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 preconceptions. Central to their argument is the assertion that there are different rates of chronic whiplash in different countries, and that the 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 recognised 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, treating 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 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 compensation system.2 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%. The German and later Lithuanian studies, on which Ferrari and Russell rely, also lack the power to detect a significant chronicity rate.

Magnetic resonance imaging (MRI) is insensitive to abnormalities of the soft tissue components of the cervical zygapophysial joint.3 Consequently, studies of patients with whiplash who have normal MRIs cannot exclude important injury. Furthermore, both ultrasound4 and bone scan studies have shown potentially painful pathology.5 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.9 They were intentionally representative and typical of 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 about 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 paper, apparently accepting the methodological criticisms.7 These flaws alone raise grounds for concern that the opinions of Ferrari and Russell are not responsibly based. 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’s venture to raise alarm 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.9 Most 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 overmedicalise the problem by emphasising the complaint. However, even so, some 10–20% of patients remained symptomatic at 6 months.7 Two questions arise: why are these patients symptomatic, and what should be done? The approach that has been to investigate these patients for a possible source of pain. Under stringent, double-blind, controlled conditions, we have found that we can pinpoint a source of pain in the zygapophysial joints in some 50% of these patients. Moreover, by surgical treatment we can relieve their pain and their psychological distress and return them to normal life.

These patients may not be typical of acute patients, but they are quite typical of chronic patients. Ferrari and Russell9 contend that zygapophysial joint pain must be rare. Indeed, it is, for it accounts for only half of 5–10% of the original population; but it accounts for 50% of the chronic population. Elsewhere, Ferrari and Russell deny that persistent symptoms can be attributed to the original whiplash, but this is a legal matter, not a medical one. There are no medical tests by which to falsify an imputation. Ferrari and Russell invoke the studies of Schraeder et al 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 refute individual claims that their chronic pain resulted from the whiplash.9

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 fiercely interrogate research that criticise the work of Radanov, by claiming that it is “fraught with at least 15 significant methodological flaws”. They do not enumerate these flaws but instead cite four references, therefore relying on sophist and maybe even on 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.8

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. Simply, they cite van Akkerkveven and Vredin,9 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 subsequently accordingly guarded overestimating its 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 insignificant, perhaps they might organise some volunteers to undergo a series of AV30 khp and AV60 khp collisions, which are what many of our patients underwent.
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 arising from the “leader’s” 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 syndrome based on articles such as the cervical whiplash syndrome study. The “leader” emphasized 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 Swiss Medical Weekly Journal and repeatedly distributed letters to primary care doctors.” Beyond this false reporting is probably the hope that the scientific community will eventually become tired of commenting, which eventually will let them introduce the malinger 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 try- ing to blur and indeed do away with for vari- ous reasons, most notably that dualistic approaches have been largely unhelpful to the understanding the behaviour that promotes chronic pain. The “leader” comments 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 admission of anecdotal reports from Australian rheuma- tologists, nor with the evidence from Lithuania (she does not quote the subse- quent prospective study), Germany, and Greece. Dr Barnsley is also invited to read the impressive study presented at the World Whiplash Congress in Vancouver which sug- gests that changing the claim scheme has dramatic effects on recovery rates, as indi- cated by various patients.

Both Drs Barnsley and Bogduk have missed the key message in the epidemiologi- cal 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 say, Canada. We find that whiplash in Canada (and reportedly in many other countries) is a major public health and eco- nomic 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 nec- essary to understand why some subjects recover within six weeks or fewer and others do not. As no one has suggested that Lithua- nians, Greeks, and Germans have a different anatomy, Dr Barnsley and Bogduk agree, once again, that over- treatment and medicalisation are likely to be 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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6 Cassidy JD, Carroll L, Lemstra M, Cote P, Berthiaume T. Rehabilitation of the industrial worker. Class and society, and dichotomous approaches taken by 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- ing 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 Swit-zerland. 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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*Literature is available. We thus refer him to a more comprehensive resource.

**P<0.00001; ***P<0.05.

Table 1

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Inflammatory polyarthritis cases Norfolk and Norwich’ (154) 51 (33) 73 (47) 30 (19)
RA cases Merseyside (239) 28 (12) 87 (36)** 124 (52)***

*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 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 areas of lower socioeconomic status. 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 overtly from our study. Furthermore, the presence of infection cohorts in areas of affluence and deprivation would prove valuable in determining the epidemiology of RA.

In our study, 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 influence of deprivation in 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 according to social class in other important determinants of health, including diet, alcohol consumption, obesity, hypertension, lung function, fibrinogen levels, general health perception, and psychological state. 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.

Diagnostic evaluation of classification criteria for RA and reactive arthritis

We read with interest the recent article by Hülsemann and Zeidler regarding 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 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 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 interesting to note that the diagnoses were inferred 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, polycarticular 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 (nodules, 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 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 the trained observer could 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 the criteria as 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 on whether to treat aggressively patients presenting with early disease.

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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 arthritides 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 arthritides as being at least as high as 54%.1 When patients were seen in this early synovitis outpatient clinic between 1984 and 1986, the 1985 American Rheumatism Association (ARA) criteria had not been revised. Expert diagnoses were made with knowledge of the 1985 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 criteria applied. These criteria for classification of RA. The intention was to investigate the performance of these criteria in early synovitis with a high proportion of undifferentiated 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.1 Only two of these patients developed rheumatoid factor negative RA, 15 patients showed complete remission, two showed partial remission, four had unchanged progressive unclassified arthritis, and one patient had developed ankylosing spondylitis.

In accordance with our experience, van der Horst-Bruinisma et al have shown, in a special early arthritis clinic, that early diagnosis of RA is possible and reliable.2 Compared with routine patient care, of 74 patients with definite RA according to the 1987 ACR criteria, diagnosis at two weeks after the first visit, 66 still had definite RA after one year, and in only one of four patients was the diagnosis changed to systemic lupus erythematosus (one), unclassified 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 fulfil the 1987 ARA criteria do not have RA. If they do not fulfil the criteria at this early stage, we classify them as having undifferentiated arthritis. This is a working diagnosis, which can be changed to a definite diagnosis during follow up, but is only rarely necessary, as our experience and that of others show. The 1987 ACR criteria are not valid for prognostic purposes as Harrison et al stated.3 Other prognostic factors exist and can easily be applied to patients with RA.4 But the ACR criteria for RA are still very 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 treatment 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 treatment decisions.

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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. This 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 synovitis and disease activity 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 synovia, 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 after 18 months. It was 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 CRP (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 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. This is consistent 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 anti-CD4 immunisation achieved 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 is 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.

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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 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-CD8 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 therapeutic studies in rheumatoid arthritis, three patients had sero-positive active rheumatoid arthritis, four patients had seronegative spondyloarthritis (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 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-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 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 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. 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. 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

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 sero-positive active rheumatoid arthritis, four patients had seronegative spondyloarthritides and 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-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 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 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. 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. 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
Non-periodic leg pain in patients with familial Mediterranean fever

Familial Mediterranean fever (FMF) is a chronic inflammatory disease that predominantly affects the Mediterranean Basin. It is characterized by recurrent attacks of fever, polyarthritis, peritonitis, pleuritis, arthropathy, and pericarditis. The symptoms are usually self-limiting, and the disease is often associated with mild to moderate disability.

The pathogenesis of FMF is not fully understood, but it is believed to be caused by a mutation in the pyrin gene (MIP). The mutation leads to the accumulation of pyrin, a protein that regulates the activity of the NLRP3 inflammasome. This results in the activation of the inflammasome, leading to the production of mature interleukin-1β (IL-1β), which can cause inflammation.

Patients with FMF experience periodic attacks of fever, usually accompanied by other symptoms such as polyarthritis, peritonitis, pleuritis, and pericarditis. These attacks are usually preceded by a prodromal phase, characterized by symptoms such as malaise, fatigue, and myalgia.

The hallmark of FMF is the sudden onset of fever, often accompanied by abdominal pain, and fever lasting for several days. The fever usually resolves spontaneously, but it can recur several times a year. The episodes are often triggered by stress, infection, or other factors, such as changes in temperature, humidity, or diet.

The management of FMF is typically centered around the prevention of attacks and the treatment of complications. The treatment options include non-steroidal anti-inflammatory drugs (NSAIDs), colchicine, and corticosteroids. Colchicine is the first-line treatment for FMF, and it is effective in preventing attacks and reducing the duration and severity of the attacks.

In addition to the standard treatment, researchers are investigating the role of other treatments, such as biologics, anti-inflammatory agents, and immunosuppressants. These treatments are being explored in clinical trials to determine their efficacy in managing FMF.

Despite the advances in treatment, FMF remains a significant public health issue in the Mediterranean region. The disease affects millions of people, and it can have long-term complications, such as damage to the kidneys, eyes, and joints. Therefore, early diagnosis and prompt treatment are crucial in managing FMF and minimizing the risk of complications.

In conclusion, FMF is a chronic inflammatory disease that is characterized by recurrent attacks of fever, polyarthritis, peritonitis, pleuritis, arthropathy, and pericarditis. The disease is often associated with mild to moderate disability, and it is believed to be caused by a mutation in the pyrin gene. The management of FMF is typically centered around the prevention of attacks and the treatment of complications. The treatment options include non-steroidal anti-inflammatory drugs (NSAIDs), colchicine, and corticosteroids. Colchicine is the first-line treatment for FMF, and it is effective in preventing attacks and reducing the duration and severity of the attacks.

Non-periodic leg pain in patients with familial Mediterranean fever

Familial Mediterranean fever (FMF) is charac-terized by recurrent bouts of fever and peritonitis, pleuritis, arthritis or erysipelas-like skin disease. Between the episodes, FMF patients are free of symptoms and appear healthy. However, interestingly we observe leg complaints after prolonged standing or sitting, or both, in FMF patients, who usually experience these painful manifestations during standing or after long distance bus trips.

Although several mechanisms have been proposed 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, and episodes may be prevented by prazosin hydrochloride, as reported recently.

Leucocytes may need adequate perfusion (driving) pressure to pass through capillaries in microcirculation. 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 process is involved in developing lower extremities pain 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 compen-sate the inflammatory reaction that is prob-ably initiated in a stressful microenvironment caused by not only microtrauma, but also increased hydrostatic pressure.

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Table 1 Questionnaire on lower extremity complaints

A Have you ever had foot or leg pain events after prolonged standing and/or bus travel lasted more than six hours?
B Has it been existed since childhood or adolescence?
C Does it occur after prolonged periods of standing or sitting?
D Does it occur mostly bilateral?
E Does it persist at least 30 minutes after rest?
F All of the answers are yes, then the case was considered to be positive.


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.
CD36 and CD14 immunoreactivity of Reiter cells in inflammatory synovial fluids

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