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 kinetic injury related to damage 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.4

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 comparisons5 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.6 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 external to the injury itself. The Victorian experience in Australia is particularly pertinent. Fewer claims for whiplash were noted after the introduction of legislation treating bureaucratic barriers, disincentives, and upfront costs for potential claimants. Some then concluded that whiplash is a behaviour and not an injury.7 A more sober view is that if it is in fact 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 compensatory system.8 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 a rate of chronicity of up to 10%. The German and later Lithuanian studies, on which Ferrari and Russell rely, also lack the power to detect a rate of chronicity of up to 10%. Therefore, the data are consistent with a rate of chronicity of up to 10%. Therefore, the data are consistent with a rate of chronicity of up to 10%. Therefore, the data are consistent with a rate of chronicity of up to 10%. Therefore, the data are consistent with a rate of chronicity of up to 10%. Therefore, the data are consistent with a rate of chronicity of up to 10%. Therefore, the data are consistent with a rate of chronicity of up to 10%.

Magnetic resonance imaging (MRI) is insensitive to abnormalities of the soft tissue components of the cervical zygapophysial joint.9 Consequently, studies of patients with whiplash who have normal MRIs cannot exclude important injury. Furthermore, both ultrasound10 and bone scan studies have shown potentially painful pathology.11 In considering our studies of chronic zygapophysial joint pain after whiplash, Ferrari and Russell argue that our patients were unrepresentative. However, most of our patients developed pain within 72 hours of the accident and were passengers or drivers of motor vehicles.1 They were intentionally representative of typical patients with chronic whiplash. Radanov’s work is criticised on the basis that they “selectively gathered 117 patients through advertisement”. This would imply that patients answered advertisements for whiplash, producing a biased sample. However, the advertisement was in a medical journal, seeking doctors to enrol participants, producing a representative sample. Concurrently, Ferrari and Russell have used these studies in a previous article, apparently accepting the methodology then.12 These flaws alone raise grounds for concern that the opinions of Ferrari and Russell are not responsible enough for an appraisal of the literature and will raise alarm and reinforce prejudice against genuinely afflicted patients.

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Through their leader, Ferrari and Russell venture to raisealarm about whiplash, repeating the same arguments that they have already raised in two previous editorials and a letter to the editor. But their alarm is overstated and misplaced.

Acute whiplash is not a problem. Even the studies of Radanov et al show that only some 5% of patients have severe symptoms at 12 months.13 Meanwhile, the study of Borchgrevink et al shows that more than 5% of patients can be adequately treated simply by advising them to act as usual. If there is any psycho-social problem with acute whiplash, it is on the part of doctors and therapists who overmedicate to prove that chronic whiplash does not occur. However, they cannot argue from the general to the specific. Indeed, even Schraeder et al themselves point out that their results cannot be used to argue that chronic pain resulted from the whiplash.14 Ferrari and Russell argue that there is no persisting lesion, and that psychological and social factors totally explain the chronic complaints of these patients. They then criticise the work of Radanov, by claiming that it is “fraught with at least 15 significant methodological flaws”. They do not even enumerate these flaws but instead cite four references, thereby relying on sophistry to seduce their readers. If these references are consulted, the last three offer no criticism of Radanov. Only the first, a letter, offers criticism, but cleverly Ferrari and Russell do not inform the reader of Radanov’s rebuttal of these criticisms.15

Yet even if we accept that psychosocial factors are important in these patients, Ferrari and Russell do not provide an answer as to what to do about them. They cite van Akkervegden and Veldrij, 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 accordingly 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 AV30kph and AV60kph collisions, which are what many of our patients underwent.

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References

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 malingered. 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 a ‘non-eloquent’ 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. Methodological flaws of 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 as based on the ‘false’ 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 many years in USA is discussed in Miller's 1961 BMJ article, which reports 200 cases examined between 1955 and 1957. This is well within the time frame of the 1953 JAMA whiplash paper. Miller reported an inverse relation between accident neurosis and the severity of injury and emphasised that the occurrence of "psychoneurosis in patients who were never unconscious was 42%". Reporting on patients who were never unconscious in a concussion series reflects the problems of definition. What was described as whiplash in North America at that time was probably described as concussion in Britain. Statements in defining concussion have been discussed previously. These differences in terminology may be explained by the mechanism of concussion and whiplash, which are acceleration-deceleration of the head. In addition, symptoms of concussion and whiplash are almost identical. Accordingly, an individual who sustained acceleration-deceleration of the head without loss of consciousness probably has whiplash.

Previously, neck pain in the general population has been reported to vary between 14% in Norway and 33% in Lithuania. These variations were interpreted as ‘due to sociocultural factors.’ Differences in questionnaire figures are considerably lower than in the Lithuanian studies. Accordingly, the method of assessment in the Lithuanian studies or reporting of the data may have had the effect. The influence of psychosocial factors, which are secondary to the initial consequences of whiplash (that is, pain), on the further development or increase in symptoms has never been questioned. The ‘significant methodological flaws or sources of bias’ of the Swiss study quoted in the ‘leader’ represent an unwillingness of Ferrari and Russell to analyse in detail results from previous research while continuing to promote their own perspective. In addition, the ‘leader’ emphasised that methodologically improved studies showed ‘that the current state of reporting ... is best predicted by non-related accident stressors’. The study quoted in the leader used a biased selection of 39 patients, which was three times fewer than the Oregon state study. The ‘leader’ emphasised the Swiss study ‘selectively gathered 117 patients by advertising’. 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 malingerer hypothesis for whiplash injury.

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Authors’ reply to Drs Barnsley and Bogduk

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 in practice. We do not think that chronic pain is all in the mind, nor all in the body. 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. It is 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 prevalences 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 with chronic pain at six months14 that we are concerned with, and the cervical zygapophysial studies are not relevant for this larger group. Indeed, we were not aware that the subjects of Dr Bogduk’s studies had undergone such high velocity impacts (a AV of 30–60 kph) 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 joint 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, and understood by, the therapeutic community and society at
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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*Sentence of the Inquisition—burning of the heretic.

Rheumatoid arthritis, poverty and smoking

Maiden et al raise a number of important and interesting points in their paper.1 Does social disadvantage contribute to the excess mortality in rheumatoid arthritis patients?2

They have observed that mortality in rheumatoid arthritis (RA) correlates with social disadvantage. 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.1 Cigarette smoking kills 120 000 people a year in Britain.1 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 and increases morbidity in late middle age. Cigarette smoking is associated with an increased risk of RA in both men and women.1 The increased mortality seen in patients with RA of low socioeconomic status could be explained by part 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 is likely to 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.1 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 survival 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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Table 1

<table>
<thead>
<tr>
<th>Social class</th>
<th>RA cases Merseyside (239)</th>
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<tr>
<td>1 – 2N o (%)</td>
<td>51 (33)</td>
</tr>
<tr>
<td>3N – 4M o (%)</td>
<td>73 (47)</td>
</tr>
<tr>
<td>5 – 7 (%)</td>
<td>30 (19)</td>
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1 *Social class based on the Office of National Statistics classification of occupations.
2 †Social class based on the O

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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 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 overtly from our study. Previous studies demonstrate the importance of ecological factors in areas of affluence and deprivation would prove valuable in determining the epidemiology of RA.

A recent cohort 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 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 difference of deprivation would suggest that even in RA is less commonly 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 pain in general. 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.

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 Zeidler, 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 the study, the “gold standard” against which the criteria are compared is 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 facing the rheumatologist 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 diagnosis were informed by their knowledge of the individual components of the criteria. Therefore, the high sensitivity (90%) they reported means that most of the patients with a clinical diagnosis of RA will have had seropositive, erosive, polyarticular 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 anti-rheumatic 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 aggressiveness 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 in 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 in a group of patients who did not satisfy the criteria developed erosions. However, given that the 1987 ACR criteria were developed to distinguish between hospital attenders with established RA and patients with early disease, further 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 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 the 1987 ACR 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 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 as to whether to treat aggressively patients presenting with early disease.

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Early arthritis clinic, that early diagnosis of RA Horst-Bruinsma et al had developed ankylosing spondylitis. Serogressive unclassified arthritis, and one patient tial remission, eight had unchanged or pro- showed complete remission, two showed par- The 1987 ACR criteria are not valid for prognostic purposes as Horst et al stated. Other prognostic factors exist and can easily be applied to patients with RA. But the ACR criteria for RA differ from the important means of helping family doctors and general practitioners not trained in rheumatology to make a diagnosis of RA and to differentiate between RA and other forms of arthritis as soon as possible in the course of the disease. Thus by early referral to a rheumatologist an adequate treatment can be started as soon as possible. Even rheumatologists, who are familiar with the criteria used in all controlled trials to establish therapeutic guidelines, are, 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 treat-ment decisions.

Authors’ reply

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

We have described the incidence of undifferen-tiated arthritis to be as high as 54%1. When patients were seen in this early synovi-tis 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 the diagnosis of RA but were not the basis of diagnoses. Trained as clinicians, rheumatologists never used the ACR criteria for diagnosis making. Only in retrospect, were the 1987 revised ACR cri- teria applied. These criteria are for classification of RA. The intention was to investigate the performance of these criteria in early synovitis with a high proportion of un differ-en-tiated and reactive arthritides. Since the performance was good with a high sensitivity (90%) and a high specificity (90%), we suggested, that these criteria could be used not only as classification criteria but also as criteria for the diagnosis of RA.

Criteria should be applied longitudinally at follow up, rather than simply at baseline. We applied criteria cross sectionally on the day of their first visit. We can not present follow up data on the whole group, but of a subgroup of 28 patients with undifferentiated arthritis. Only two of these patients developed rheu-matoid factor negative RA, 15 patients showed complete remission, two showed par-tial remission and had unchallenged progres-sive unclassified arthritis, and one patient had developed ankylosing spondylitis.

In accordance with our experience, van der Horst-Bruinsma et al have shown, in a special early arthritis clinic, that early diagnosis of RA is possible and reliable.2 Compared with rou-tine patient care, of 74 patients with definite RA according to the 1987 ACR criteria, diagnos-d at two weeks after the first visit, 66 still had definite RA after one year, and in only one four patients was the diagnosis changed to systemic lupus erythematosus (one), undi- differentiated arthritis (one), gout (one), and probable RA (one). Two patients had died and two were lost to follow up. This shows, that the validity is high for the 1987 ACR criteria for differentiating between RA and non-RA arthritides in an early synovitis clinic.

We do not imply that patients who do not fulf 1987 ARA criteria do not have RA. If they do not fulfill the criteria at this early stage, we classify them as undifferentiated arthritides. This is a working diagnosis, which can be changed to a definite diagnosis during follow up, but is only rarely necessary, as our experienced rheumatologists show.

The 1987 ACR criteria are not valid for prognostic purposes as Horst et al stated. Other prognostic factors exist and can easily be applied to patients with RA. But the ACR criteria for RA differ from the important means of helping family doctors and general practitioners not trained in rheumatology to make a diagnosis of RA and to differentiate between RA and other forms of arthritis as soon as possible in the course of the disease. Thus by early referral to a rheumatologist an adequate treatment can be started as soon as possible. Even rheumatologists, who are familiar with the criteria used in all controlled trials to establish therapeutic guidelines, are, 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 treat-ment decisions.

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

An interesting paper was published recently in the domain of therapy resistance. Dunlop 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 sup-posed pivotal role of CD4 positive T cells in the chronic synovitis therapy response. The paper showed an apparent improve-ment 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 synovium, and immunohisto-chemical labelling of the synovial biopsy specimens.

An obvious omission from this paper was any doctor or patient derived clinical param-eters 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 doses and all seven receiving high dose had not required any further local injection treatment at follow up for 18 months. It is curious that no clinical parameters were measured in this study, with a complete reliance on imaging and labora-tory procedures to measure outcome, which leads me to speculate that there might have been no discernible clinical difference be-tween the treatment groups, as assessed by the patient or doctor.

Also, there was a marked disparity in base-line C reactive protein (CRP) levels between the three treatment groups, with the placebo treatment group having far (on average) a far lower (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 15% 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 typically 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 syno-vial membrane with anti-CD4 antibodies will label CD4 positive T cells and macrophages (which also express CD4), so the authors cannot estimate whether the reduced CD4 staining in the synovial biopsy speci mens as a result of treatment is due to a decrease in T cells, macrophages, or both, unless dual immunohistochemical labelling for CD4 and a cell lineage marker (e.g., CD68, 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.
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 clear and the mean duration of the 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 T cells or macrophages...”

In summary, we believe that this was an important study, firstly, as a proof of concept approach for therapeutics 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.

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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.1 Of interest, their role in the process of adhesion and phagocytosis of apoptotic cells has been recently demonstrated.2

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.3

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 spondyloarthropathy (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-Grunwald-Giemsa (MGG) reagent. Reiter cells were counted on the basis of the first 500 cells encountered on MGG stained slides. In addition, two cytcentrifuge 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 monocye CD14 antibody (DAKO-Denmark) diluted 1:10 in TRIS-HCL 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 monolayers 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 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 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.5 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.6 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 CD14.8 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-Grüновald-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</td>
</tr>
<tr>
<td></td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>SsA (n=4)</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>2</td>
</tr>
<tr>
<td>CIA (n=3)</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>3</td>
</tr>
</tbody>
</table>

RA: rheumatoid arthritis, SsA: seronegative spondyloarthropathy, CIA: crystal induced arthritis.
a process leading to cell clearance. However, as CD14 and CD36 are known to play a part in different biological processes, the demonstration of these multifunctional adhesion molecules on Reiter cells is not a definitive evidence concerning their role for apoptotic cell clearance in the synovial fluid. Additional functional investigations are required to establish the exact role of CD14 and CD36 in the clearance of the PMN in synovial effusions.

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### 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.