapophysial joint pain must be rare. Indeed, it is “fraught with at least 15 significant methodological flaws.” They do not enumerate these flaws but instead cite four references, three of which rely on sophistry and misrepresentation of data to mislead readers. If these references are consulted, the last three offer no criticism of Radanov. Only the first, a letter, offers criticism, but cleverly and effortlessly Ferrari and Russell do not inform the reader of Radanov’s rebuttal of these criticisms.

Yet even if we accept that psychosocial factors are important in these patients, Ferrari and Russell do not provide an answer as to what they do about them. Sectioning, advertising if you have whiplash, encouraging the public to sue—van Akkerveken and Vanguard, but do not explain to readers that this was not a peer reviewed publication, that it was only a preliminary study, that it was not controlled, and that the authors themselves were overwhelmingly guarded about overstating their results. No other literature is provided to vindicate cognitive intervention.

Finally, if Ferrari and Russell are so convinced that experimental studies of whiplash are so innocuous, perhaps they might organise some volunteers to undergo a series of Av30 kph and Av60 kph collisions, which are what many of our patients underwent.

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Making selective use of the literature and incorrect quoting of previous research, the January 1999 “leader” intends to support the view of the whiplash syndrome as malinger- ing. This reply cannot be exhaustive but will address the following:

The Ballas paper lacked a definition of the whiplash syndrome and did not describe the assessment of 300 selected cases seen in a single practice. Moreover, selection bias appears to have been an important factor in the study. The Ballas publication and the Anglican Church should be aware of the malinger hypothesis for whiplash injury.

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References


We thank Drs Barnsley and Bogduk for their comments. Dr Barnsley reiterates a dualistic (mind-body) approach that we have been trying to blur and indeed do away with for various reasons, most notably that dualistic approaches have been largely unhelpful to doctors. We also believe, to use her term, that these patients are “genuinely affected”. Dr Barnsley’s comment that a “more sober view” suggests a reduction in insurance claims does not reflect a reduction in symptom prevalence requires proof, and is not in accord with admitting anecdotal reports from Australian rheumatologists, nor with the evidence from Lithuania (she does not quote the subsequent prospective study), Germany, and Greece. Dr Barnsley is also less than fulsome in her praise of the impressive study presented at the World Whiplash Congress in Vancouver which suggests that changing the claim scheme has dramatic effects on recovery rates, as indicated by various patients.

Both Drs Barnsley and Bogduk have missed the point: the epidemiological literature—the rapid recovery rate seen in some countries is not being duplicated in others. The studies in Lithuania, Greece, and Germany cannot rule out the possibility of a small number of subjects having chronic pain and disability, but they do show that recovery (as measured by absence of symptoms and return to normal activities, as well as other patient-centred outcomes) occurs in 90–95% of subjects in six weeks or less. It is this fact that compels us to question the basis for chronic pain in Canada. We find that whiplash in Canada (and reportedly in many other countries) is a massive public health and econonic burden, with more than 50% of accident victims reporting chronic pain six months after the accident. The patients of Dr Bogduk’s study represent merely the tip of a large iceberg. Thus, new paradigms are necessary to understand why some subjects recover within six weeks or fewer and others do not. As no one has suggested that Lithuanians, Greeks, and Germans have a different anatomy, we need to look for an explanation for this difference in recovery rates.

It is certainly possible that a small proportion of subjects could have chronic structural damage in countries like Lithuania, as Dr Bogduk suggests, and that current studies with background prevalence of neck pain in the control population of up to 10% are not large enough to distinguish an additional 2–3%. Yet, this additional 2–3% of patients are not the group of patients we are describing. It is the 50% of patients who continue to have pain at six months that we are concerned with, and the cervical zygopophyseal studies are not relevant for this larger group. Indeed, we were not aware that the subjects of Dr Bogduk’s studies had whiplash due to frontal-impact collisions (a AV of 30–60 km) as Dr Bogduk indicates. This fact makes it even less likely that their study group is typical of most patients with chronic whiplash, who instead undergo much lower velocity collisions. Clearly, and for good reasons, Dr Bogduk’s study patient spectrum is very different from the group we are concerned with. Our disagreement is not substantially with the few per cent that he may see with facet problems, but rather with the rest of the iceberg of chronic pain.

The purpose of our model is to develop discussion on research questions and develop bona fide research efforts to understand what explains different recovery rates, so we can use that understanding in changing both the approach of the therapeutic community and society in response to acute whiplash. Understanding the behaviour that promotes chronic pain is the first, best step to changing it. We agree with Bogduk, once again, that over-treatment and medicalisation are likely to be part of the problem. Yet, until it is thoroughly demonstrated to us, and understood by the therapeutic community and society at

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large, that this is part of the problem, this practice is unlikely to change.

By setting forth this model we can now investigate it. We are making efforts to do this, and we hope that quality researchers such as Drs Barnsley and Bogduk will engage in such efforts as well.

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Authors’ reply to Dr Radanov

Dr Radanov’s expressed concerns and cry for auto-da-fé are based on their perception that our biopsychosocial model is one of malinger as an explanation for the late whiplash syndrome. As we have explicitly stated, in both our article and in a previous review on this topic, we reject a model based on malingering and we consider this to be a rare or uncommon presentation. Dr Radanov’s concerns are therefore misplaced. That Dr Radanov is unable to appreciate that our biopsychosocial model presents alternatives to the otherwise unhelpful, unidimensional, and dichotomous approaches taken by himself and others is a problem for him, but one which we cannot ameliorate in the space available. We thus refer him to a more comprehensive resource.

Once again, we reject the view that the chronic pain of whiplash is due to an enigmatic and inexplicable chronic injury, and we simultaneously reject the view that the best explanation (or even a common explanation) for the late whiplash syndrome is malinger or psychological models that place the pain “all in one’s head”. The biopsychosocial model includes physical sources for pain, and incorporates psychosocial factors to explain both the severity and attribution of the pain, as well as further behaviour enacted upon this substrate of otherwise benign physical sources of pain. Thus we maintain that the most helpful focus of discussion and research should be on identifying how the various elements of the biopsychosocial model explain the variance in epidemiology of the late whiplash syndrome, and why, even within a given culture some accident victims recover quickly and others do not. Dr Radanov’s views may be coloured by the relatively benign nature of the problem he sees in Switzerland. Even with an advertising campaign to recruit subjects, the Swiss outcomes were very much better than those currently being described in North America. We maintain that the Swiss effort at understanding these issues has been a start, but is a mere footnote in a much longer journey of inquisition.

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†Social class based on the Office of National Statistics classification of occupations. The patients with RA in Merseyside were of significantly lower social class than the patients with inflammatory polyarthritis studied in Norfolk. Table 1 summarises these findings. If the findings reported by Maiden et al. are supported by further studies, health would seem to be significant differences in incidence, severity, and mortality in RA according to socioeconomic profiles. This would mean that increased resources should be allocated to regions of greatest need and not, as at present, to areas where socioeconomic class is highest, such as the south of England.

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Rheumatoid arthritis, poverty and smoking

Maiden et al raise a number of important and interesting points in their paper. Does social disadvantage contribute to the excess mortality in rheumatoid arthritis patients?

They have observed that mortality in rheumatoid arthritis (RA) correlated with social grouping on the west coast of Scotland. Patients with RA of the lowest socioeconomic classes have an increased mortality when compared with patients of a higher socioeconomic class. Moreover, RA was more prevalent in patients with RA of lower socioeconomic class. We propose that these two important observations can both be explained by cigarette smoking.

The authors commented that cigarette smoking was more prevalent in the patients with RA of lower socioeconomic class in their study. In Britain there is a marked difference in smoking prevalence between social classes. In the 1996 census 41% of lower social class men (social class 4) were current smokers, with only 12% of men in the highest social class (social class 1) currently smoking. Cigarette smoking kills 120 000 people a year in Britain. Most of these deaths are as a result of cardiovascular disease, respiratory disease, and lung cancer. Maiden et al. observed that 65% of the deaths in their study occurred as a result of these diseases. Current data show that continued cigarette smoking throughout adult life doubles age-specific mortality rates even in achieving them in late middle age. Cigarette smoking is associated with an increased risk of RA in both men and women. The increased mortality seen in patients with RA of low socioeconomic status could be explained in part by cigarette smoking, and that cigarette smoking itself might have contributed to the excess RA seen in the most socially deprived.

Since the poorest in our society appear to have an increased risk of RA, studies designed to identify risk factors for RA may best be focused on those with the highest risk. Cigarette smoking may be especially important to study, because its most powerful effect might be seen in the poorest socioeconomic population with RA. Laudable attempts to study the epidemiology of RA in Britain have been set up. One example is the Norfolk Arthritis Register. However, we would suggest such populations, in which there are a large proportion of higher socioeconomic groups, are unrepresentative of the large industrial cities in Britain. In 239 patients with RA in the Merseyside region under hospital follow up, the social class of our patients was identified using the Office of National Statistics classification of occupations. The patients with RA in Merseyside were of significantly lower social class than the patients with inflammatory polyarthritis studied in Norfolk.

Table 1 summarises these findings. If the findings reported by Maiden et al. are supported by further studies, health would seem to be significant differences in incidence, severity, and mortality in RA according to socioeconomic profiles. This would mean that increased resources should be allocated to regions of greatest need and not, as at present, to areas where socioeconomic class is highest, such as the south of England.

Table 1

<table>
<thead>
<tr>
<th>Social class</th>
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<th>Social class</th>
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<tbody>
<tr>
<td>1-2 No (%)</td>
<td>3N-5M No (%)</td>
<td>5-7 No (%)</td>
</tr>
<tr>
<td>RA cases Merseyside (239)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>51 (33)</td>
<td>73 (47)</td>
<td>30 (19)</td>
</tr>
<tr>
<td>20 (12)*</td>
<td>87 (36)**</td>
<td>124 (52)*</td>
</tr>
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</table>

*p<0.0001; **p<0.05.

†Social class based on the Office of National Statistics classification of occupations.
Authors’ reply

We welcome the letter entitled “Rheumatoid arthritis, poverty, and smoking” in response to our article “Does social disadvantage contribute to the excess mortality in rheumatoid arthritis patients?” The importance of looking as a contributor to the influence of socioeconomic deprivation on mortality is rightly emphasised. However, as Black has pointed out eloquently, smoking alone does not account for the excess mortality seen among lower socioeconomic groups. We observed a higher mortality rate among patients with rheumatoid arthritis (RA) living in deprived areas relative to those living in affluent areas. Our methodology did not determine the social class of individual patients according to the Office of National Statistics classification of occupations. Nevertheless, whether measured by income, occupation, educational level, social class, or ecological variables such as the Carstairs score, socioeconomic deprivation has been shown to influence health. In addition, we observed that there were more patients with RA living in deprived areas of the general population in Scotland. Although this may result from a higher prevalence of RA among the lower socioeconomic classes, this conclusion cannot be drawn outright from our study. People in deprived areas of Scotland may have had a higher rate of smoking. In areas of affluence and deprivation would prove valuable in determining the epidemiology of RA.

Over a short 40% of the most affluent group (Carstairs 1 and 2), 45% of Carstairs 4, 5, and 6, and 65% of the most deprived group (Carstairs 6 and 7) were current smokers; figures much higher than the 1996 census figures of 12% and 41% for social classes 1 and 2 respectively. This difference may reflect the fact that our patients were recruited a decade earlier (1984–85), but there are also social/cultural differences between Scotland and the United Kingdom as a whole. The prevalence of smoking in Scotland from the Scottish Health Survey 1995 was 23% in social classes 1 and 2 and 49% in social classes 4 and 5.

Although differences in mortality rates according to smoking with RA according to socioeconomic deprivation can be explained, in part, by differences in the prevalence of smoking, the observed influence of deprivation on mortality in RA is less easily accounted for by smoking. Functional ability is an important outcome measure in RA and is a predictor of mortality in this disease.

The Scottish Health Survey 1995 showed that there were differences across social class in other important determinants of health, including diet, alcohol consumption, obesity, hypertension, lung function, fibrinogen levels, general health perception, and physical and social activity. Further research is required to establish the relative importance of these and other factors in determining the influence of socioeconomic deprivation on outcome and mortality in RA and other chronic diseases. The factors which can be modified most effectively to reduce the inequalities in health outcome also require investigation.

If our findings are supported by further studies, then socioeconomic status of populations should influence resource allocation. In addition, these important factors should assist rheumatologists when deciding which patients with RA should receive more intensive, multidisciplinary intervention.

Diagnostic evaluation of classification criteria for RA and reactive arthritis

We read with interest the recent article by Hülsemann and Zeidler, which the 1987 American College of Rheumatology (ACR) classification criteria for rheumatoid arthritis (RA) were evaluated for their ability to identify patients with a clinical diagnosis of RA among 217 patients referred to an early arthritis clinic. The authors concluded that the 1987 ACR criteria can be used to make a diagnosis of RA in this setting.

In this study, the “gold standard” against which the criteria can be evaluated as an “expert diagnosis” made by one of the authors when the patient was first seen (within one year of symptom onset). However, the main difficulty faced in evaluating criteria for patients with early disease is that patients who ultimately develop RA appear clinically similar to those who have self-limiting disease or other forms of inflammatory arthritis. It is therefore too early to make an accurate diagnosis at this stage. More importantly, RA is a heterogeneous disease with a prognosis which varies from complete symptom remission to severe disability. Therefore simply categorizing patients into those who do and do not have “RA” is not necessarily important when considering which patients require early treatment. Although the authors made a clinical diagnosis without using the classification criteria, it is important to note that the diagnoses were informed by their knowledge of the individual components of the criteria. Therefore the high sensitivity (90%) they reported means that many of the patients with a clinical diagnosis of RA will have had seropositive, erosive, polychondritic disease with hand involvement. Whereas we have no problem in recognising these patients as having RA, it represents only one end of the spectrum. The proportion of patients with “undiagnosed arthritis” in this study is high (54%), though this has been reported in other series. It is likely that many of these patients have atypical RA which may still require treatment with disease modifying antirheumatic drugs. Further, in early disease, patients often do not satisfy one of the criteria (nodule erosions) which are features of established RA. We therefore think it is misleading to imply that patients who do not satisfy the 1987 ACR criteria (a) do not have RA; and (b) do not require early, aggressive treatment.

We recently evaluated the performance of the 1987 ACR criteria in an unselected cohort of 486 patients newly presenting with inflammatory polyarthritis to the Norfolk Arthritis Register. We considered the practical question of whether the criteria could identify which patients would have a poor prognosis after three years as assessed by (a) persistent synovitis; (b) functional disability and (c) radiological erosions. Although we applied the criteria in a number of different ways, we found they had a low ability to discriminate between patients who developed persistent, disabling, and erosive disease and those who did not. For example, applying the criteria using the traditional “list” format, the positive predictive value for erosions was only 45% and the negative predictive value 67%. In practical terms, this means that patients who did not satisfy the criteria developed erosions. However, given the fact that the 1987 ACR criteria were developed to distinguish between hospital attenders with established RA and patients with other musculoskeletal conditions, and were never intended to be used as diagnostic criteria, it is not surprising that they do not perform well in this setting.

Finally, we wish to point out that the proportion of patients who satisfy the 1987 ACR criteria is highly dependent on how the criteria are applied. For example, in our study, the proportion of patients who satisfied the criteria at one year of follow up varied from 28% if applied “cross sectionally” (on the day of assessment) to 61% if applied “cumulatively” (each criterion satisfied if “ever” positive). Further difficulties are likely to be encountered using criteria ascertained from case note review. It is therefore more appropriate in a group with early synovitis to assess the criteria applied longitudinally at follow up, rather than simply at baseline. In the study by Hülsemann and Zeidler we were given no information about how or when the criteria were applied apart from that they were applied “retrospectively”.

We agree with Hülsemann and Zeidler that there is a need to “...differentiate RA as early as possible from the often benign and self-limited forms of undifferentiated arthritis, as there is a need for early treatment of RA”. However, we strongly disagree with the use of the 1987 ACR criteria. Until we understand more about the pathogenesis of RA, clinicians will have to rely on clinical judgment and the presence of poor prognostic factors to make decisions whether to treat aggressively patients presenting with early disease.

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The paper correctly detailed the criteria used in all controlled trials to enable comparisons. Three treatment guidelines, in our view, well supported in every day practice by applying the 1987 ACR criteria to differentiate RA from other forms of arthritis, enabling early diagnosis and treatment decisions.

**Authors’ reply**

We agree with Harrison et al that the main difficulty for a rheumatologist in early arthritis is to distinguish progressive rheumatoid arthritis from self-limiting disease and other forms of arthritis that do not show a progressive course. Nevertheless, there is also a need in clinical practice for the primary care doctor and the patient to perform, as early as possible, a nosological differentiation between RA and the whole spectrum of other arthritides and spondarthritides.

We have described the incidence of undifferentiated arthritis to be as high as 54%.

When patients were seen in this early arthritis clinic, that early arthritis clinic, that early diagnosis of RA had developed ankylosing spondylitis.

Efficacy of intra-articular primatised anti-CD4 in resistant rheumatoid knees

An interesting paper was published recently in the *Annals of the Rheumatic Diseases* examining the effect of intra-articular administration of primatised anti-CD4 antibody in the knee joints of patients with rheumatoid arthritis and persistent synovitis, unresponsive to treatment. The paper correctly detailed the disappointing results obtained in clinical trials with parenteral treatment with anti-CD4 antibodies, particularly in view of the supposed pivotal role of CD4 positive T cells in the chronic synovial inflammation of RA.

The paper showed an apparent improvement in the knee synovitis in patients treated with a low (three patients) and high (seven patients) dose of intra-articular anti-CD4 antibody and no response in two patients treated with placebo, using a combination of magnetic resonance imaging, arthroscopic scoring of the synovial tissue, and immunohistochemical labelling of the synovial biopsy specimens.

An obvious omission from this paper was any doctor or patient derived clinical parameters to allow the reader to assess the benefit, if any, of this treatment for the patient. The only indication of the clinical efficacy of this treatment in the paper was the statement that two of the patients receiving low dose and all seven receiving high dose had not required any further local injection treatment at follow up 18 months. It is curious that no clinical parameters were measured in this study, with a complete reliance on imaging and laboratory procedures to measure outcome, which leads me to speculate that there might have been no discernible clinical difference between the treatment groups, as assessed by the patient or doctor.

Also, there was a marked disparity in baseline C reactive protein (CRP) levels between the three treatment groups, with the placebo treatment group having a far higher level (presumably more active disease). There was no evidence that this treatment had any effect on systemic parameters of disease activity, with the CRP actually increasing in the three patients receiving 0.4 mg anti-CD4 antibody into the knee joint.

Turning to the outcome measures used in this study, the changes in the MRI measures were small (ranging from a 15% deterioration to a 10% improvement in different measures in the groups receiving active treatment), which is unimpressive for a treatment which targets a cell with a “pivotal” role in synovitis in rheumatoid arthritis. The results with treatment illustrated in fig 3 (see ref 1) are also unimpressive and it is difficult to see a great difference between the MRI images obtained before and after treatment.

Finally, the reader should be aware that immunohistochemical labelling of the synovial membrane with anti-CD4 antibodies will label CD4 positive T cells and macrophages (which also express CD4), so the authors cannot establish whether the effect of CD4 staining in the synovial biopsy specimens as a result of treatment is due to a decrease in T cells, in macrophages, or both, unless dual immunohistochemical labelling for CD44 and a cell lineage marker was performed. A close inspection of fig 4 (see ref 1) suggests that the major change in CD4 labelling is in the lining region of the membrane, indicating an effect on macrophages rather than CD4 positive T cells.

In conclusion, this interesting paper has, like the clinical studies on anti-CD4 antibody treatment for rheumatoid arthritis, promised much to the reader but has ultimately been disappointing.

**Considerable doubt about the central role of the CD4 positive T cell in sustaining the chronic synovial inflammation in rheumatoid arthritis remains and this study has not altered this conclusion.**

**References**

CD36 and CD14 immunoreactivity of Reiter cells in inflammatory synovial fluids

Reiter cells are macrophages containing ingested polymorph nuclei that are commonly found in most inflammatory synovial fluids. Available data indicate that CD36 and CD14 on human monocyte derived macrophages are adhesion molecules involved in several biological processes. Of interest, their role in the process of adhesion and phagocytosis of apoptotic cells has been recently demonstrated.15

Jones and colleagues demonstrated reduced Reiter cells in the synovial fluids from patients with rheumatoid arthritis. This observation is consistent with the hypothesis that Reiter cells play a regulatory part in preventing autolysis of polymorphonuclear neutrophils (PMN) and thus local tissue damage.7

The purpose of this study was to evaluate by histochemical technique whether Reiter cells express CD36 and CD14 in inflammatory synovial fluids.

We analysed the synovial fluids obtained from the knee joints of 10 patients suffering from inflammatory joint diseases of recent onset (< 6 weeks). Three patients had sero-positive active rheumatoid arthritis, four patients had seronegative spondyloarthritides (two reactive arthritis, one psoriatic arthritis, one enteritis) and three patients had crystal induced arthritis (two cases of acute gout and one case of acute pseudogout). Synovial fluids were processed within one hour of aspiration. Two slides were stained with May-Grünwald-Giemsa (MGG) reagent. Reiter cells were counted on the basis of the first 500 cells encountered on MGG stained slides. In addition, two cytocentrifuge monolayer preparations were processed for immunohistochemistry using the monoclonal anti-human-CD36 antibody (Boehringer Mannheim-Germany) diluted to 3.5 mg/ml and the monoclonal antihuman monocyte CD14 antibody (DAKO-Denmark) diluted 1:10 in TRIS-HEPES buffer. In brief, specimens were air dried, fixed with acetone and then stored at −70°C until processing. The specimens were incubated for 60 minutes at room temperature with the primary antibody. For the conjugation of peroxidase an En Vision+TM Kit (Dako) was used. The monoclonal layers were then incubated for five minutes with a prediluted diamino-benzidine solution (Dako) and countercoloured with Mayer’s haematoxylin. All incubation steps were preceded by washes in 0.1 M PBS (five minutes × three). The slides were examined at 400 × magnification.

Omission of primary antisera, use of normal rabbit serum, or one of subsequent steps in the staining method was included as controls for specificity. Macrophages as well as Reiter cells could be observed on MGG stained slides. Reiter cells were more abundant in synovial fluids from patients with seronegative spondyloarthritides and crystal induced arthritis compared with synovial fluids from RA (table 1).

On immunohistochemistry preparations, numerous mononuclear cells showed a CD36 positive reaction, while all the Reiter cells observed displayed a positivity for the thrombospondin receptor. CD14+ mononuclear cells outnumbered CD36+ cells; similarly, all the Reiter cells observed were immunoreactive for the anti-CD14 antibody (fig 1A, 1B).

Our findings show that Reiter cells do express both CD36 and CD14 adhesion molecules. CD36 expression on Reiter cells seems to support the notion of the involvement of this receptor in the clearance of apoptotic PMN during synovial inflammation. In vitro data have shown that thrombospondin receptor and CD14 are some of the most important adhesion molecules involved in cell clearance. The expression of the thrombospondin receptor turns an amateur phagocyte into a professional one.16 It has been hypothesised that dysregulation of this receptor and the ensuing impairment of inflammatory cell elimination could play a part in inducing chronicity as well as tissue damage and scarring.7 Recently, CD14 has been demonstrated to mediate recognition and phagocytosis of apoptotic cells. This interaction depends on a region of CD14 that is supposed to be identical to a region that binds bacterial lipopolysaccharide,7 triggering the release of proinflammatory cytokines from macrophages. On the other hand, the interaction with self components acts as an initial step leading to apoptotic cell elimination. A major role for CD36 in the uptake of apoptotic neutrophils has been recently hypothesised, but it seems likely that micro-environmental modifications could promote the switch from a CD36 dependent pathway to pathways using other adhesion molecules such as CD14.7 The removal of inflammatory PMN is mediated by several surface molecules and modulated by microenvironmental modifications; it seems to be a crucial, although only partially understood event for the control and resolution of inflammation. Our results suggest that CD14 and CD36 could be involved in the adhesion of the macrophage to the apoptotic cell, the first step of

Table 1 The number of Reiter cells calculated on the first 500 cells encountered on May-Grünwald-Giemsa stained slides

<table>
<thead>
<tr>
<th>Sample</th>
<th>Reiter cells (n)</th>
</tr>
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<tbody>
<tr>
<td>RA (n=3)</td>
<td>1 1</td>
</tr>
<tr>
<td>1 2</td>
<td></td>
</tr>
<tr>
<td>SsA (n=4)</td>
<td>1 3</td>
</tr>
<tr>
<td>2 2</td>
<td></td>
</tr>
<tr>
<td>CIA (n=3)</td>
<td>1 4</td>
</tr>
<tr>
<td>3 3</td>
<td></td>
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RA: rheumatoid arthritis, SsA: seronegative spondyloarthritides, CIA: crystal induced arthritis.


Figure 1 (A) CD36+ mononuclear phagocytes (arrowhead) and Reiter cell (arrow) in cytospin preparation of an inflammatory synovial effusion (enteritis). (B) CD14+ Reiter cell observed in a knee synovial fluid sample from a patient with monoarticular acute gout.
Non-periodic leg pain in patients with familial Mediterranean fever

Familial Mediterranean fever (FMF) is characterized by recurrent bouts of fever and peritonitis, pleuritis, arthritis or cryopyeliasis-like skin disease. Between the episodes, FMF patients are free of symptoms and appear healthy.1 However, interestingly we observe leg complaints after prolonged standing or sitting, or both, in FMF patients, who usually experience these painful manifestations during evenings or after long distance bus trips. Thus we conducted a questionnaire study on 40 FMF patients (age, mean (SD): 16 (2.7) years; F: M; 2: 38) and 180 healthy male subjects (age, 21.3 (0.2) years) to ascertain the frequency of these complaints, and some of FMF patients were also included in a test to provoke these symptoms. Table 1 shows the questionnaire. Positive cases were also questioned for the presence of swelling or redness during these painful periods, and whether these complaints followed by an episode. Although 14 of the 180 healthy subjects responded positively to the first question (question A), none of them were considered to be positive after any of the other questions (questions B). All FMF patients reported foot or leg pain after prolonged standing periods (first part of question A). They described that, at the onset, the pain was merely confined to the foot, but later spread to the ankles, the calves, the knees or even the thighs were involved in an additive manner as the intensity of pain increased unless resting ensued. Thirty five FMF patients have experienced foot pain (with or without subcutaneous swelling) during or after long distance bus travel and they also described an area of redness, which typically located on the soles of the feet, but never reached them. Thirty three patients define a period of fatigue accompanied a low grade fever subsequent to the episodes with severe lower extremity symptoms.

In a provocation test, 30 volunteer male FMF patients (age, 21.2 (1.8)) without proteinuria and 30 volunteer male healthy subjects (age, 21.1 (0.8)) were kept in an upright position (standing, walking or dependent sitting) for six hours. At the beginning, all participants were symptom free and none of them had any other disorder that may cause foot pain. Thirteen FMF patients were receiving colchicine treatment. Bilateral ankle and the mid-foot, circumference were measured from the marked points at the onset and the termination of the test. The mean change in circumference per measurement site (mean (SD)) was 1.2 (0.7) mm and 1.3 (1.5) mm in the patient and the control group, respectively. Although the comparison was statistically significant (p=0.014; Mann-Whitney U), we think that our method was not reliable to detect those small changes precisely. At the end of the provocation test, none of the healthy controls had lower extremity pain or tenderness. Apart for one patient, all FMF patients had intense foot or calf pain, which interfered with walking. Tenderness was so profound that it could be elicited even by a gentle touch. Widespread tenderness was detected in 12, whereas localised tenderness was detected in 17 of the patients. Although swelling was not noticed in anyone, focal erythematosus areas (not cryopyeliasis) were seen in five patients. After five hours of resting, palpation showed that tenderness was sustained (14 widespread and 16 localised). A localised pain and tenderness was also developed in the symptom free patient. Colchicine use did not change the results of provocation test (p=0.24; Fisher's test).

Although leg pain induced by exercise or prolonged standing has already been discussed in FMF patients,2 we are unaware of any report about leg pain and swelling episodes after prolonged sitting in these patients. Increased hydrostatic pressure in the lower extremities may be the main factor responsible for those symptoms experienced during bus trips. It was suggested that FMF is related to catecholamine metabolism as metaraminol infusion may provoke an acute episode,3 and episodes may be prevented by prazosin hydrochloride, as reported recently.4 Leucocytes may need adequate perfusion (driving) pressure to pass through capillaries in microcirculation.5 These findings raise the possibility that catecholamines may increase the hydrostatic pressure of capillary bed, which may be an inciting factor for episodes. Our findings show that an inflammatory cascade involving lower extremities occurs after prolonged standing and sitting periods in FMF patients. We think that genetically low level of inhibitory activity (that is, mutated pyrin) may not be able to compensate the inflammatory reaction that is probably initiated in a stressful microenvironment caused by not only microtrauma,6 but also increased hydrostatic pressure.

We are greatly indebted to Professor Hasan Yazici for constructive criticism and help in preparation.

CORRECTION


We regret that the references in this article are incorrectly numbered. Owing to the splitting of reference 7, references numbered from 9 onwards in the text are listed as 10 onwards in the reference list.

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Epidemiology of whiplash

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MATTERS ARISING

Incidence of RA in people with persistently raised RF

A criticism of the study reported in the Annal1 is that age was not taken into account in the evaluation of the probability of development of rheumatoid arthritis (RA) among symptom free subjects with persistently raised rheumatoid factor (RF). The prevalence of RF can be as high as 14.1% in apparently healthy people aged 67–95 (mean age 81).1 RF is also 3.5 times more common in healthy elderly subjects (aged >65) than in their younger counterparts.1 All these factors may alter the natural history of arthritis in elderly patients who have RF either in good health or in a non-arthritic presentation of RA.

The latter is exemplified by a patient admitted at the age of 76 with symptomatic, as well as echocardiographically validated rheumatoid pericarditis in the absence of arthritis. Rheumatoid arthritis latex fixation test (RA LFT) was positive with a titre of 1/160, antinuclear factor (ANF) titre was 1/250, and signs of active inflammatory disease included a platelet count of 750 × 10⁹/l, and an erythrocyte sedimentation rate (ESR) of 98 mm/1st h (Westergren). Arthralgia of the hands and wrists developed for the first time two years later (when she was no longer taking steroids), with a subsequent RA LFT titre of 1/80 and an ANF titre of 1/320 about four months after the onset of arthralgia. Radiography showed narrowing of the joint spaces of the hands 12 months later, but there were as yet no erosions at this stage. Erosions were seen in March 1992, approximately two and a half years after the onset of arthralgia, when the RA LFT titre was 1/160, ANF titre 1/160, platelet count 421 × 10⁹/l, ESR 18 mm/1st h. At her most recent attendance, on 2 February 2000, she was still very active, having continued to receive prednisolone (maximum dose 5 mg/d) continuously since 1989. Her only complaint was a little pain in the left thernal eminence and painful heels. RF was now 768 IU/ml, ANF titre 1/320, platelet count 340 × 10⁹/l, ESR 42 mm/1st h. Antibodies against double stranded DNA had not been reported at any stage.

COMMENT

This case shows a remarkable dissociation between arthritic symptoms and levels of RF, perhaps signifying that when the immune status is altered in old age,1 the relation between RF and the natural history of RA might be less clear than it is in younger people.

Author’s reply

It is certainly well documented that the incidence of rheumatoid factor (RF) increases with age. However, we are not aware of any study of different RF isotypes in this context, but our own unpublished observation indicates that it is mainly IgM RF that tends to increase in symptom free elderly people.

However, increased incidence of raised RF in elderly people is not relevant to the findings that we published recently in the Annal.1 We simply observed increased prevalence and incidence of rheumatoid arthritis (RA) in elderly subjects who had one or more RF isotypes persistently raised, usually IgM and IgA, compared with those with a transient increase in RF or persistent increase in only one RF isotype. There was no significant age difference between these three groups of subjects studied.

Dr Jolobe’s case history simply confirms what has already been often reported previously that an increase of RF often precedes clinical manifestation of RA.1 It would have been interesting to know about the RF isotype pattern of his patient. We have noted that the pulmonary manifestation of RA is strongly associated with raised IgA RF.3

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LETTERS TO THE EDITOR

The HLA-B*2709 subtype in a patient with undifferentiated spondarthropathy

In 1998, in this journal, we reported the cases of two B27 positive patients with undifferentiated spondyloarthropathy (sSpA) and shared spondylitis also affecting the synovial sheaths in the palm of the hand.1 Neither patient had axial disease but showed peripheral manifestations of spondyloarthropathy (SpA), such as peripheral arthritis, peripheral enthesitis, and dactylitis.

Recently, one of our two patients (No 2) was subtyped and typed B*2709 positive. As far as we know this subtype has never been found in patients with SpA.

DNA typing of HLA class I alleles was performed using a DNA sample prepared from peripheral blood lymphocytes by the salting out procedure. The class I ABC SSP UNITRAY low resolution kit (Pel-Freeze) was used. The primer sets amplify all alleles described by the International Nomenclature Committee of WHO in 1995 and in 1997. Polymerase chain reaction amplification with sequence-specific primers (PCR-SSP) was used. A control primer pair was present to verify the integrity of the PCR reaction. Molecular typing of B27 variants was subtyped out by a PCR-SSP technique with a DYNA LHA B27 kit (DYNAL AS, Oslo, Norway), which identifies all the phenotypically different HLA-B27 alleles, B*2701–11, recognised by the HLA Nomenclature Committee in 1973. The typing results for our patients were: HLA-A*0101-02, *3201-02; HLA-B*0801, 2709; HLA-C*0102-03, *0701-07.

To confirm these results HLA B locus sequence based typing was performed. A unique DNA amplification, encompassing exon 1 to intron 3, and four fluorescent sequencing reactions, covering exon 2 and 3, were used. Two intronic amplifiers generated a 1 kb length product useful for direct sequencing. For complete subtyping of the allelic variants PCR-SSP was used. Cycle sequencing reactions allowed the incorporation of four fluorescently labelled dideoxy terminators for detection on a DNA automated sequencer (ABI PRISM 377, Perkin Elmer). Data processing and allele assignment were performed automatically with specific analysis software that compares the sequenced results against a sequence library and provides individual allele assignment for each sequence. The HLA-B class 1 high resolution typing of our sample was HLA-B*0801:2709 in agreement with the low resolution typing performed by PCR-SSP.

SpA has a strong association with the HLA-B27 molecule. Studies in humans and transgenic rodents suggest a direct involvement of HLA-B27 in the pathogenesis of the disease. Thirteen subtypes of HLA-B27 (B*01-13) have been described, differing from each other by one or more amino acid changes, mainly in the peptides recognized by the T cells. Of these B*2701, 02, 03, 04, 05, 07, 08, and 10 are associated with ankylosing spondylitis (AS). B*2711–13 are rare, which has previously been found in patients with SpA.

Recently it has been suggested that the B*2706 might protect against SpA. Recently, a study on families in which both B*2704 and B*2706 might protect against SpA. Recently, a study on families in which both B*2706 and B*2706 occurred has suggested that B*2706, although not associated with SpA, does not protect against SpA.

B*2709 has been found in Sardinia and in continental Italy, where the frequency of HLA-B27 in the general population is around 2%. B*2709 accounts for 25% of HLA-B27 subtypes in Sardinia and 3% in continental Italy.1 D’Amato and coworkers have tested 35 Sardinian patients with AS and 40 Sardinian B27 positive healthy subjects by genomics typing.2 None of the patients with AS were found to be B*2709 positive, in contrast with 25% among the healthy controls. The authors suggested that B*2709 is not
Y chromosome microchimerism in rheumatic autoimmune disease

It is well known that some features of chronic graft-versus-host disease (GVHD) resemble those of other rheumatic autoimmune diseases, such as systemic sclerosis (SSc), Sjögren’s syndrome (SS), and primary biliary cirrhosis (PBC). Furthermore, the development of systemic lupus erythematosus (SLE)-like diseases has been seen in murine models of GVHD. The pathogenesis of rheumatic autoimmune diseases is still unknown. One possibility that has been suggested is that these diseases are associated with pregnancy because of their strong female predilection and, especially in SSc, a peak incidence after parturition. In 1996 Bianchi et al reported that fetal cells could survive in the maternal circulation for up to 27 years after parturition, a phenomenon termed fetal microchimerism. These observations led the hypothesis that persistent fetal cells in the maternal circulation could mediate a graft-versus-host reaction, resulting in autoimmune disease.

Nelson et al have previously carried out a quantitative assay for male DNA in women with SSc and normal women who had delivered at least one son. They indicated that the mean number of male cell DNA equivalents among controls was 0.38 cells/16 ml whole blood and 11.1 among patients with SSc. In addition, Artlett et al have shown Y chromosome-specific sequences in the DNA extracted from peripheral blood in 32 of 69 women with SSc (46%) as compared with 1 of 25 normal women (4%). They also reported that those allo-cells were T lymphocytes and infiltrated lesional skin. These findings support the hypothesis that persistent fetal cells in the maternal circulation may contribute to the pathogenesis of SSc. However, this is still controversial because Murata et al have recently reported that there is no significant difference in the presence of fetal DNA in peripheral blood between Japanese patients with SSc and healthy women with non-quantitative assays. Here we report further studies of fetal microchimerism in SSc, SLE, and SS.

We assayed for a specific Y chromosome sequence in the DNA extracted from peripheral blood by a nested polymerase chain reaction (PCR) in 20 patients with SSc, 21 patients with SLE, 18 patients with SS, and 41 healthy volunteers. All patients and healthy volunteers were Asian-Japanese females that may reflect polyclonal activation of immune cells. Anticentromere antibodies were detected more commonly in the DY1 positive group (eight of 10). All three patients with SSc who had PBC were DY1 positive and had anticientromere antibodies (table 2).

Our data confirm that male DNA is found more commonly in women with SSc than in normal women. Interestingly, DY1 was not detected in patients with SLE and there was no significant difference between patients with SS and healthy volunteers. These data suggest that fetal microchimerism may be a phenomenon which is strongly associated with the pathogenicity of SSc and not with the related autoimmune diseases, SLE and SS.

Table 1 Patients' characteristics

<table>
<thead>
<tr>
<th>SS</th>
<th>SLE</th>
<th>SS</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>21</td>
<td>18</td>
</tr>
</tbody>
</table>

Age (years, mean (range)) 56.1 (44–74) 50.2 (34–82) 54.8 (27–74) 53.2 (39–59)

Duration of illness (years, mean (range)) 10.2 (1–26) 11.9 (1–24) 8.7 (1–19)

DY1 positive (No (%)) 10% (50) 0% (0) 6% (33) 8% (20)

*p=0.017, systemic sclerosis (SSc) v healthy volunteers. †p=0.028, healthy volunteers and systemic lupus erythematosus (SLE). SS = Sjögren's syndrome.

Table 2 Comparison of clinical findings of DY1 positive and negative systemic sclerosis groups

<table>
<thead>
<tr>
<th>DY1</th>
<th>Positive (n=10)</th>
<th>Negative Total (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>*Barnet's type.</td>
<td>I</td>
<td>3</td>
</tr>
<tr>
<td>II</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>III</td>
<td>4</td>
<td>1</td>
</tr>
</tbody>
</table>

Autoantibodies

<table>
<thead>
<tr>
<th></th>
<th>PBC</th>
<th>Anti-nuclear factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>III</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>Topoisomerase I</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

Centromere (PBC*)

<table>
<thead>
<tr>
<th></th>
<th>(3) (3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RNP</td>
<td>4</td>
</tr>
<tr>
<td>ss-A(Re)</td>
<td>2</td>
</tr>
<tr>
<td>SS-B(La)</td>
<td>0</td>
</tr>
<tr>
<td>RA</td>
<td>3</td>
</tr>
<tr>
<td>ssDNA</td>
<td>2</td>
</tr>
<tr>
<td>Mitochondria</td>
<td>0</td>
</tr>
<tr>
<td>Smooth muscle</td>
<td>1</td>
</tr>
</tbody>
</table>

*PBC = primary biliary cirrhosis.
controls and patients with other types of
disease.

patients with disseminated malignant
trols, but with raised concentrations in
receptor (suPAR) which is detectable in
surface bound anchor, forming a free soluble
degradation and remodelling,
enzyme plasmin, which plays a part in tissue
Urokinase plasminogen activator (uPA) ca-
progression in RA

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The study group comprised 11 women and
five men with a median age of 53.5 years
(range 25–80) and a median disease duration
of 57 months (range 5–360). Fifteen patients
were rheumatoid factor positive and 10 had
bony erosions on prestudy radiographs.
Antirheumatic treatment included metho-
trexate (11 patients), hydroxychloroquine
(two), sulfasalazine (one), and low dose ster-
toids (eight). Clinical evaluation and measure-
ments during a 12 month period. The present
was measured and other clinical and para-
variables (two), sulfasalazine (one), and low dose ster-
toids (eight). Clinical evaluation and measure-
ments during a 12 month period. The present
was measured and other clinical and para-
variables (two), sulfasalazine (one), and low dose ster-
toids (eight). Clinical evaluation and measure-
ments during a 12 month period. The present
was measured and other clinical and para-
variables (two), sulfasalazine (one), and low dose ster-

Table 1. Period average values of corresponding paraclinical and clinical variables of 16 patients with rheumatoid arthritis followed up prospectively and subsequently divided into two groups with or
without progressive erosive changes on radiographs. Values are medians with range

<table>
<thead>
<tr>
<th>Erosive progression (n=5)</th>
<th>No erosive progression (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>suPAR (μg/l)</td>
<td>1.51 (0.93–2.73)*</td>
</tr>
<tr>
<td>CRP (mg/l)</td>
<td>11.4 (6.1–30.1)</td>
</tr>
<tr>
<td>ESR (mm/1st h)</td>
<td>24 (15–24)</td>
</tr>
<tr>
<td>Tender joints (of 28)</td>
<td>6 (3–20)</td>
</tr>
<tr>
<td>Swollen joints (of 28)</td>
<td>4 (1–8)</td>
</tr>
</tbody>
</table>

*p<0.05, non-parametric Mann-Whitney test.

Table 1 shows the results of the study. We
found significantly higher suPAR concentra-
tions (p<0.05) in plasma from those patients
with RA whose x ray findings showed disease
progression than in the patients who had no
radiographic signs of progression, but the dif-
fences in ESR, CRP, and clinical variables
were not significantly different.

This study was a pilot study in a clinical
setting and conclusions must be drawn
cautiously. The main problems, apart from
the small number of patients, are, firstly, that
in some of the patients prestudy radiographs
were one to two years old. However, this
would tend to diminish the differences found
between the erosive progressive and non-
erosive progressive groups as patients in remis-
sion, or with low activity in the study
period, could be classified as progressive due
to previous activity. Secondly, another possi-
ble bias, tending to increase the difference in
suPAR between the two groups in this study,
is that patients with high clinical activity
would probably have had more extensive x
ray examinations, increasing the chance of
finding new erosions. We did not, however,
find a difference in the number of radio-
graphically investigated joints between our
two groups of patients.

In conclusion, we find that this study indi-
cates that plasma suPAR may be an easily
accessible plasma marker of erosive progres-
sion in RA, and further studies on the subject
are warranted.

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Matters arising, Letters, Correction

CORRECTION


The Editor of the Annals regrets that we inadvertently published a reply to Dr Barnsley from Drs Ferrari and Russell that contained some misinformation, and offers his apologies to Dr Barnsley.
Possibly, Drs Ferrari and Russell were confusing Dr Barnsley with someone else. Firstly, Dr Barnsley is a man and not a
woman, as they stated. Secondly, Dr Barnsley did not attend the World Whiplash Congress in Vancouver and has not read the transcripts
of it and thus could not be, as Drs Ferrari and Russell commented, “well aware of an impressive study presented there”.
(Note: Corrections print in the journal only appear on the Annals web page (www.annrheumdis.com) and are linked to the
original publication.)