Epidemiology of whiplash

Space restrictions prohibit a comprehensive refutation of the uneven treatment of the whiplash literature presented by Ferrari and Russell. 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 medical injury related damage cannot account for the wide differences.

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. 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 grasped 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 extraneous 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 concluded that whiplash is a behaviour and not an injury.1 A more sober view is that if it is a claim, fewer people will make one. To extrapolate beyond this is unjustifiable: the apparent change in incidence may simply be due to reporting bias.

The study has been used to argue that chronic symptoms after whiplash do not occur in communities lacking a compensation system. However, only 31 patients developed any neck pain as a result of the accident, with none reporting chronic pain. The 95% confidence limits of this estimate range up to 10%. Therefore, the data are consistent with a rate of chronicity of up to 10%. Therefore, the data are consistent with the specific. Indeed, even Schraeder and Russell invoke the studies of Schraeder et al themselves point out that their results cannot be used to extrapolate beyond this. Hence, we can pinpoint a source of pain in the zygapophysial joints.

Conrad NSW 2139, Australia

LES BARNESLEY
Senior Lecturer in Rheumatology,
University of Sydney,
Department of Rheumatology,
Concord Hospital,
Concord NSW 2139,
Australia
Email: lesliz@card.org.nsw.gov.au

5 Schraeder H, Obelieniene D, Bogum B, Sark...
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-
ging. 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 arises among patients who were “nec-
dotal” control group too. Furthermore, in 20 patients in Singapore with acute whiplash, the injury severity or risk of developing long term symptoms was not specified. Methodo-
logical issues: The Ballas publication are reflected by the fact that this study was not considered relevant by the Quebec Task Force and neither were a number of other references in the “leader.” To interpret late whiplash in the light based on articles such as these is in contradiction to a claim of methodological soundness.

The non-existence of whiplash in the United Kingdom while it has been described for more than 30 years USA and UK while it has been described incorrect quoting of previous research, the Ballas publication are reflected by the fact that this study was not considered relevant by the Quebec Task Force and neither were a number of other references in the “leader.” To interpret late whiplash in the light based on articles such as these is in contradiction to a claim of methodological soundness.

The “leader” states that the Swiss study “selectively gathered 117 patients by advertisement”. The truth is that “to obtain a non-selected sample the authors announced the study in the Medical Weekly Journal and repeatedly distributed letters to primary care doctors.” Behind this false reporting is probably the hope that the scientific community will eventually become tired of commenting, which eventually may help them to introduce the malingering hypothesis for whiplash injury.

Bogdan P Radanov
Associate Professor of Psychiatry,
University of Berne, Inselspital,
CH-1010 Berne, Switzerland

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.

R FERRARI
Department of Rheumatic Diseases, 562 Heritage Medical Research Centre University of Alberta Edmonton, Alberta Canada T6G 2S2

A S RUSSELL
Department of Rheumatic Diseases, 562 Heritage Medical Research Centre University of Alberta Edmonton, Alberta Canada T6G 2S2

R FERRARI
12779-50 Street, Edmonton, Alberta, Canada T5A 4L8

ANTHONY S RUSSELL
Department of Rheumatic Diseases, 562 Heritage Medical Research Centre, University of Alberta, Edmonton, Alberta Canada T6G 2S2


R FERRARI
12779-50 Street, Edmonton, Alberta, Canada T5A 4L8

ANTHONY S RUSSELL
Department of Rheumatic Diseases, University Hospital Aintree, Longmoor Lane Liverpool L9 7AL, UK

Authors’ reply to Dr Radanov
Dr Radanov’s expressed concerns and cry for auto-da-fé are based on his perception that our biopsychosocial model is one of malinger ing as an explanation for the late whiplash syndrome. As we have explicitly stated, in both our current article and in a thorough 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 how 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 malingering 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.

R FERRARI
12779-50 Street, Edmonton, Alberta, Canada T6G 2S2

ANTHONY S RUSSELL
Department of Rheumatic Diseases, University Hospital Aintree, Longmoor Lane Liverpool L9 7AL, UK

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 non-smokers. 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 effects would 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 significant 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 interventions 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.

D HUTCHINSON
R J MOOTS
Department of Rheumaticology, University Hospital Aintree, Longmoor Lane Liverpool L9 7AL, UK

Table 1

<table>
<thead>
<tr>
<th>Social class</th>
<th>Social class</th>
<th>Social class</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–2</td>
<td>3–5</td>
<td>6–10</td>
</tr>
<tr>
<td>N</td>
<td>n(M:F)</td>
<td>n(M:F)</td>
</tr>
<tr>
<td><strong>RA cases Merseyside (239)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>51 (33)</td>
<td>73 (47)</td>
<td>30 (19)</td>
</tr>
<tr>
<td>28 (12*)</td>
<td>87 (36**)</td>
<td>124 (52*)</td>
</tr>
</tbody>
</table>

*p<0.00001; **p<0.05.
†Social class based on the Office of National Statistics classification of occupations.
‡N = non-manual; M = manual.
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 asking 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 than in 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 overly from our study. Prospective assessment of the proportion of patients in areas of affluence and deprivation would prove valuable in determining the epidemiology of RA.

Our data show that 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 4 respectively. This discrepancy 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 across social groups 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 readily 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 according to social class in other important determinants of health, including diet, alcohol consumption, obesity, hypertension, lung function, fibrinogen levels, general health perception, and poorer educational status. 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, the 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.

References


4 Pincus T, Callahan LF, Burkhauser RV. Most chronic diseases are reported more frequently by individuals with fewer than 12 years of formal education in the age 18–64 United States population. J Chronic Dis 1987;40:865–74.


Diagnostic evaluation of classification criteria for RA and reactive arthritis

We read with interest the recent article by Hülsemann and Ziedler, in 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 were compared was 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 applying the criteria to 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 categorising 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 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 some 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 that 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 traditional “list” format, the positive predictive value for erosions was only 45% and the negative predictive value 67%. In practical terms, this means that when we applied the criteria to a new group of patients we were informed by their knowledge of the disease modifying antirheumatic drugs. Further difficulties are likely to be encountered using the criteria as ascertainment 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 Ziedler 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 Ziedler 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 in this setting. 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 about whether to treat aggressively patients presenting with early disease.

Beverley Harrison
Alan Silman
Deborah Symmons
ARC Epidemiology Unit, St Jude’s Building, Oxford Rd, Manchester M13 9PT, UK

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 doctors 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 synovitis outpatient clinic between 1984 and 1986, the 1958 American Rheumatism Association (ARA) criteria had not been revised. Expert diagnoses were made with knowledge of the 1958 ARA criteria for rheumatoid arthritis and a complete reliance on imaging and laboratory 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 (and 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 50% 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 and which is postulated to alter this function (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.

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 any fusion is due to a complete absence 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 CD4 and a cell lineage marker such as CD68 has been 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.

MALCOLM SMITH
Division of Medicine, Repatriation General Hospital, Daw Park, South Australia 5041, Australia

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

An interesting paper was published recently in the domain of rheumatology disease 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 inflammatory response.

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 synovitis, 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 this 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 up to follow up at 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.

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.


1


Authors’ reply

We thank Professor Smith for his interesting comments. Professor Smith refers to an “obvious omission...any doctor or patient derived clinical parameters”. Clearly, we had measured the knee circumference of the target knee in this situation and we were using knee swelling as a clinical parameter; in table 1 of our paper it can be seen that there was no significant change in the knee circumference in any of the treatment or placebo groups during the study. Although we did not show the data in the results section, we stated that there was no statistically significant improvement in the doctor’s assessment of knee synovitis over the study period. Therefore, we do not suggest that there was a marked clinical response to treatment in these patients. We agree that there was a marked disparity in the baseline CRP levels within the three groups, but this was a result of randomisation and therefore something over which we had no control.

As regards the changes in MRI measurements, and the quantitative maps showing the reduction in gadolinium uptake, we believe that the trend towards the dose response across the three groups was clearly the most important interpretation of these results. We do not agree, however, with the reader’s interpretation that a possible range of change of 25% is small, especially as the patients had longstanding, resistant disease. The mean duration of disease for these patients was about 12 years and they had undergone multiple treatments with disease modifying antirheumatic drugs.

Professor Smith’s final point about anti-CD3 antibodies, which label macrophages as well as T cells, we clearly discussed in the third paragraph of the discussion—“There are a number of possible explanations for this apparent reduction in the number of CD4+ cells, which may represent a reduction in the T cells or macrophages...”

In summary, we believe that this was an important study, firstly, as a proof of concept approach for therapeutic studies in rheumatoid arthritis, and secondly, as a unique combination of imaging techniques, using arthroscopy, magnetic resonance imaging, and histology, enabling a direct comparison of these techniques.

P EMERY
School of Medicine, Rheumatology and Rehabilitation Research Unit, University of Leeds, 36 Clarendon Road, Leeds LS2 9NZ, UK
Email: p.emery@leeds.ac.uk

LETTERS TO THE EDITOR

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. 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.

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 seropositive active rheumatoid arthritis, four patients had seronegative spondyloarthritids (two reactive arthritis, one psoriatic arthritis, one enteropathic arthritis) 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 cytospin centrifuge 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 monocoyte 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 at 3 times). The slides were examined at 400× magnification.

Omission of primary antiserum, use of normal rabbit serum, or one of subsequent steps in the staining method were 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 spondyloarthritids 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 extreme phagocyte into a professional one. It has been hypothesised that deregulation 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. 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, 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. 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>
</thead>
<tbody>
<tr>
<td>RA (n=3)</td>
<td>1 1</td>
</tr>
<tr>
<td>2 1</td>
<td></td>
</tr>
<tr>
<td>3 1</td>
<td></td>
</tr>
<tr>
<td>SaA (n=4)</td>
<td>1 3</td>
</tr>
<tr>
<td>2 2</td>
<td></td>
</tr>
<tr>
<td>3 5</td>
<td></td>
</tr>
<tr>
<td>CIA (n=3)</td>
<td>1 4</td>
</tr>
<tr>
<td>3 3</td>
<td></td>
</tr>
</tbody>
</table>

RA: rheumatoid arthritis, SaA: seronegative spondyloarthritids, CIA: crystal induced arthritis.

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

Familial Mediterranean fever (FMF) is a hereditary condition characterised by recurrent bouts of fever, polyarthritis, serositis, peritonitis, and pleurisy which can cause severe disability. FMF is an autoinflammatory disease that affects people of Mediterranean ancestry. The disease is caused by mutations in the pyrin gene, which results in a deficiency of the natural inhibitor of inflammatory pathways, allowing for chronic inflammation.

### 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.