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 dynamic 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.2 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 considered by Ferrari and Russell.3 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.4 A more sober view is that if it is a behaviour, then 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 Ferrari and Russell 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 harder to make a claim, fewer people will not engage in the cervical zygapophysial joint pain after whiplash, Ferrari and Russell have used these studies in a previous article, apparently accepting the methodology then.6 These flaws alone raise grounds for concern that the opinions of Ferrari and Russell are not responsible appraisal of the literature and will raise alarm and reinforce prejudice against genuinely afflicted patients.

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Through their leader, Ferrari and Russell2 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.2 show that only some 5% of patients have severe symptoms at 12 months.1 Meanwhile, the study of Borchgrevink et al.5 is a benchmark.2 Most patients can be adequately treated simply by advising them to act as usual. If there is any psychological problem with acute whiplash, it is on the part of doctors and therapists who overmedicalise this problem. Ferrari and Russell argue that there is no persistence and that psychological and social factors totally explain the chronic complaints of these patients. They fiercely interrogate research on whiplash that does not 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 determine the psychological or medical one. There are no medical tests by which to falsify an imputation. Ferrari and Russell invoke the studies of Schraeder, van Akkerveeken and Vendrig,2 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 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 insignificant, perhaps they should organise some volunteers to undergo a series of AV 300 kph and AV60 kph collisions, which are what many of their patients underwent.

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Making selective use of the literature and incorrect quoting of previous research, the January 1999 "leader" intends to support the view of the whiplash syndrome as 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 among participants was likely a "nondetal)" 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 publications are reflected in 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 "whiplash" 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 in discussions in Miller's 1961 BMJ article, which reports 200 cases examined between 1955 and 1957. This is well within the time frame of the 1953-1957 "leader". 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 Europe; the problems in defining concussion might have been biased.

Accordingly, the method of assessment in the "leader" represents 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 symptom reporting ... is best predicted by non-accident related stressors". The study quoted in the leader used a biased selection of 39 patients, which was three times fewer than the cervical whiplash syndrome study. The "leader" emphasised 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 will introduce the malingered 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 unethical and of little use. We do not believe 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 admission by both experts of anecdotal reports from Australian rheumatologists, nor with the evidence from Lithuania (she does not quote the subsequent prospective study), Germany,1 and Greece. Dr Barnsley seeks to adduce the impressive study presented at the World Whiplash Congress in Vancouver which suggests that changing the claim scheme has dramatic effects on recovery rates, as indicated by various outstanding authors.

Both Drs Barnsley and Bogduk have missed the key message in the epidemiologic 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 billing of economic burden, with more than 50% of accident victims reporting chronic pain six months after the accident. The patients of Dr Bogduk's study represent merely the tip of a large iceberg. Thus new paradigms are necessary to understand why some subjects recover within six weeks or fewer and others do not. As no one has suggested that Lithuanians, Greeks, and Germans have a different anatomy, we need to look for an explanation for this difference in recovery rates. It is certainly possible that a small proportion of subjects could have chronic structural damage in countries like Lithuania, as Dr Bogduk suggests, and that current studies with background 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 months1 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 were examined with high velocity impacts (a V 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 research on 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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Authors’ reply to Dr Radanov

Dr Radanov’s expressed concerns and cry for auto-da-fé are based on their perception that our biopsychosocial model is one of malingerin as an explanation for the late whiplash syndrome. As we have explicitly stated, in both our article and in a previous review on this topic, we reject a model based on malingering and we consider this to be a rare or uncommon presentation. Dr Radanov’s concerns are therefore misplaced. That Dr Radanov is unable to appreciate 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 malingerin 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 foothold in a much longer journey of investigation.

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Table 1

<table>
<thead>
<tr>
<th>Social class</th>
<th>Social class</th>
<th>Social class</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-2N</td>
<td>3N-M</td>
<td>4-5N</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 (42*)</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.

R Ferrari


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

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Matters arising, Letters, Correction


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?”1 The importance of smoking 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.2

We observed a higher mortality rate among patients with rheumatoid arthritis (RA) living in deprived areas relative to those living in affluent areas. In our methodology we 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.3 4 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 over from our study. People living in areas of infection cures in areas of affluence and deprivation would prove valuable in determining the epidemiology of RA.

RA occurred in 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 amongst hospital attenders with RA according to socioeconomic deprivation can be explained, in part, by differences in the prevalence of smoking, the observed influence of deprivation on mortality in RA is less easily accounted for by smoking.1 Functional ability is an important outcome measure in RA and is a predictor of mortality in this disease.2

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 physical activity. Further research is required to establish the relative importance of these and other factors in determining the influence of socioeconomic deprivation on outcome and mortality in RA and other chronic diseases.3 4 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, 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 the classification of RA which may still require treatment with conventional RA which may still require treatment with conventional anti-rheumatic drugs. Although we applied the criteria in a number of different ways, we found they had a low ability to discriminate between patients who did have established RA 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 33% of individuals were falsely identified as having RA whereas patients who did not satisfy the criteria developed erosions. However, given the fact that the 1987 ACR criteria were developed to distinguish between hospital attenders with established RA and patients with the often benign and self-limiting forms of undifferentiated arthritis, 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 varies from complete symptom remission to 61% if applied “cumulatively” (on the day of assessment) to 61% if applied “retrospectively” (each criterion satisfied if “ever” positive). Further difficulties are likely to be encountered using incomplete data 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 alone. 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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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 polyarthritis 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 polyarthritis 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 criteria applied. These are criteria for the 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 believe that the main 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 experienced rheumatologists show.

The 1987 ACR criteria are not valid for prognostic purposes as Harrison et al stated. Other prognostic factors exist and can easily be applied to patients with RA. But the ACR criteria for RA are so inclusive that an important means of helping family doctors and general practitioners trained not to differentiate rheumatoid arthritis to make a diagnosis of RA and to differentiate between RA and other forms of arthritides 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 a treatment guideline, 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 domain of the anti-CD4 therapy. Davis et al examined 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 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 immunohistochemical labelling of the synovial biopsy specims.

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 dose 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 baseline C reactive protein (CRP) levels between the three treatment groups, with the placebo treated group having a (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 20% improvement in different measures in the groups receiving active treatment), which is unimpressive for a treatment which targets a cell with a “pivotal” role in synovitis in rheumatoid arthritis. The major findings 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 establish whether the anti-CD4 antibody has any effect on 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 specific antibody 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 joint 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-CD9 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, 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. 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 seronegative spondyloarthritides (two reactive arthritis, one psoriatic arthritis, one enterocr accusis) 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-Gruenwald-Giems (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 anti-CD14 antibody (DAKO-Denmark) diluted 1:10 in TRIS-HCL buffer. In brief, 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 and countercoloured with Mayer’s haematoxylin. All incubation steps were preceded by washes in 0.1 M PBS (five minutes × three). The slides were examined at 400 × magnification.

Omission of primary antisera, use of normal rabbit serum, or one of subsequent steps in the staining method were included as controls for specificity.

Macrophones 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).

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

<table>
<thead>
<tr>
<th>Sample</th>
<th>Reiter cells (n)</th>
</tr>
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<tbody>
<tr>
<td>RA (n=3)</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>2</td>
</tr>
<tr>
<td>SsA (n=4)</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>3</td>
</tr>
<tr>
<td>CIA (n=3)</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>4</td>
</tr>
</tbody>
</table>

RA: rheumatoid arthritis, SsA: seronegative spondyloarthritides, CIA: crystal induced arthritis.

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 genetic disorder characterised by recurrent attacks of fever and polyserositis. These attacks are usually preceded by mild remissions. The symptom-free period varies in length, and these periods may last for months, years, or even decades. The disease is most common in the Middle East and the Mediterranean region and is caused by mutations in the pyrin gene.

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 involving lower extremities occurs after prolonged standing and sitting periods in FMF patients. We think that genetically low level of inhibitory activity (that is, mutated pyrin) may not be able to compensate the inflammatory reaction that is probably initiated in a stressfull microenvironment caused by not only microtrauma, but also increased hydrostatic pressure.

I am greatly indebted to Professor Hasan Yazici for constructive criticism and help in preparation.

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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.

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 periods of prolonged 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.

CORRECTION
Incidence of RA in people with persistently raised RF

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

The latter is exemplified by a patient admitted at the age of 76 with symptomatic, as well as echocardiographically validated rheumatoid pericarditis in the absence of arthritis. Rheumatoid arthritis latent fixation test (RA LFT) was positive with a titre of 1/160, antinuclear factor (ANF) titre was 1/250, and signs of active inflammatory disease included a platelet count of 750 × 10³/l, and an erythrocyte sedimentation rate (ESR) of 98 mm/1st h (Westergren). Arthralgia of the hands and wrists developed for the first time two years later (when she was no longer taking steroids), with a subsequent RA LFT titre of 1/80 and IgM and IgA, compared with those with a transient increase in RF or persistent increase in only one RF isotype. There was no significant age difference between these three groups of subjects studied.

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

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Author's reply

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

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

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LETTERS TO THE EDITOR

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

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

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

DNA typing of HLA class I alleles was performed using a DNA sample prepared from peripheral blood lymphocytes by the salting out procedure.2 The class I ABC SSP UNITRAD low resolution kit (Pel-Freeze) was used. The primer sets amplify all alleles described by the International Nomenclature Committee of WHO in 1993 and in 1997.3 Polymerase chain reaction amplification with sequence-specific primers (PCR-SSP) was used. A control primer pair was present to verify the integrity of the PCR reaction. Molecular typing of B27 variants was performed by a PCR-SSP technique with a DYNAL HLA-B27 kit (DYNAL AS, Oslo, Norway), which identifies all the phenotypically different HLA-B27 alleles, B*2701-11, recognised by the HLA Nomenclature Committee in 1973.4 The typing results for our patients were: HLA-A*0101-02, *3201-02; HLA-B*0801, *2709; HLA-C*0102-03, *0701-07.

To confirm these results HLA-B locus sequence based typing was performed. A unique DNA amplification, encompassing exon 1 to intron 3, and four fluorescent sequencing reactions, covering exon 2 and 3, were analysed.5 Two intronic amplification primer pairs generated a 1 kb length product useful for direct sequencing. For complete subtyping of the allelic variants PCR-SSP was used. Cycle sequencing reactions allowed the incorporation of a fluorescently labelled dideoxy terminator for detection on a DNA automated sequencer (ABI PRISM 377, Perkin Elmer). Data processing and allele assignment were performed automatically with specific analysis software that compares the sequenced results against a sequence library and provides individual allele assignment for each sequence. The HLA-B class I high resolution typing of our sample was HLA-B*0801:2709 in agreement with the low resolution typing performed by PCR-SSP.

SpA has a strong association with the HLA-B27 molecule. Studies in humans and transgenic rodents suggest a direct involvement of HLA-B27 in the pathogenesis of the disease. Thirteen subtypes of HLA-B27 (B*01-13) have been described, differing from each other by one or more amino acid changes, mainly in the peptide binding groove. Of these B*2701, 02, 03, 04, 05, 07, 08, and 10 are associated with ankylosing spondylitis (AS). B*2701-13 are rare, which has precluded assessing their putative association with AS. B*2706 is not associated with AS in South East Asia. However some B*2706 positive patients with AS have been reported in China.6 It has been suggested that the B*2706 might protect against SpA. Recently, a study on families in which both B*2706 and B*2706 occurred has suggested that B*2706, although not associated with SpA, does not protect against SpA.

B*2709 has been found in Sardinia and in continental Italy, where the frequency of HLA-B27 in the general population is around 2%. B*2709 accounts for 25% of HLA-B27 subtypes in Sardinia and 3% in continental Italy.7 D’Amato and coworkers have tested 35 Sardinian patients with AS and 40 Sardinian B27 positive healthy subjects by genomic typing.8 None of the patients with AS were found to be B*2709 positive, in contrast with 25% among the healthy controls. The authors suggested that B*2709 is not

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8 None of the patients with AS were found to be B*2709 positive, in contrast with 25% among the healthy controls. The authors suggested that B*2709 is not...
Y chromosome microchimerism in rheumatic autoimmune disease

It is well known that some features of chronic graft-versus-host disease (GVHD) resemble those of other rheumatic autoimmune diseases, such as systemic sclerosis (SSc), Sjögren’s syndrome (SS), and primary biliary cirrhosis (PBC). Furthermore, the development of systemic lupus erythematosus (SLE)-like diseases has been seen in murine models of GVHD.\(^1\) The pathogenesis of rheumatic autoimmune diseases is still unknown. One possibility that has been suggested is that these diseases are associated with pregnancy because of their strong female predilection and, especially in SSc, a peak incidence after parturition. In 1996 Bianchi et al. reported that fetal cells could survive in the maternal circulation for up to 27 years after parturition, a phenomenon termed fetal microchimerism.\(^2\) These observations led the hypothesis that persistent fetal cells in the maternal circulation could mediate a graft-versus-host reaction, resulting in autoimmune disease.

Nelson et al. have previously carried out a quantitative assay for male DNA in women with SSc and normal women who had delivered at least one son. They indicated that the mean number of male cell DNA equivalents among controls was 0.38 cells/16 ml whole blood and 11.1 among patients with SSc. In addition, Artlett et al. have shown Y chromosome-specific sequences in the DNA extracted from peripheral blood in 32 of 69 women with SSc (46%) as compared with 1 of 25 normal women.\(^3\) They also reported that those allo-cells were T lymphocytes and infiltrated lesional skin. These findings suggest the hypothesis that fetal microchimerism may contribute to the pathogenesis of SSc. However, this is still controversial because Murata et al. have recently reported that there is no significant difference in the presence of fetal DNA in peripheral blood between Japanese patients with SSc and healthy women with non-quantitative assay.\(^4\) Here we report further studies of fetal microchimerism in SSc, SLE, and SS.

We assayed for a specific Y chromosome sequence in the DNA extracted from peripheral blood by a nested polymerase chain reaction (PCR) in 20 patients with SSc, 21 patients with SLE, 18 patients with SS, and 41 healthy volunteers. All patients and healthy volunteers were Asian-Japanese women.\(^5\) Our data confirm that male DNA is found in 10 of the 20 patients with SSc (50%), eight of 41 healthy volunteers (20%, p=0.017), and six of 18 patients with SS (33%). No Y chromosome-specific DNA was detected in any of the patients with SLE (table 1).\(^6\) The DY1 was most commonly found in Barnett’s type III (four of five). The DY1 positive patients with SSc also had a variety of antibodies including anti-RNP, antimitochondrial, and anti-smooth muscle antibodies that may reflect polyclonal activation of immune cells. Anticentromere antibodies were detected more commonly in the DY1 negative group (eight of 10). All three patients with SSc who had PBC were DY1 positive and had anticentromere antibodies (table 2).

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

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Patients’ characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSc</td>
<td>SLE</td>
</tr>
<tr>
<td>Age (years, mean (range))</td>
<td>56.1 (44-74)</td>
</tr>
<tr>
<td>Duration of illness (years, mean (range))</td>
<td>10.2 (1-26)</td>
</tr>
<tr>
<td>DY1 positive (No (%))</td>
<td>10% (30)</td>
</tr>
</tbody>
</table>

*PBC = primary biliary cirrhosis.

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

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

<table>
<thead>
<tr>
<th>Autoantibodies</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Antinuclear factor</td>
<td>10</td>
</tr>
<tr>
<td>Topoisomerase I</td>
<td>4</td>
</tr>
<tr>
<td>Centromere (PBC*)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>RNP</td>
<td>4</td>
</tr>
<tr>
<td>ss-A(Re)</td>
<td>2</td>
</tr>
<tr>
<td>SS-B(Le)</td>
<td>0</td>
</tr>
<tr>
<td>RA</td>
<td>3</td>
</tr>
<tr>
<td>ssDNA</td>
<td>2</td>
</tr>
<tr>
<td>Mitochondria</td>
<td>1</td>
</tr>
<tr>
<td>Smooth muscle</td>
<td>1</td>
</tr>
</tbody>
</table>

*PBC = primary biliary cirrhosis.
The study group comprised 11 women and five men with a median age of 53.5 years (range 25–80) and a median disease duration of 57 months (range 5–360). Fifteen patients were rheumatoid factor positive and 10 had bony erosions on pre-study radiographs. Antirheumatic treatment included methotrexate (11 patients), hydroxychloroquine (two), sulfasalazine (one), and low dose ster- 

eoids. (8). Clinical evaluation and measurement of suPAR, erythrocyte sedimentation rate (ESR), and C reactive protein (CRP) were done a median number of three times, and the time interval between radiographs was a median of 22 months.

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

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

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

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4 Rondzy HK, Smits HH, van Muijen GNP, Puszynski RMS, Dolhain RJVM, van Lange-
23.
5 Stephens RW, Pedersen AN, Nielsen HJ, Ham-

CORRECTION


The Editor of the Annals regrets that we inadvertently published a reply to Dr Barnsley from Drs Ferrari and Russell that contained some misinformation, and offers his apologies to Dr Barnsley.

Possibly Drs Ferrari and Russell were confusing Dr Barnsley with someone else. Firstly, Dr Barnsley is a man and not a woman, as they stated. Secondly, Dr Barnsley did not attend the World Whiplash Congress in Vancouver and has not read the transcripts of it and thus could not be, as Drs Ferrari and Russell commented, “well aware of an impressive study presented there”.

(Note: Corrections printed in the journal will appear on the Annals web page (www.annrheumdis.com) and are linked to the original publication.)