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 this 'overmedicalise this problem'. The Australian study of Ferrari and Russell, they say, is 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 fit, 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 responsibly based on appraisal of the literature and will raise alarm and reinforce prejudice against genuinely afflicted patients.

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


Through their leader, Ferrari and Russell ventured 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 5% of patients have severe symptoms at 12 months. More recently, the studies of Borgchrevink et al show that 82% of patients can 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 overmedicalise this problem.

However, even so, some 10-20% of patients remained symptomatic at 12 months. Two questions arise: why are these patients symptomatic, and what should we do about it? This 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 zygapophyseal joints in some 50% of these patients. Moreover, by surgically treating this 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 zygapophyseal joint pain must be rare. Indeed, it is, for it accounts for only half of 5-10% of the original population; but it accounts for 50% of the chronic population. Elsewhere, Ferrari and Russell indicate that symptoms can be attributed to the original whiplash, but this is a legal matter, not a medical one. There are no medical tests by which to falsify an imputation. Ferrari and Russell invoke the studies of Radanov and 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, thereby relying on sophistry to seduce their readers. If these references are consulted, the last three offer no criticism of Radanov. Only the first, a letter, offers criticism, but cleverly Ferrari and Russell do not inform the reader of Radanov's rebuttal of these criticisms.

Yet even if we accept that psychosocial factors are important in these patients, Ferrari and Russell do not provide an answer as to what to do about them. Studies, they cite, 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, thereby relying on sophistry to seduce their readers. If these references are consulted, the last three offer no criticism of Radanov. Only the first, a letter, offers criticism, but cleverly Ferrari and Russell do not inform the reader of Radanov's rebuttal of these criticisms.

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.

NIKOLAI BOGDUK
Newcastle Bone and Joint Institute,
Royal Newcastle Hospital,
Newcastle NSW 2300,
Australia

Making selective use of the literature and incorrect quoting of previous research, the January 1999 “leader” intends to support the view of the whiplash syndrome as malinger- ing. This reply cannot be exhaustive but will address the following:

The Ballas paper lacked a definition of the whiplash syndrome and did not describe the assessment of 300 selected cases seen in a single practice. Moreover, selection bias affecting the Ballas publication cannot be excluded. The Babo paper has not been questioned.

Furthermore, in 20 patients in Singapore with acute whiplash, the injury severity or risk of developing long term symptoms was not specified. Methodological flaws of the Ballas publication are reflected by the fact that this study was never considered relevant by the Quebec Task Force and were not a number of other references in the “leader”. To interpret late whiplash syndrome based on articles such as these is in contradiction to a claim of methodological soundness.

The non-existence of whiplash in the United Kingdom while it has been described for more than 30 years USA and UK while it has been described in the cervical whiplash syndrome. The late whiplash syndrome: a study of whiplash injuries. Current concepts in prevention, diagnosis, and treatment of the cervical whiplash syndrome. Philadelphia: Lippincott-Raven, 1998:183–91.


The Swiss study quoted in the “leader” represent an unwillingness of Ferrari and Russell to analyse in detail results from previous research while continuing to promote their own perspective. In addition, the “leader” emphasised that methodologically improved studies showed that “the scientific community has been told that reporting …is the best predicted by non-related accident stressors”. The study quoted in the leader used a biased selection of 39 patients, which was three times fewer than in 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 Swiss 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 was the approach used to introduce the malingering hypothesis for whiplash injury.

BOGDAN P RADANOV
Associate Professor of Psychiatry, University of Berne, Inselspital, CH-3010 Berne, Switzerland


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 vari- ous reasons, most notably that dualistic approaches have been largely unhelpful to the therapeutic community and society in response to acute whiplash. Under- standing 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

12-13
large, that this is part of the problem, this practice is unlikely to change. By setting forth this model we can now investigate it. We are making efforts to do this, and we hope that quality researchers such as Drs Barnsley and Bogduk will engage in such efforts as well.

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

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


Rheumatoid arthritis, poverty and smoking

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

They have observed that mortality in rheumatoid arthritis (RA) correlated with social grouping on the west coast of Scotland. Patients with RA of the lowest socioeconomic classes have an increased mortality when compared with patients of a higher socioeconomic class. Moreover, RA was more prevalent in patients with RA of lower socioeconomic class. We propose that these two important observations can both be explained by cigarette smoking.

The authors commented that cigarette smoking was more prevalent in the patients with RA of lower socioeconomic class in their study. In Britain there is a marked difference in smoking prevalence between social classes. In the 1996 census 41% of lower social class men (social class 4) were current smokers, with only 12% of men in the highest social class (social class 1) currently smoking. Cigarette smoking kills 120 000 people a year in Britain. Most of these deaths are as a result of cardiovascular disease, respiratory disease, and lung cancer. Maiden et al observed that 65% of the deaths in their study occurred as a result of these diseases. Current data show that continued cigarette smoking throughout adult life doubles age-specific mortality rates, even among those in late middle age. Cigarette smoking is associated with an increased risk of RA in both men and women. The increased mortality seen in patients with RA of low socioeconomic status could be explained in part by cigarette smoking, and that cigarette smoking itself might have contributed to the excess RA seen in the most socially deprived.

Since the poorest in our society appear to have an increased risk of RA, studies designed to identify risk factors for RA may best be focused on those with the highest risk. Cigarette smoking may be especially important to study, because its most powerful effects could be seen in the poorest socioeconomic population with RA. Laudable attempts to study the epidemiology of RA in Britain have been set up. One example is the Norfolk Arthritis Register. However, we would suggest such populations, in which there are a large proportion of higher socioeconomic groups, are unrepresentative of the large industrial cities in Britain. In 239 patients with RA in the Merseyside region under hospital follow up, the social class of our patients was identified using the Office of National Statistics classification of occupations. The patients with RA in Merseyside were of significantly lower social class than the patients with inflammatory polyarthritis studied in Norfolk. Table 1 summarises these findings. If the findings reported by Maiden et al are supported by further studies, there would seem to be significant differences in incidence, severity, and mortality in RA according to socioeconomic profiles. This would mean that increased resources should be allocated to regions of greatest need and not, as at present, to areas where socioeconomic class is highest, such as the south of England.

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

Table 1

<table>
<thead>
<tr>
<th>Social class</th>
<th>Social class</th>
<th>Social class</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–2 No (%)</td>
<td>3N–3MNo No (%)</td>
<td>4–5 No (%)</td>
</tr>
<tr>
<td>RA cases Merseyside (239)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>51 (33)</td>
<td>73 (47)</td>
<td>30 (19)</td>
</tr>
<tr>
<td>28 (12)*</td>
<td>87 (36)**</td>
<td>124 (42)*</td>
</tr>
</tbody>
</table>

*p<0.0001; **p<0.05.

Social class based on the Office of National Statistics classification of occupations. 

*SN = non-manual; M = manual.

Inflammatory polyarthritis cases Norfolk and Norwich* (154)

SNA's

†N = non-manual; M = manual.

Inflammatory polyarthritis cases Norfolk and Norwich* (154) (SN–SMNo, No (%))

RA cases Merseyside (239)

51 (33) 73 (47) 30 (19)

28 (12)* 87 (36)** 124 (42)*
Authors’ reply

We welcome the letter entitled “Rheumatoid arthritis, poverty, and smoking” in response to our article “Does social disadvantage contribute to the excess mortality in rheumatoid arthritis patients?” The importance of looking as a contributor to the influence of socioeconomic deprivation on mortality is rightly emphasized. However, as Black has pointed out eloquently, smoking alone does not account for the excess mortality seen among lower socioeconomic groups.

We observed a higher mortality rate among patients with rheumatoid arthritis (RA) living in deprived areas relative to those living in areas of affluence. 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. In addition, we observed that there were more patients with RA living in deprived areas relative to the general population. Although this may result from a higher prevalence of RA among the lower socioeconomic classes, this conclusion cannot be drawn overly from our study. People from areas of high deprivation tend to live in areas of affluence and deprivation would prove valuable in determining the epidemiology of RA.

Therefore, our cohort 40% of the most affluent group (Carstairs 1 and 2), 45% of Carstairs 4, 5, and 6, and 65% of the most deprived group (Carstairs 6 and 7) were current smokers; figures much higher than the 1996 census figures of 12% and 41% for social classes 1 and 2, 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 likely accounted for by smoking. Functional ability is an important outcome measure in RA and is a predictor of mortality in this disease.

The Scottish Health Survey 1995 showed that there were differences according to social class in other important determinants of health, including diet, alcohol consumption, obesity, hypertension, lung function, fibrinogen levels, general health perception, and psycho-social 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 with heterogeneous disease.

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, 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 et al. with regard to the 1987 American College of Rheumatology (ACR) classification criteria for rheumatoid arthritis (RA) were evaluated for their ability to identify patients with a clinical diagnosis of RA among 217 patients referred to an early arthritis clinic. The authors concluded that the 1987 ACR criteria can be used to make a diagnosis of RA in this setting.

In this study, the “gold standard” against which the criteria were compared was an “expert diagnosis” made by one of the authors when the patient was first seen (within one year of symptom onset). However, the main difficulty facing criteria for patients with early disease is that patients who ultimately develop RA appear clinically similar to those who have self-limiting disease or other forms of inflammatory arthritis. It is therefore too early to make an accurate diagnosis at this stage. More importantly, RA is a heterogeneous disease with a prognosis which varies from complete symptom remission to severe disability. Therefore simply categorizing patients into those who do and do not have “RA” is not necessarily important when considering which patients require early treatment. Although the authors made a clinical diagnosis without using the classification criteria, it is interesting that the diagnoses were informed by their knowledge of the individual components of the criteria. Therefore the high sensitivity (90%) they reported means that most of the patients with a clinical diagnosis of RA will have had seropositive, erosive, polyarticular disease with hand involvement. Whereas we have no problem in recognizing these patients as having RA, it represents only one end of the spectrum. The proportion of patients with “undiagnosed arthritis” in this study is high (54%), though this has been reported in other series. It is likely that many of these patients have atypical RA which may still require treatment with disease modifying antirheumatic drugs. Further, in early disease, patients often do not satisfy one of the criteria (nodules, erosions) which are features of established RA. We therefore think it is misleading to imply that patients who do not satisfy the 1987 ACR criteria (a) do not have RA; and (b) do not require early, aggressive treatment.

We recently evaluated the performance of the 1987 ACR criteria in an unselected cohort of 486 patients newly presenting with inflammatory polyarthritis to the Norfolk Arthritis Register. We considered the practical question of whether the criteria could identify which patients would have a poor prognosis after three years as assessed by (a) persistent synovitis; (b) functional disability and (c) radiological erosions. Although we applied the criteria in a number of different ways, we found they had a low ability to discriminate between patients who developed persistent, disabling, and erosive disease and those who did not. For example, applying the criteria as 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 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 early musculoskeletal conditions, and were never intended to be used as diagnostic criteria, it is not surprising that they do not perform well in this setting.

Finally, we wish to point out that the proportion of patients who satisfied the 1987 ACR criteria is highly dependent on how the criteria are applied. For example, in our study, the proportion of patients who satisfied the criteria at one year of follow up varied from 28% if applied “cross sectionally” (on the day of assessment) to 61% if applied “cumulatively” (each criterion satisfied if “ever” positive). Further difficulties are likely to be encountered using the criteria as ascertained from case note review. It is therefore more appropriate in a group with early synovitis to assess the criteria applied longitudinally at follow up, rather than simply at baseline.

In the study by Hülsemann and Zeidler we were given no information about how or when the criteria were applied apart from that they were applied “retrospectively”. We agree with Hülsemann and Zeidler that there is a need to “…differentiate RA as early as possible from the often benign and self-limited forms of undifferentiated arthritis, as there is a need for early treatment of RA”. However, we strongly disagree with the use of the 1987 ACR criteria. Until we understand more about the pathogenesis of RA, clinicians will have to rely on clinical judgment and the presence of poor prognostic factors to make decisions about whether to treat aggressively patients presenting with early disease.

Authors’ reply

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

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

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

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

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

We do not imply that patients who do not fulfil the 1987 ARA criteria do not have RA. If they do not fulfil the criteria at this early stage, we classify them as having undifferentiated arthritis. This is a working diagnosis, which can be changed to a definite diagnosis during follow up, but is only rarely necessary, as our experience of these authors 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 is one of the most important means of helping family doctors and general practitioners not trained in rheumatology to make a diagnosis of RA and to differentiate between RA and other forms of arthritis as soon as possible in the course of the disease. Thus by early referral to a rheumatologist an adequate treatment can be started as soon as possible. Even rheumatologists, who are familiar with the criteria used in all controlled trials to establish treatment guidelines, are, in our view, well supported in every day practice by applying the 1987 ACR criteria to differentiate RA from other forms of arthritis, enabling early diagnosis and treatment decisions.

Authors’ reply

With the intention to investigate the performance of these criteria in early synovitis with a high proportion of undifferentiated arthritis and reactive arthritis. Since the performance remained good with a high sensitivity (90%) and a high specificity (90%), we suggested, that these criteria could be used not only as classification criteria but also as criteria for the diagnosis of RA.

Criteria should be applied longitudinally at follow up, rather than simply at baseline. We applied criteria cross sectionally on the day of their first visit. We cannot 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, two had unchanging progressive unclassified arthritis, and one patient had developed ankylosing spondylitis. In accordance with our experience, van der Horst-Bruinsma et al have shown, in a special early arthritis clinic, that early diagnosis of RA is possible and reliable. Compared with routine patient care, of 74 patients with definite RA according to the 1987 ACR criteria, diagnosis at two weeks after the first visit, 66 still had definite RA after one year, and in only one of four patients was the diagnosis changed to systemic lupus erythematosus (one), unclassified arthritis (one), gout (one), and probable RA (one). Two patients had died and two were lost to follow up. This shows, that the validity is high for the 1987 ACR criteria for differentiating between RA and non-RA arthritides in an early synovitis clinic. We do not imply that patients who do not 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 experience of these authors 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 is one of the most important means of helping family doctors and general practitioners not trained in rheumatology to make a diagnosis of RA and to differentiate between RA and other forms of arthritis as soon as possible in the course of the disease. Thus by early referral to a rheumatologist an adequate treatment can be started as soon as possible. Even rheumatologists, who are familiar with the criteria used in all controlled trials to establish treatment guidelines, are, in our view, well supported in everyday practice by applying the 1987 ACR criteria to differentiate RA from other forms of arthritis, enabling early diagnosis and treatment decisions.


Matters arising, Letters, Correction.
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. A number of 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 spondyloarthritis (two reactive arthritis, one psoriatic arthritis, one enterorheumthritis), and three patients had crystal induced arthritis (two cases of acute gout and one case of acute pseudogout). Synovial fluids were processed for immunohistochemistry using the monoclonal anti-human-CD36 antibody (Boehringer Mannheim-Germany) diluted to 3.5 mg/ml and the monoclonal antihuman monococyte CD14 antibody (DAKO-Denmark) diluted 1:10 in TRIS-HEPES buffer. In brief, specimens were air dried, fixed with acetone and then stored at −70 °C until processing. The specimens were incubated for 60 minutes at room temperature with the primary antibody. For the conjugation of peroxidase an En Vision+TM Kit (Dako) was used. The monoclonal antibodies were then incubated for five minutes with a prediluted diamino benzidine solution (Dako) and countercoloured with Mayer's haematoxylin. All incubation steps were preceded by washes in 0.1 M PBS (five minutes × three). The slides were examined at 400 × magnification.

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

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 spondyloarthritis and crystal induced arthritis compared with synovial fluids from RA (table 1). On immunohistochemistry preparations, neutral mononuclear cells showed a CD36 positive reaction, while all the Reiter cells observed displayed a positivity for the thrombospondin receptor. CD14+ mononuclear cells outnumbered CD36+ cells; similarly, all the Reiter cells observed were immunoreactive for the anti-CD14 antibody (fig 1A, 1B).

Our findings show that Reiter cells do express both CD36 and CD14 adhesion molecules.

CD36 expression on Reiter cells seems to support the notion of the involvement of this receptor in the clearance of apoptotic PMN during synovial inflammation. In vitro data have shown that thrombospondin receptor and CD14 are some of the most important adhesion molecules involved in cell clearance. The expression of the thrombospondin receptor turns an amateur phagocyte into a professional one. It has been hypothesised that dysregulation of this receptor and the ensuing impairment of inflammatory cell elimination could play a part in inducing chronicity as well as tissue damage and scarring. Recently, CD14 has been demonstrated to mediate recognition and phagocytosis of apoptotic cells. This interaction depends on a region of CD14 that is supposed to be identical to a region that binds bacterial lipopolysaccharide, triggering the release of proinflammatory cytokines from macrophages. On the other hand, the interaction with self components acts as an initial step leading to apoptotic cell elimination. A major role for CD36 in the uptake of apoptotic neutrophils has been recently hypothesised, but it seems likely that microenvironmental 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 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...
a process leading to cell clearance. However, as CD14 and CD36 are known to play a part in different biological processes, the demonstration of these multifunctional adhesion molecules on Reiter cells is not a definitive evidence concerning their role for apoptotic cell clearance in the synovial fluid. Additional functional investigations are required to establish the exact role of CD14 and CD36 in the clearance of the PMN in synovial effusions.

We thank Dr Nicolò Pipitone for reviewing the manuscript, and Ms Eleonora Franceschini for technical assistance.

ENRICO SELVI
STEFANIA MANGANELLI
RENATO DE STEFANO
ELENA FRATI
ROBERTO MARCOCOLONI
Institute of Rheumatology, Loc Le Scotte
University of Siena, 53100 Siena, Italy

Correspondence to: Dr Selvi


9 Fadok VA, Warner ML, Bratton DL, Henson PM. CD36 is required for phagocytosis of apoptotic cells by human macrophages that use either a phosphatidyserine receptor or the vitronectin receptor or the vitronectin receptor (alpha v beta 3). J Immunol 1998;161:6250–7.

Non-periodic leg pain in patients with familial Mediterranean fever

Familial Mediterranean fever (FMF) is characterised by recurrent bouts of fever and peritonitis, pleuritis, arthritis or erysipelas-like skin disease. Between the episodes, FMF patients are free of symptoms and appear healthy.1 However, interestingly we observe leg complaints after prolonged standing or sitting, or both, in FMF patients, who usually experience these painful manifestations during evenings or after long distance bus trips. Thus we conducted a questionnaire study on 40 FMF patients (age, mean (SD); 21.6 (2.7) years; F: M; 2: 38) and 180 healthy male subjects (age, 21.3 (0.2) years) to ascertain the frequency of these complaints, and some of FMF patients were also included in a test to provoke these symptoms. Table 1 shows the questionnaire. Positive cases were also questioned for the presence of swelling or redness during these painful periods, and whether these complaints followed by an episode.

Although 14 of the 18 healthy subjects responded positively to the first question (question A), none of them were considered to be positive after six painful periods. All FMF patients 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 was typically located on the ankles. None of the subjects, however, had other sites (the ankles, the calves, the knees or even the thighs) involved in an additive manner as the intensity of pain increased unless resting ensued. Thus we performed provocation tests (question B). All FMF patients reported foot or leg pain after prolonged standing periods (first part of question A). They described, that at the onset, the pain was merely confined to the mid-foot, however other sites (the ankles, the calves, the knees or even the thighs) were involved in an additive manner after being awake for at least one hour. Although 30 FMF patients 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 was typically located on the ankles, none of the subjects had any other disorder that could cause foot pain. Thirteen FMF patients were receiving colchicine treatment. Bilateral ankle and foot swelling, localised to the toes, were measured from the marked points at the onset and the termination of the test. The mean change in circumference per measuring site (mean (SD)) was 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 provocation 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 interfered 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 provocation test (p=0.240; Fisher’s test). Although leg pain induced by exercise or prolonged standing has already been discussed in FMF patients,2 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,3 and episodes may be prevented by prazosin hydrochloride, as reported recently.4 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,5 but also increased hydrostatic pressure.

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

A DINC
Division of Rheumatology, Department of Internal Medicine, Gazi School of Medicine, Ankara, Turkey

Correspondence to: Dr Dinc, GATA Romatoloji Bilim Dalı, Etlik, 06010 Ankara, Turkey


Table 1 Questionnaire on lower extremity complaints

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Does it occur after almost every period of prolonged standing or bus travel?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does it occur after standing or sitting?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does it occur mostly after evening activities?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does it persist at least 30 minutes after rest?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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.

Downloaded from http://ard.bmj.com/ on June 23, 2017 - Published by group.bmj.com
Epidemiology of whiplash

LES BARNESLEY

doi: 10.1136/ard.59.5.394

Updated information and services can be found at:
http://ard.bmj.com/content/59/5/394

These include:

**References**
This article cites 36 articles, 6 of which you can access for free at:
http://ard.bmj.com/content/59/5/394#BIBL

**Email alerting service**
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

**Errata**
An erratum has been published regarding this article. Please see next page or:
/content/59/8/656.full.pdf

**Notes**

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/
Incidence of RA in people with persistently raised RF

A criticism of the study reported in the Annal" 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 younger people.1

Methods

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,2 the relation between RF and the natural history of RA might be less clear than it is in younger people.

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 symptom-free elderly people.

However, increased incidence of raised RF in elderly people is not relevant to the findings that we published recently in the Annal,3 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.

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.4 It would have been interesting to know about the RF isotype pattern of his patient. We have noted that the pulmonary manifestation of RA is strongly associated with raised IgA RF.5

HEILG VALDMARSSON
Department of Immunology,
National University Hospital,
Landspítalinn,
101 Reykjavik,
Iceland

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,3 the relation between RF and the natural history of RA might be less clear than it is in younger people.


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 (SpA) and shown that 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 enthesitis, and dactylitis.

Recently, one of our two patients (No 2) was subtyped and typed 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 1 ABC SSP UNITRAT low resolution kit (Pel-Freeze) was used. The primer sets amplify all alleles described by the International Nomenclature Committee of WHO in 19953 and in 1997.4 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 DNA sequencing reaction allowed the incorporation of fluorescently labelled dideoxynucleotides 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 1 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 region.2 Some 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.8 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.2 D’Amato and coworkers have tested 35 Sardinian patients with AS and 40 Sardinian B27 positive healthy subjects by genomic typing.2 None of the patients with AS were found to be B*2709 positive, in contrast to 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. 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. 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. They also reported that those allo-cells were T lymphocytes and infiltrated lesions. 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 without non-quantitative assay. 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 used by the primers Y1–1, Y1–2, Y1–3, and Y1–4, which are specific for a part of the Y chromosome sequence, DVZ1, as described previously.1 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 exact 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 DVZ1 was most commonly found in Barnett’s type III (four of five). The DVZ1 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 DVZ1 negative group (eight of 10). All three patients with SSc who had PBC were DVZ1 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, DVZ1 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></th>
<th>SSc</th>
<th>SLE</th>
<th>SSc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years, mean (range))</td>
<td>56.1 (44–74)</td>
<td>50.2 (34–82)</td>
<td>57.1 (27–47)</td>
</tr>
<tr>
<td>Duration of illness (years, mean (range))</td>
<td>10.2 (1–26)</td>
<td>11.9 (1–24)</td>
<td>8.7 (1–19)</td>
</tr>
<tr>
<td>DVZ1 positive (No (%))</td>
<td>10% (50)</td>
<td>0% (0)</td>
<td>0% (0)</td>
</tr>
<tr>
<td>Healthy controls</td>
<td>8 (20)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*p=0.017, systemic sclerosis (SSc) vs healthy volunteers. **p=0.028, healthy volunteers and systemic lupus erythematosus (SLE). **SSS = Sjögren’s syndrome.
This 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 (one), and low dose steroids (two). Clinical evaluation and measurement of suPAR, erythrocyte sedimentation rate (ESR), and C reactive protein (CRP) were done at a median of three times, and the time interval between radiographs was a median of 22 months.

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

<table>
<thead>
<tr>
<th></th>
<th>No erosive progression (n=11)</th>
<th>Erosive progression (n=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESR† (mm/1st h)</td>
<td>24 (15–24)</td>
<td>6 (3–20)</td>
</tr>
<tr>
<td>CRP† (mg/l)</td>
<td>11.4 (6.1–30.1)</td>
<td>1.51 (0.93–2.73)*</td>
</tr>
<tr>
<td>suPAR† (µg/l)</td>
<td>1.3 (0.56–2.90)*</td>
<td>1.03 (0.56–2.09)*</td>
</tr>
<tr>
<td>CRP</td>
<td>11.4 (6.1–30.1)</td>
<td>1.51 (0.93–2.73)*</td>
</tr>
<tr>
<td>suPAR</td>
<td>1.3 (0.56–2.90)*</td>
<td>1.03 (0.56–2.09)*</td>
</tr>
</tbody>
</table>

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 (one), and low dose steroids (two). Clinical evaluation and measurement of suPAR, erythrocyte sedimentation rate (ESR), and C reactive protein (CRP) were done at a median of three times, and the time interval between radiographs was a median of 22 months.

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

<table>
<thead>
<tr>
<th></th>
<th>No erosive progression (n=11)</th>
<th>Erosive progression (n=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESR† (mm/1st h)</td>
<td>24 (15–24)</td>
<td>6 (3–20)</td>
</tr>
<tr>
<td>CRP† (mg/l)</td>
<td>11.4 (6.1–30.1)</td>
<td>1.51 (0.93–2.73)*</td>
</tr>
<tr>
<td>suPAR† (µg/l)</td>
<td>1.3 (0.56–2.90)*</td>
<td>1.03 (0.56–2.09)*</td>
</tr>
<tr>
<td>CRP</td>
<td>11.4 (6.1–30.1)</td>
<td>1.51 (0.93–2.73)*</td>
</tr>
<tr>
<td>suPAR</td>
<td>1.3 (0.56–2.90)*</td>
<td>1.03 (0.56–2.09)*</td>
</tr>
</tbody>
</table>

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 (one), and low dose steroids (two). Clinical evaluation and measurement of suPAR, erythrocyte sedimentation rate (ESR), and C reactive protein (CRP) were done at a median of three times, and the time interval between radiographs was a median of 22 months.

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

<table>
<thead>
<tr>
<th></th>
<th>No erosive progression (n=11)</th>
<th>Erosive progression (n=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESR† (mm/1st h)</td>
<td>24 (15–24)</td>
<td>6 (3–20)</td>
</tr>
<tr>
<td>CRP† (mg/l)</td>
<td>11.4 (6.1–30.1)</td>
<td>1.51 (0.93–2.73)*</td>
</tr>
<tr>
<td>suPAR† (µg/l)</td>
<td>1.3 (0.56–2.90)*</td>
<td>1.03 (0.56–2.09)*</td>
</tr>
<tr>
<td>CRP</td>
<td>11.4 (6.1–30.1)</td>
<td>1.51 (0.93–2.73)*</td>
</tr>
<tr>
<td>suPAR</td>
<td>1.3 (0.56–2.90)*</td>
<td>1.03 (0.56–2.09)*</td>
</tr>
</tbody>
</table>

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 (one), and low dose steroids (two). Clinical evaluation and measurement of suPAR, erythrocyte sedimentation rate (ESR), and C reactive protein (CRP) were done at a median of three times, and the time interval between radiographs was a median of 22 months.

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

<table>
<thead>
<tr>
<th></th>
<th>No erosive progression (n=11)</th>
<th>Erosive progression (n=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESR† (mm/1st h)</td>
<td>24 (15–24)</td>
<td>6 (3–20)</td>
</tr>
<tr>
<td>CRP† (mg/l)</td>
<td>11.4 (6.1–30.1)</td>
<td>1.51 (0.93–2.73)*</td>
</tr>
<tr>
<td>suPAR† (µg/l)</td>
<td>1.3 (0.56–2.90)*</td>
<td>1.03 (0.56–2.09)*</td>
</tr>
<tr>
<td>CRP</td>
<td>11.4 (6.1–30.1)</td>
<td>1.51 (0.93–2.73)*</td>
</tr>
<tr>
<td>suPAR</td>
<td>1.3 (0.56–2.90)*</td>
<td>1.03 (0.56–2.09)*</td>
</tr>
</tbody>
</table>