MATTERS ARISING

Epidemiology of whiplash

Space restrictions prohibit a comprehensive refutation of the uneven treatment of the whiplash literature presented by Ferrari and Russell. They fiercely interrogate research that does not support their view, yet uncritically embrace literature favouring their pre-conceptions. Central to their argument is the assertion that there are different rates of chronic whiplash in different countries, and that motor 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 appreciated 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. But a more sober view is that if it is, how claims are made, fewer people will make one. To extrapolate beyond this is unjustifiable: the apparent change in incidence may simply be due to reporting bias.

The study has been used to argue that chronic symptoms after whiplash do not occur in communities lacking a compensation system. However, only 31 patients developed any neck pain as a result of the accident, with none reporting chronic pain. The 95% confidence limits of this estimate range up to 10%. Therefore, the data are consistent with a rate of chronicity of up to 10%. 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. Consequently, studies of patients with whiplash who have normal MRIs cannot exclude important injury. Furthermore, both ultrasound and bone scan studies have shown potentially painful pathology in these joints.

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. 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 they did not receive, producing a biased sample. However, the advertisement was in a medical journal, seeking doctors to enrol participants, producing a representative sample. Ferrari and Russell have used these studies in a previous article, apparently accepting the methodology then. These flaws alone raise grounds for concern that the opinions of Ferrari and Russell are not responsible for an appraisal of the literature and will raise alarm and reinforce prejudice against genuinely afflicted patients.

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Through their leader, Ferrari and Russell venture to 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. Meanwhile, the study of Borchgrevink et al show that a brief period of pain may be adequately treated simply by advising them to act as usual. If there is any psychosocial problem with acute whiplash, it is on the part of doctors and therapists who overmedicalize the problem.

However, even so, some 10–20% of patients remained symptomatic at six months. Two questions arise: why are these patients symptomatic, and what should be done about them? A more scientific approach 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 Russell contend that zygapophysial joint pain must be rare. Indeed, it is, for it accounts only for half of 5–10% of the original population; but it accounts for 50% of the chronic population. Elsewhere, 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 an individual claim that their chronic pain resulted from the whiplash.

Ferrari and Russell argue that there is no persisting lesion, and that psychological and social factors totally explain the chronic complaints of these patients. Schraeder et al 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 scientists who mislead their readers. If these references are consulted, the last three offer no criticism of Radanov. Only the first, a letter, offers criticism, but clearly Ferrari and Russell do not inform the reader of Radanov’s rebuttal of these criticisms.

Yet even if we accept that psychosocial factors are important in these patients, Ferrari and Russell do not provide an answer as to what makes them do so. The alternative suggestions of van Akkerveeken and Vendrig, but do not explain to readers that this was not a peer reviewed publication, that it was only a preliminary study, that it was not controlled, and that the authors themselves were accordingly guarded about overstating their results.

No other literature is provided to vindicate cognitive intervention.

Finally, if Ferrari and Russell are so convinced that experimental studies of whiplash are so innocuous, perhaps they might organise some volunteers to undergo a series of AV30 kph and AV60 kph collisions, which are what many of our patients underwent.

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Accordingly, the method of assessment in the time was probably described as concussion in Reporting on patients who were never unconscious was 42%.

This is well within the time frame of the 1953 United Kingdom while it has been described demiological studies neck pain is either the occurrence of "psychoneurosis in patients and the severity of injury and emphasised that inverse relation between accident neurosis and neither were a number of other references in the "leader". To interpret late whiplash syndrome was one of the 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 is discussed in Miller's 1961 BMJ article, which reports 200 cases examined between 1955 and 1957.

This is well within the time frame of the 1953 JAMA whiplash paper. Miller reported an inverse relation between accident neuraxis 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 Barnsley's studies in defining concussion have been discussed previously. These differences in terminology may be explained by the mechanism of concussion and whiplash, which is acceleration-deceleration of the head. In addition, symptoms of concussion and whiplash are almost identical. Accordingly, an individual who sustained acceleration-deceleration of the head without loss of consciousness probably has whiplash.

Previously, neck pain in the general population has been reported to vary between 14% in Norway and 33% in Lithuania. These variations were interpreted as due to sociocultural factors, with 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 redefinition in symptom prevalence requires proof, and is not in accord with admitting anecdotal reports from Australian rheumatologists, nor with the evidence from Lithuania (she does not quote the subsequent prospective study), Germany, and Great Britain. Dr Barnsley's logic is also problematic. The impressive study presented at the World Whiplash Congress in Vancouver which suggests that changing the claim scheme has dramatic effects on recovery rates, as indicated by various patients.

Both Drs Barnsley and Bogduk have missed the key message in the epidemiological literature—the rapid recovery rate seen in some countries is not being duplicated in others. The studies in Lithuania, Greece, and Germany cannot rule out the possibility of a small number of subjects having chronic pain and disability, but they do show that recovery (as measured by absence of symptoms and return to normal activities, as well as other patient centred outcomes) occurs in 90–95% of subjects in six weeks or less. It is this fact that compels us to question the basis for chronic pain in say, Canada. We find that whiplash in Canada (and reportedly in many other countries) is a business, a medical, an 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 who do not recover within six weeks or fewer and some patients report pain at six months¹⁷ that we are concerned with, and the cervical zygapophysial joints are not relevant for this larger group. Indeed, we were not aware that the subjects of Dr Bogduk's studies had neck acceleration-deceleration impacts (a AV of 30–60 kph) as Dr Bogduk indicates. This fact makes it even less likely that their study group is typical of most patients with chronic whiplash, who instead undergo much lower velocity collisions. Clearly, and for good reasons, Dr Bogduk's study patient spectrum is very different from the group we are concerned with. Our disagreement is not substantially with the few per cent that he may see with facet joint problems, but rather with the rest of the iceberg of chronic pain.

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

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

**R FERRARI**

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**Authors’ reply to Dr Radanov**

Dr Radanov’s expressed concerns and cry for *auto-da-fé* are based on his perception that our biopsychosocial model is one of malinger- ing as an explanation for the late whiplash syndrome. As we have explicitly stated, in both our 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 malingering or psychological models that place the pain “all in one’s head”. The biopsychosocial model includes physical sources for pain, and incorporates psychosocial factors to explain both the severity and attribution of the pain, as well as further behaviour enacted upon this substrate of otherwise benign physical sources of pain. Thus we maintain that the most helpful focus of discussion and research should be on identifying how the various elements of the biopsychosocial model explain the variance in epidemiology of the late whiplash syndrome, and why, even within a given culture some accident victims recover quickly and others do not. Dr Radanov’s views may be coloured by the relatively benign nature of the problem he sees in 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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**Table 1**

<table>
<thead>
<tr>
<th>Social class 1</th>
<th>Social class 2</th>
<th>Social class 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–2N o( % )</td>
<td>3N–3MFe No (%)</td>
<td>4–5 No (%)</td>
</tr>
</tbody>
</table>

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**Inflammatory polyarthritis cases Norfolk and Norwich**

<table>
<thead>
<tr>
<th>RA cases</th>
<th>51 (33)</th>
<th>73 (47)</th>
<th>30 (19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>28 (12)%</td>
<td>87 (36)%</td>
<td>124 (52)%</td>
<td></td>
</tr>
</tbody>
</table>

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*p<0.0001; +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?”1 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.2

We observed a higher mortality rate among patients with rheumatoid arthritis (RA) living in deprived areas relative to those living in affluent areas. Our methodology did not determine the social class of individual patients according to the Office of National Statistics classification of occupations. Nevertheless, whether measured by income, occupation, educational level, social class, or ecological variables such as the Carstairs score, socioeconomic deprivation has been shown to influence health.3 In addition, we observed that there were more patients with RA living in deprived areas compared with 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. Poor socioeconomic deprivation in areas of affluence and deprivation would prove valuable in determining the epidemiology of RA.

Our subsequent analysis of 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 RA is less readily accounted for by smoking.3 Functional ability is an important outcome measure in RA and is a predictor of mortality in this disease.4

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 status. Further research is required to establish the relative importance of these and other factors in determining the influence of socioeconomic deprivation on outcome and mortality in RA and other chronic diseases. The factors which can be modified most effectively to reduce the inequalities in health outcome also require investigation.

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

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

Diagnostic evaluation of classification criteria for RA and reactive arthritis

We read with interest the recent article by Hülsemann and co-workers, 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 tested was an “expert diagnosis” made by one of the authors when the patient was first seen (within one year of symptom onset). However, the main difficulty faced in this type of study is that 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 as a rule, this diagnosis was 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 arthritides, as there is a need for early treatment of RA”. However, we strongly disagree with the use of the 1987 ACR criteria as the gold standard. 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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The validation 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 fulfill the 1987 ARA criteria do not have RA. If they do not fulfill 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 in our view are an 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 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 the treatment guidelines, are, in our view, well supported in every day practice by applying the 1987 ACR criteria for RA in our view are an 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 arthritides, as soon as possible in the course of the disease.

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

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

When patients were seen in this early synovitis outpatient clinic and were diagnosed 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 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 of this group with a high sensitivity (90%) and a high specificity (90%), we suggested, that these criteria could be used not only as classification criteria but also as criteria for the diagnosis of RA.

Criteria should be applied longitudinally at follow up, rather than simply at baseline. We applied criteria cross sectionally on the day of their first visit. We can not present follow up data on the whole group, but of a subgroup of 28 patients with undifferentiated arthritis. Only two of these patients developed rheumatoid factor negative RA, 15 patients showed complete remission, two showed partial remission and four showed unchanged unremitting course. One patient had developed ankylosing spondylitis.

In accordance with our experience, van der Horst-Bruinsma et al have shown, in a special early arthritis clinic, that early diagnosis of RA is possible and reliable. Compared with routine patient care, of 74 patients with definite RA according to the 1987 ACR criteria, diagnosed at two weeks after the first visit, 66 still had definite RA after one year, and only in four patients was the diagnosis changed to systemic lupus erythematous (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

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

An interesting paper was published recently in the domain of CD4 in rheumatoid arthritis. This was examining the effect of intra-articular administration of primatised anti-CD4 antibody in the knee joint of patients with rheumatoid arthritis and persistent synovitis, unresponsive to treatment. The paper correctly detailed the 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 for 18 months. It is curious that no clinical parameters were measured in this study, with a complete reliance on imaging and laboratory procedures to measure outcome, which leads me to speculate that there might have been no discernible clinical difference between the treatment groups, as assessed by the patient or doctor.

Also, there was a marked disparity in baseline C reactive protein (CRP) levels between the three treatment groups, with the placebo treated patient group having a high (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 40% improvement in different measures in the groups receiving active treatment), which is unimpressive for a treatment which targets a cell with a "pivotal" role in synovitis in rheumatoid arthritis and can be performed. A close inspection of 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 treatment affects 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 has been performed. A close inspection of fig 4 (see ref 1) suggests that the major change in CD4 labelling is in the lining region of the membrane, indicating an effect on macrophages rather than CD4 positive T cells.

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

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

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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. 5 Of interest, their role in the process of adhesion and phagocytosis of apoptotic cells has been recently demonstrated. 6

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

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

We analysed the synovial fluids obtained from the knee joints of 10 patients suffering from inflammatory joint diseases of recent onset (< 6 weeks). Three patients had sero-positive active rheumatoid arthritis, four patients had seronegative spondyloarthritides (two reactive arthritis, one psoriatic arthritis, one enterococciarthritis) 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 50 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 monocye CD14 antibody (DAKO-Denmark) diluted 1:10 in TRIS-HCL buffer. In brief, specimens were air dried, fixed with acetone and then stored at −70 °C until processing. The specimens were incubated for 60 minutes at room temperature with the primary antibody. For the conjugation of peroxidase an En Vision+TM Kit (Dako) was used. The monoclonal antibodies were then incubated for five minutes with a prediluted dianno-benzidine solution (Dako) and countercoloured with Mayer’s haematoxylin. All incubation steps were preceeded by washes in 0.1 M PBS (five minutes × three). The slides were examined at 400 × magnification.

Omision 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. 3 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. 3 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. 3 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 hereditary disease characterized by recurrent bouts of fever, peritonitis, pleuritis, arthritis or erysipelas-like skin disease. Between the episodes, FMF patients are free of symptoms and appear like skin disease. Between the episodes, FMF patients with familial Mediterranean fever (FMF) characteristically have recurrent bouts of fever, 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 pain in patients with FMF who have experienced foot pain (with or without subcutaneous swelling) during or after long distance bus travelling and they also described an area of redness, which typically located on the soles of their feet. Thirty patients defined a period of fatigue accompanied a low grade fever subsequent to the episodes with severe lower extremity symptoms.

In provocateur test, 30 volunteer male FMF patients (age, 21.2 (1.8)) without proteinuria and 30 volunteer male healthy subjects (age, 21.1 (0.8)) were kept in an upright position (standing, walking or derect sitting) for six hours. At the beginning, all participants were symptom free and none of them had any other disorder that may cause foot pain. Thirteen FMF patients were receiving colchicine treatment. Bilateral ankle and the midfoot circumference were measured from the marked points at the onset and the termination of the test. The mean change in circumference per measurement site (mean (SD)) was 3.0 (2.7) mm and 1.3 (1.5) mm in the patient and the control group, respectively. Although the comparison was statistically significant (p=0.014; Mann-Whitney U), we think that our method was not reliable to detect those small changes precisely.

At the end of the provocateur test, none of the healthy controls had lower extremity pain or tenderness. Apart for one patient, all FMF patients had intense foot or calf pain, which interleaved with walking. Tenderness was so profound that it could be elicited even by a gentle touch. Widespread tenderness was detected in 12, whereas localised tenderness was detected in 17 of the patients. Although swelling was not noticed in anyone, focal erythematous areas (not erysipelas) were seen in five patients. After five hours of resting, palpation showed that tenderness was sustained (14 widespread and 16 localised). A localised pain and tenderness was also developed in the symptom free patient. Colchicine use did not change the results of provocateur test (p=0.240; Fisher’s test).

Although leg pain induced by exercise or prolonged standing has already been discussed in FMF patients, we are unaware of any report about leg pain and swelling episodes after prolonged sitting in these patients. Increased hydrostatic pressure in the lower extremities may be the main factor responsible for those symptoms experienced during bus trips.

It was suggested that FMF is related to catecholamine metabolism as metaraminol infusion may provoke an acute episode, 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 stressful 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.

Non-periodic leg pain in patients with familial Mediterranean fever

Table 1 Questionnaire on lower extremity complaints

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Have you ever had foot or leg pain events after prolonged standing and/or bus travel lasted more than six hours?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>B. Has it been existed since childhood or adolescence?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>C. Does it occur after prolonged standing or sitting?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>D. Does it occur mostly bilateral?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>E. Does it persist at least 30 minutes after rest?</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

If all of the answers are yes, then the case was considered to be positive.

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

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Have you ever had foot or leg pain events after prolonged standing and/or bus travel lasted more than six hours?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>B. Has it been existed since childhood or adolescence?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>C. Does it occur after prolonged standing or sitting?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>D. Does it occur mostly bilateral?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>E. Does it persist at least 30 minutes after rest?</td>
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If all of the answers are yes, then the case was considered to be positive.

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.
**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 latex fixation test (RA LFT) was positive with a titre of 1/160, antinuclear factor (ANF) titre was 1/250, and signs of active inflammatory disease included a platelet count of 750 × 10^3/l, and an erythrocyte sedimentation rate (ESR) of 98 mm/1st h (Westergren). Arthralgia of the hands and wrists developed for the first time two years later (when she was no longer taking steroids), with a subsequent RA LFT titre of 1/80 and an ANF titre of 1/320 about four months after the onset of arthralgia. Radiography showed narrowing of the joint spaces of the hands 12 months later, but there were as yet no erosions at this stage. Erosions were seen in March 1992, approximately two and a half years after the onset of arthralgia, when the RA LFT titre was 1/160, ANF titre 1/160, platelet count 421 × 10^3/l, ESR 18 mm/1st h. At her most recent attendance, on 2 February 2000, she was still very active, having continued to receive prednisolone (maximum dose 5 mg/d) continuously since 1989. Her only complaint was a little pain in the left thorn eminence and painful heels. RF was now 768 IU/ml, ANF titre 1/320, platelet count 340 × 10^3/l, ESR 42 mm/1st h. Antibodies against double stranded DNA had not been reported at any stage.

**COMMENT**

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

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**LETTERS TO THE EDITOR**

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

In 1998, in this journal, we reported the cases of two B27 positive patients with undifferentiated spondyloarthropathy (sSpA) and shown that dactyliitis also affecting the synovial sheaths in the palm of the hand. 1

Neither patient had axial disease but showed peripheral manifestations of spondyloarthropathy (SpA), such as peripheral arthritis, peripheral enthesitis, and dactylitis.

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

DNA typing of HLA class I alleles was performed using a DNA sample prepared from peripheral blood lymphocytes by the salting out procedure. The class I ABC SSP UNITRAY low resolution kit (Pel-Freez) was used. The primer sets amplify all alleles described by the International Nomenclature Committee of WHO in 1995 and in 1997. Polymerase chain reaction amplification with sequence-specific primers (PCR-SSP) was used. A control primer pair was present to verify the integrity of the PCR reaction. Molecular typing of B27 variants was carried out 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. 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 exons 1 to intron 3, and four fluorescent sequencing reactions, covering exons 2 and 3, were used. Two intrinsic automatic sequencers 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 fluorescently labelled dyes. These primers were used 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 compared 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 the 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*2711–13 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. It has been suggested that the B*2706 might protect against SpA. Recently, a study on families in which both B*2706 and B*2709 occurred has suggested that B*2709, 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. D’Amato and coworkers have tested 35 Sardinian patients with AS and 40 Sardinian B27 positive healthy subjects by genomic typing. 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 associated with RA.
associated with AS, B*2709 differs from B*2705 by a single substitution (His→Asp) at position 116, which is located in the F pocket of the peptide-binding site. In the opinion of D’Amato and his colleagues the substitution at position 116 might exclude the acceptance of arthrographic peptide from the B*2709.

Our patient was born in the south of Italy, she is B27 positive, and has SpA with an erosive and disabling peripheral arthritis. Our case, also, suggests that the B*2709 might be associated with SpA and that the negative association found in Sardinian patients with AS⁵ should be confirmed in other studies. These should include the full spectrum of SpA and not be limited to AS.

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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 rheumatoid autoimmune diseases is still unknown. One possibility that has been suggested is that these diseases are associated with pregnancy because of their strong female predestination 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.³ They indicated that the mean number of male cell DNA equivalents among controls was 0.38 cells/16 ml whole blood and 11.1 among patients with SSc. In addition, Artlett et al have shown Y chromosome-specific sequences in the DNA extracted from peripheral blood in 32 of 69 women with SSc (46%) as compared with 1 of 25 normal women.⁴ They also reported that those allo-cells were T lymphocytes and infiltrated lesional skin. These findings support the hypothesis that 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.⁵ 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 who had delivered at least one son. The nested PCR was done using the primers Y1–1, Y1–2, Y1–3, and Y1–4, which are specific for a part of the Y chromosome sequence, DYZ1, as described previously.⁶ The identity of the detected PCR product was confirmed by nucleotide sequencing. The results from healthy volunteers and test groups were compared by Fisher’s extract probability test.

Y chromosome-specific DNA was detected 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). The DYZ1 was most commonly found in D’Amato’s type III (four of five). The DYZ1 positive patients with SSc also had a variety of antibodies including anti-RNP, anti-centromere, and anti-smooth muscle antibodies that may reflect polyclonal activation of immune cells. Anticentromere antibodies were detected more commonly in the DYZ1 negative group (eight of 10). All three patients with SSc who had PBC were DYZ1 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, DYZ1 was not detected in patients with SLE and there was no significant difference between patients with SS and healthy volunteers. These data suggest that fetal microchimerism may be a phenomenon which is strongly associated with the pathogenicity of SSc and not with the related autoimmune diseases, SLE and SS.

Table 1 Patients’ characteristics

<table>
<thead>
<tr>
<th>SSc</th>
<th>SLE</th>
<th>SS‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>20</td>
<td>21</td>
</tr>
<tr>
<td>Age (years, mean (range))</td>
<td>56.1 (44–74)</td>
<td>50.2 (34–82)</td>
</tr>
<tr>
<td>Duration of illness (years, mean (range))</td>
<td>10.2 (1–26)</td>
<td>11.9 (1–24)</td>
</tr>
<tr>
<td>DYZ1 positive (No (%))</td>
<td>10 (50)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

*PBC = primary biliary cirrhosis.

Table 2 Comparison of clinical findings of DYZ1 positive and negative systemic sclerosis groups

<table>
<thead>
<tr>
<th>DYZ1</th>
<th>Positive</th>
<th>Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (n=10)</td>
<td>5 (50)</td>
<td>5 (50)</td>
</tr>
<tr>
<td>Barnett’s type</td>
<td>I</td>
<td>2 (40)</td>
</tr>
<tr>
<td>II</td>
<td>2 (40)</td>
<td>3 (60)</td>
</tr>
<tr>
<td>III</td>
<td>1 (20)</td>
<td>4 (80)</td>
</tr>
</tbody>
</table>

Autoantibodies

<table>
<thead>
<tr>
<th>Factor</th>
<th>Positive (n=10)</th>
<th>Negative (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antinuclear</td>
<td>1 (10)</td>
<td>4 (40)</td>
</tr>
<tr>
<td>Topoisomerase I</td>
<td>0 (0)</td>
<td>4 (40)</td>
</tr>
<tr>
<td>Centromere (PBC*)</td>
<td>3 (30)</td>
<td>7 (70)</td>
</tr>
<tr>
<td>RNP</td>
<td>0 (0)</td>
<td>4 (40)</td>
</tr>
<tr>
<td>SS-A (Ro)</td>
<td>2 (20)</td>
<td>3 (30)</td>
</tr>
<tr>
<td>SS-B (La)</td>
<td>0 (0)</td>
<td>3 (30)</td>
</tr>
<tr>
<td>RA</td>
<td>1 (10)</td>
<td>4 (40)</td>
</tr>
<tr>
<td>dsDNA</td>
<td>2 (20)</td>
<td>3 (30)</td>
</tr>
<tr>
<td>Mitochondria</td>
<td>0 (0)</td>
<td>2 (20)</td>
</tr>
<tr>
<td>Smooth muscle</td>
<td>1 (10)</td>
<td>1 (10)</td>
</tr>
</tbody>
</table>

*PBC = primary biliary cirrhosis.

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Marker of erosive progression in RA

Urokinase plasminogen activator (uPA) catalyzes the activation of the proteolytic enzyme plasmin, which plays a part in tissue degradation and remodelling, and seems to have an important role in the erosive growth of pannus in rheumatoid arthritis (RA). The activity of uPA is localised and intensified by a cell bound receptor (uPAR), expressed by some malignant cells and some inflammatory cell types, including activated synoviocytes in the marginal zone between pannus and cartilage. The uPAR may become cleaved at the cell surface bound anchor, forming a free soluble receptor (suPAR) which is detectable in surface bound anchor, forming a free soluble receptor (suPAR) which is detectable in plasma of patients with RA whose x-ray findings showed disease progression in the patients who had no radiographic signs of progression, but the differences in ESR, CRP, and clinical variables were not significantly different.

In a pilot study we followed up outpatients with RA to evaluate the relation between suPAR and disease activity. Plasma suPAR was measured and clinical and paraclinical variables of disease activity determined in these patients on two or more occasions during a 12 month period. The present study included all patients (n=16) for whom comparable radiographs of the wrists and hands were obtainable, and also, when relevant, other symptomatic joints, taken before and after the period of suPAR measurements. The x-ray films of participating patients were read independently by a radiologist unaware of the patient’s clinical status and suPAR values. An enzyme linked immunoassay (ELISA) was used to measure suPAR in plasma, as previously described.† ✤

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

<table>
<thead>
<tr>
<th>Erosive progression (n=5)</th>
<th>No erosive progression (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>suPAR† (µg/l)</td>
<td>1.51 (0.93–2.73)*</td>
</tr>
<tr>
<td>CRP† (mg/l)</td>
<td>11.4 (6.0–30.1)</td>
</tr>
<tr>
<td>ESR† (mm/h)</td>
<td>24 (15–24)</td>
</tr>
<tr>
<td>Tender joints (of 28)</td>
<td>6 (3–20)</td>
</tr>
<tr>
<td>Swollen joints (of 28)</td>
<td>4 (1–8)</td>
</tr>
</tbody>
</table>

*P<0.05, non-parametric Mann-Whitney test. †suPAR = soluble urokinase plasminogen activator in plasma; CRP = C reactive protein; ESR = erythrocyte sedimentation rate.

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), sulphasalazine (one), and low dose steroids (eight). 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 concentrations (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 differences in ESR, CRP, and clinical variables were not significantly different.

The 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 the study period, could be classified as progressive due to previous activity. Secondly, another possible 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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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 only appear on the Annals web page (www.annrheumdis.com) and are linked to the original publication.)