Epidemiology of whiplash

Space restrictions prohibit a comprehensive refutation of the uneven treatment of the whiplash literature presented by Ferrari and Russell.1 They fiercely interrogate research that does not support their view, yet uncritically embrace literature favouring their preconceptions. Central to their argument is the assertion that there are different rates of chronic whiplash in different countries, and that injury-related damage cannot account for the wide differences.1

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.1 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 front costs for potential claimants. Some then venture to raise alarm about whiplash, suggesting a biased sample. However, the advertisement was in a medical journal, seeking doctors to enrol participants, producing a self-selected, self-representative sample. Ferrari and Russell have used these studies in a previous article, apparently accepting the methodology then.3 These flaws alone raise grounds for concern that the opinions of Ferrari and Russell are not responsibly based. An appraisal of the literature and will raise alarm and reinforce prejudice against genuinely afflicted patients.

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Through their leader, Ferrari and Russell’ 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.4 Meanwhile, the study of Borchgreivik et al. of a placebo-controlled trial of treatment during the first 14 days after a car accident.5 


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Making selective use of the literature and incorrect quoting of previous research, the January 1999 “leader” intends to support the view of the whiplash syndrome as malinger.

This reply cannot be exhaustive but will address the following:

The Ballas paper lacked a definition of the whiplash syndrome and did not describe the assessment of 300 selected cases seen in a single practice. Moreover, selection bias among patients who were “nontreated” control group too. Furthermore, in 20 patients in Singapore with acute whiplash, the injury severity or risk of developing long term syndromes was not specified. Methodological flaws of the Ballas publication are reflected by the fact that this study was not considered relevant by the Quebec Task Force and neither were a number of other references in the “leader.” To interpret late whiplash as based on 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 in USA is discussed in Miller's 1961 BMJ article, which reports 200 cases examined between 1955 and 1957.

This is well within the timeframe of the 1953 JAMA whiplash paper. Miller reported an inverse relation between accident severity 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 major interest of the “leader.” The non-existence of whiplash in the United Kingdom while it has been described for more than 30 years in USA is discussed in Miller's 1961 BMJ article, which reports 200 cases examined between 1955 and 1957. This is well within the timeframe of the 1953 JAMA whiplash paper. Miller reported an inverse relation between accident severity 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 major interest of the “leader.”

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 more cautious reporting is best predicted by non-related accident stressors”. The study quoted in the leader used a biased selection of 39 patients, which was three times fewer than 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 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 be more tired of commenting, which eventually may help them to introduce the malinger hypothesis for whiplash injury.

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11 Elliott AM, Smith BH, Penny KI, Smith WC, et al. Chronic pain in say, Canada. We find that whiplash in Canada (and reportedly in many other countries) is an illness in a non-accident related stressor, 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 discuss an explanation for this difference in recovery rates.

It is certainly possible that a small proportion of subjects could have chronic structural damage in countries like Lithuania, as Dr Bogduk suggests, and that current studies with background prevalences of neck pain in the control population of up to 10% are not large enough to distinguish an additional 2–3%. Yet, this additional 2–3% of patients are not the group of patients we are describing; it is the 50% of patients with chronic pain at six months11 that we are concerned with, and the cervical zygapophysial studies are not relevant for this larger group. Indeed, we were not aware that the subjects of Dr Bogduk’s study had a reported decrease in velocity impacts (a AV of 30–60 kph) as Dr Bogduk indicates. This fact makes it even less likely that their study group is typical of most patients with chronic whiplash, who instead undergo much lower velocity collisions. Clearly, and for good reasons, Dr Bogduk’s study patient spectrum is very different from the group we are concerned with. Our disagreement is not substantially with the few per cent that he may see with facet 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 understand that 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, both the therapeutic community and society at...
large, that this is part of the problem, this practice is unlikely to change.

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

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6 Cassidy JD, Carroll L, Lemstra M, Cote P, Berden J, MacIntyre K. The biopsychosocial model incorporates psychosocial factors to explain sometimes enigmatic and inexplicable chronic injury, chronic pain of whiplash is due to an underlying problem. As we have explicitly stated, in our biopsychosocial model is one of maladaptive beliefs and the patient may be thought of as not merely a biological being but also a social being.

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

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**Table 1**

<table>
<thead>
<tr>
<th>Social class</th>
<th>RA cases Merseyside (239)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-2 No (%)</td>
<td>35 (15)</td>
</tr>
<tr>
<td>3N-4M No (%)</td>
<td>73 (47)</td>
</tr>
<tr>
<td>4-5 No (%)</td>
<td>30 (19)</td>
</tr>
</tbody>
</table>

*p<0.0001; †p<0.05.*

†Social class based on the Office of National Statistics classification of occupations. §N = non-manual; M = manual.
We welcome the letter entitled “Rheumatoid arthritis, poverty, and smoking” in response to our article “Does social disadvantage contribute to the excess mortality in rheumatoid arthritis patients?” The importance of looking as a contributor to the influence of socioeconomic deprivation on mortality is rightly emphasised. However, as Black has pointed out eloquently, smoking alone does not account for the excess mortality seen among lower socioeconomic groups.

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

In this study, the “gold standard” against which the criteria performance is to be measured is the presence of RA, generally defined as a clinical diagnosis. Although the factors which can be modified most effectively to reduce the inequalities in health outcome also require investigation.

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

Diagnostic evaluation of classification criteria for RA and reactive arthritis

We read with interest the recent article by Hölsemann and Zeidler, in which the 1987 American College of Rheumatology (ACR) classification criteria for rheumatoid arthritis (RA) were evaluated for their ability to identify patients with a clinical diagnosis of RA among 217 patients referred to an early arthritis clinic. The authors concluded that the 1987 ACR criteria can be used to make a diagnosis of RA in this setting.

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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.
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 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 our early arthritis out-patient clinic, the diagnosis between 1984 and 1986, the 1985 American Rheumatism Association (ARA) criteria had not been revised. Expert diagnoses were made with knowledge of the 1985 ARA criteria for the diagnosis of RA but were not the basis of diagnoses. Trained as clinicians, rheumatologists never used the ACR criteria for diagnosis making. Only in retrospect, were the 1987 revised ACR criteria applied. These criteria 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 arthritides. Since the performance was good with a high sensitivity (90%) and a high specificity (90%), we suggested, that these criteria could be used not only as classification criteria but also as criteria for 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, one had unchanged progressive uncphilized arthritis, and one patient had developed ankylosing spondylitis. In accordance with our experience, van der Horst-Bruinsema et al have shown, in a special early arthritis study, 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 diagnosis, diagnosed at two weeks after the first visit, 66 still had definite RA after one year, and in only four patients was the diagnosis changed to systemic lupus erythematosus (one), undifferentiated 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 their arthritis as undifferentiated arthritis. This is a working diagnosis, which can be changed to a definite diagnosis during follow up, but is only rarely necessary, as our experience and Harrison et al shows. The 1987 ACR criteria are not valid for prognostic purposes as Harrison et al stated. Other prognostic factors exist and can easily be applied to patients with RA. But the ACR criteria for RA are not 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 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 arthritides, enabling early diagnosis and treatment decisions.

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

An interesting paper was published recently in the domain of rheumatology, discussing the effect of intra-arterial administration of primatised anti-CD4 antibody in the knee joints of patients with rheumatoid arthritis and persistent synovitis, unresponsive to treatment. The paper correctly detailed the disappointing results obtained in clinical trials with parenteral treatment with anti-CD4 antibodies, particularly in view of the supposed pivotal role of CD4 positive T cells in the chronic synovitis of rheumatoid arthritis.

The paper showed an apparent improve-ment in the knee synovitis in patients treated with a low (three patients) and high (seven patients) dose of intra-arterial anti-CD4 antibody and no response in two patients treated with placebo, using a combination of magnetic resonance imaging, arthroscopic scoring of the synovium, and immunohistochemical labelling of the synovial biopsy specimens.

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

Also, there was a marked disparity in baseline C reactive protein (CRP) levels between the three treatment groups, with the placebo group having a far greater level (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 25% 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 (the T cell and anti-CD4 antibody and its obvious lack of activity on macrophages). There was with treatment illustrated in fig 3 (see ref 1) are also unimpressive and it is difficult to see a great difference between the MRI images obtained before and after treatment.

Finally, the reader should be aware that immunohistochemical labelling of the syno-vial membrane with anti-CD4 antibodies will label CD4 positive T cells and macrophages (which also express CD4), so the authors cannot establish whether or not their treatment has had an effect on macrophages rather than CD4 positive T cells.

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

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

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Authors’ reply

We thank Professor Smith for his interesting comments. Professor Smith refers to an “obvious omission...any doctor or patient derived clinical parameters”. Clearly, we had measured the knee circumference of the target knee in this situation, and we were using knee swelling as a clinical parameter; in table 1 of our paper it can be seen that there was no significant change in the knee circumference in any of the treatment or placebo groups during the study. Although we did not show the data in the results section, we stated that there was no statistically significant improvement in the doctor’s assessment of knee synovitis over the study period. Therefore, we do not suggest that there was a marked clinical response to treatment in these patients. We agree that there was a marked disparity in the baseline CRP levels within the three groups, but this was a result of randomisation and therefore something over which we had no control.

As regards the changes in MRI measurements, and the quantitative maps showing the reduction in gadolinium uptake, we believe that the trend towards the dose response across the three groups was clearly the most important interpretation of these results. We do not agree, however, with the reader’s interpretation that a possible range of change of 25% is small, especially as the patients had longstanding, resistant disease. The mean duration of disease for these patients was about 12 years and they had undergone multiple treatments with disease modifying antirheumatic drugs.

Professor Smith’s final point about anti-CD14 antibodies, which label macrophages as well as T cells, we clearly discussed in the third paragraph of the discussion—“There are a number of possible explanations for this apparent reduction in the number of CD14+ cells, which may represent a reduction in T cells or macrophages...”

In summary, we believe that this was an important study, firstly, as a proof of concept that 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, CD14+ mononuclear cells outnumbered CD36+; 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.

Letters to the Editor

CD36 and CD14 immunoreactivity of Reiter cells in inflammatory synovial fluids

Reiter cells are macrophages containing ingested polymorph nuclei that are commonly found in most inflammatory synovial fluids. Available data indicate that CD36 and CD14 on human monocyte derived macrophages are adhesion molecules involved in several biological processes. Of interest, their role in the process of adhesion and phagocytosis of apoptotic cells has been recently demonstrated.

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

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

We analysed the synovial fluids obtained from the knee joints of 10 patients suffering from inflammatory joint diseases of recent onset (<6 weeks). Three patients had sero-positive active rheumatoid arthritis, four patients had seronegative spondyloarthritis (two reactive arthritis, one psoriatic arthritis, one enteroarthritis) and three patients had crystal induced arthritis (two cases of acute gout and one case of acute pseudogout). Synovial fluids were processed within one hour of aspiration. Two slides were stained with May-Grunwald-Giemsa (MGG) reagent. Reiter cells were counted on the basis of the first 500 cells encountered on MGG stained slides. In addition, two cytocentrifuge monolayer preparations were processed for immunohistochemistry using the monoclonal anti-human-CD36 antibody (Boehringer Mannheim-Germany) diluted to 3.5 mg/ml and the monoclonal anti-human CD14 antibody (DAKO-Denmark) diluted 1:10 in TRIS-HCL buffer. In brief, specimens were air dried, fixed with acetone and then stored at −70°C until processing. The specimens were incubated for 60 minutes at room temperature with the primary antibody. For the conjugation of peroxidase an En Vision+TM Kit (Dako) was used. The monoclonal layers were then incubated for five minutes with a prediluted diaminobenzidine 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 antisera, 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 spondyloarthritis 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 results suggest that CD14 and CD36 are adhesion molecules. CD36 expression on Reiter cells seems to support the notion of the involvement of this receptor in the clearance of apoptotic PMN during synovial inflammation. In vitro data have shown that thrombospondin receptor and CD14 are some of the most important adhesion molecules involved in cell clearance. The expression of the thrombospondin receptor turns an amateur phagocyte into a professional one. It has been hypothesised that dysregulation of this receptor and the ensuing impairment of inflammatory cell elimination could play a part in inducing chronicity as well as tissue damage and scarring. Recently, CD14 has been demonstrated to mediate recognition and phagocytosis of apoptotic cells. This interaction depends on a region of CD14 that is supposed to be identical to a region that binds bacterial lipopolysaccharide, triggering the release of proinflammatory cytokines from macrophages. On the other hand, the interaction with self components acts as an initial step leading to apoptotic cell elimination. A major role for CD36 in the uptake of apoptotic neutrophils has been recently hypothesised, but it seems likely that micro-environmental modifications could promote the switch from a CD36 dependent pathway to pathways using other adhesion molecules such as CD14. The removal of inflammatory PMN is mediated by several surface molecules and modulated by microenvironmen- tal 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 characteristic 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 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 proveck these symptoms. Table 1 shows the questionnaire. Positive cases were also questionned for the presence of swelling or redness during these painful periods, and whether these complaints followed by an episode. Although 14 of the 180 healthy subjects responded positively to the first question (question A), none of them were considered to be positive after further questions (questions 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 toes, however other sites (the ankles, the calves, the knees or even the thighs) were involved in an additive manner as the intensity of pain increased unless resting ensued. Thirty five 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 typically located on the soles or ankles of those occasions. Thirty five patients define a period of fatigue accompanied a low grade fever subsequent to the episodes with severe lower extremity symptoms.

In provocation test, 30 voluntary male FMF patients (age, 21.2 (1.8)) without proteinuria and 30 voluntary male healthy subjects (age, 21.1 (0.8)) were kept in an upright position (standing, walking or walking, and sitting for six hours. At the beginning, all participants were symptomatic 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 knee circumference changes 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 1.3 (0.5) 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, and those 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 erythematicous 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 developped 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, 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 compense 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.

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Table 1 Questionnaire on lower extremity complaints

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

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

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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.