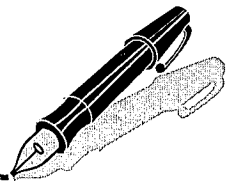
Correspondence



INSTRUCTIONS FOR LETTERS TO THE EDITOR

Editorial comment in the form of a Letter to the Editor is invited; however, it should not exceed 800 words, with a maximum of 10 references and no more than 2 figures (submitted as camera ready hard copy per Journal Guidelines) or tables and no subdivision for an Abstract, Methods, or Results. Letters should have no more than 3 authors. Full name(s) and address of the author(s) should accompany the letter as well as the telephone number, fax number, or E-mail address.

Contact. **The Managing Editor, The Journal of Rheumatology, 920 Yonge Street, Suite 115, Toronto, Ontario M6J 3G7, CANADA. Tel: 416-967-5155; Fax: 416-967-7556; E-mail: jrheum@jrheum.com Financial associations or other possible conflicts of interest should always be disclosed.**

Do Elevated Levels of Serum C-Reactive Protein Predict Rheumatoid Arthritis in Men: Correlations with Pre-RA Status and Baseline Positive Rheumatoid Factors

To the Editor:

A recent case-control (n = 124, 365) cohort study[1] concluded that, "pre-rheumatoid immunological process as reflected in RF production is not associated with any marked inflammation or tissue injury heightening C-reactive protein (CRP)." That study including 39 male and 85 female pre-RA cases[1] also showed no difference in CRP concentrations between subjects positive and negative for RF at baseline. Authors inferred that the prerheumatoid immunological process reflected in RF production is not associated with any marked inflammation or tissue injury[1].

Our baseline findings in adult males from a case-control study nested within a community cohort (n = 8745 males) offer a different perspective from the reported interpretations[1]. The 18 incident male RA cases developed American College of Rheumatology (+) disease 3 to 20 years (median 12) after entry at baseline in 1974[2]. Four controls (CN) from the same entry cohort were matched to each case for age, sex, and race (all Caucasian).

Rheumatoid factors were assayed by 3 methods. The 2 whole sera assays were Behring nephelometer and ELISA (Hemagen Diagnostics Inc, Waltham, MA, USA, according to manufacturers' instructions) techniques against human IgG[3,4]. The third assay was an IgM isotype-specific ELISA against rabbit IgG[5]. Elevated concentrations for both whole sera methods are 20 IU/ml. For purposes of this study, elevated levels for the IgM method are 52 IU/ml. Serum CRP was assayed by an ultrasensitive antigen capture ELISA (Hemagen Diagnostics) with a detection threshold of 0.1 µg/ml and elevated levels of 8.0 µg/ml[6]. Acute serum amyloid-A (ASAA) concentrations were assayed by ELISA (Hemagen Diagnostics) with a detection threshold of 1.0 µg/ml and elevated levels for males of 10.0 µg/ml[7].

Associations among only the elevated concentrations of CRP, ASAA, and RF were determined (Table 1), unlike the previous study[1], which analyzed CRP concentrations across the full ranges of values, stratified by either quintiles or the highest deciles. Fisher's exact test was used to determine p values (2 tailed) for comparisons of the 18 pre-RA versus the 72 controls in dichotomous distributions of their elevated analyte values. This test was also used to assess the probability of associations of elevated CRP with other elevated analyte values in single samples, in either the pre-RA cases (i.e., *,† in Table 1) or controls (i.e., ‡ in Table 1).

Baseline rheumatoid factor elevation (RF+) by one or more methods was found in 6 (33.3%) of 18 pre-RA cases versus 6 (8.3%) of 72 controls (p = 0.012). RF+ by 2 or more methods was observed in 4 (22.2%) pre-RA cases, but in no controls (p = 0.001). Elevated CRP levels (CRP+) were found in 4 (22.2%) pre-RA cases versus 4 (5.6%) controls (p = 0.048). Concordance of CRP+ and any RF+ was found only in the pre-RA cases (p = 0.005), and the overlap was complete in the 4 pre-RA cases having 2 or more RF+ (p < 0.001).

Elevated ASAA levels occurred in 5.6 % of both pre-RA and control subjects. The one pre-RA case with an elevated ASAA level was CRP+ and had all 3 RF+. In controls, CRP and ASAA concentrations were each elevated in 4 subjects, 3 of whom had positive concordance (p < 0.001), and none had elevation of any RF. Thus, elevated CRP concentrations were associated with pre-RA status (p = 0.048), but not independently of RF+. Elevated CRP was associated significantly (p = 0.005) with RF+ only in the pre-RA cases. As expected[8], CRP+ was associated significantly (p < 0.001) with ASAA+ in controls (Table 1).

A subset of 16 (44.4%) of our 36 pre-RA females had assays of serum CRP, ASAA, and IgM isotype-specific RF. Baseline serum RF+ was significantly associated with pre-RA status to a similar degree as in males. In controls, CRP was significantly (p < 0.001) associated with ASAA (data not shown). In our female subjects, CRP did not associate with either pre-RA status or baseline RF+, as reported[1].

The prerheumatoid immunologic associations in our male sample differ from control findings (Table 1) and support recent observations of significant correlations between hormones and biological mediators or modulators of inflammation long before clinical onset of RA[2]. The prerheumatoid immunological process, as reflected in RF production[1-4], may be associated with longterm, systemic physiological perturbations of the normal counter-regulatory cytokine and modulator networks of inflammation[2,9]. Putative asymptomatic synovitis or other intraarticular inflammatory processes may be hypothesized as preceding clinical disease and causing immunological activation[1]. However, an alternative physiological perspective was proposed that chronic perturbations of the neuroendocrine, immunological, and microvascular endothelial systems may contribute to imbalances in the

Table 1. Relationships of elevated levels of rheumatoid factors (RF), C-reactive protein (CRP), and acute serum amyloid-A (ASAA) in 18 male incident RA cases before (3–20 yrs) clinical onset (pre-RA) and in 72 matched controls.

	18 Pre-RA*		72 Controls†		
	n Positive	%	n Positive	%	p
Elevations of analytes					
RF by any method	6*	33.3	6	8.3	0.012
Two or more RF	4†	22.2	0	—	0.001
CRP	4	22.2	4‡	5.6	0.048
CRP and any RF	4*	22.2	0	—	(0.005)*
CRP and 2 or more RF	4 †	22.2	0	—	(<0.001)†
ASAA	1	5.6	4‡	5.6	NS
ASAA and any RF	1	5.6	0	—	NS
ASAA and 2 or more RF	1	5.6	0	—	NS
CRP and ASAA	1	5.6	3‡	4.2	(<0.001)‡

*† Probability of CRP and RF associations in the pre-RA cases alone (in parentheses). ‡ Probability of CRP and ASAA association in the control subjects alone (in parentheses).

normal cytokine counter-regulatory processes that may predispose to chronic synovitis[9].

By interpreting results from both studies conjointly (Table 1 and[1]), and analyzing the sex-specific findings, a broader understanding of RA precursors may be achieved. Further prospective investigations of systemic physiological perturbations before the clinical onset of RA promise to clarify its complex and likely prolonged physiopathogenesis[1,2,9].

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The opinions expressed here do not necessarily reflect those of the National Institutes of Health.

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Dr. Aho, et al reply

To the Editor:

Clinical rheumatoid arthritis (RA) is preceded by an immunological process characterized by the occurrence of serum rheumatoid factor (RF) and certain other marker antibodies of RA[1]. Any satisfactory explanation for the etiopathogenesis of RA should account for this process. Pre-illness sera from healthy subjects who are known to have later developed RA are available from few population based series. Thus, it is important to try to extract all relevant information from such sera. Although there is consensus concerning the existence of the pre-rheumatoid immunological process, some variation has been noted in certain details. Thus, we did not find any increase in C-reactive protein (CRP) concentrations in pre-illness specimens compared to sera from matched controls[2], whereas Masi, *et al* in their letter report a statistically significant difference in men (but not in women). This may have been due to chance but it is possible that there are underlying differences in the immunological background of the patient series. Indeed, some interesting differences between populations have been observed, e.g., anti-RA33, one marker antibody of RA, is present in some 30–40% of Central European patients with RA. Yet this antibody occurs very seldom in Finnish RA patients and it proved to be virtually absent in a large patient series collected from the Bethesda area in the United States[3].

In view of the findings by Masi, *et al*, we now report on determinants of CRP concentrations among the control subjects who did not develop RA[2]. We analyzed such available measures for their associations with CRP that have been connected with or may be involved in the prerheumatoid

Table 1. Adjusted* odds ratio (95% CI) of elevated serum CRP concentration (≥ 1.9 μg/l, the highest tertile) for different factors.

Factor	Unit or Category	No. of Subjects Examined	No. of Subjects with Elevated CRP	OR	95%CI
Age	Per each SD, 12.2 yrs	368	121	1.01	0.75–1.38
Sex	Men	115	37	1.00	
	Women	253	67	0.51	0.28–0.92
Perceived health	Good	174	41	1.00	
	Average	140	48	1.21	0.67–2.18
	Poor	54	32	3.55	1.63–7.74
Smoking	Never smoked	230	61	1.00	
	Quit	51	19	1.66	0.77–3.57
	Cigars, pipe or < 20 cigarettes/day	51	18	1.78	0.84–3.76
	≥ 20 cigarettes/day	36	23	5.82	2.34–14.46
Body mass index, kg/m²	< 25.0	170	38	1.00	
	25.0–29.9	146	52	2.07	1.15–3.74
	30.0–34.9	40	21	5.14	2.24–11.80
	≥ 35.0	12	10	24.16	4.61–126.51

* Adjusted for all the other factors given in this table.

process. Male sex, poor perceived health, heavy smoking, and high body mass index, independent of each other, were significantly associated with an elevated CRP (Table 1). No association was noted with serum RF, antifilaggrin antibody, dehydroepiandrosterone sulfate, testosterone, alpha-tocopherol, or selenium concentrations (data not shown).

Our findings are in agreement with earlier observations indicating that slightly heightened CRP, yet within the "normal" range, is associated with a multitude of factors. It is likely that the association between smoking and elevated CRP is causal, whereas the sequence of events in most instances is not known. Smoking has to be taken into account as a confounder if some factor seems to be associated with an increased risk of RA.

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Are Care Pathways the Answer?

To the Editor:

In rheumatology we are used to the idea that there are therapies that in theory ought to work and when tested in small open studies seem to work, yet in the hard world of controlled trials are found wanting. Anti-CD4 therapy for rheumatoid arthritis (RA) is one example. I was disappointed to find neither of the recent otherwise excellent editorials[1,2], commenting on the failure by March, *et al*[3] to find benefit from an evidence based clinical pathway (or guideline), seemed prepared to grasp this option. That is, that in a similar manner guidelines that should work commonly do not in practice achieve their intended results, perhaps because the "best practice" on which they are based is itself unproven, and often even untested. A perhaps provocative corollary is that those multitudes, myself included, participating in the churning out of evidence based "best practice guidelines" should implicitly accept the imemdiate responsibility for testing them in a controlled trial setting rather than puzzling over why their acceptance is so poor.

This is perhaps only a restatement of the last paragraph of Naglie and Alibha[1], but I believe it requires emphasis. This allocation of responsibility, if accepted, might slow down or even interrupt the current torrent of often conflicting guidelines and allow the poor clinician time to catch their breath, and actually get on with treating the patients.

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Drs. Naglie and Alibhai reply

To the Editor:

We share Dr. Russell's concerns about the lack of evidence supporting many common medical practices. We agree that many interventions that have been supported only by observational data have subsequently been shown to be ineffective when subjected to well designed randomized controlled trials (RCT). As we highlighted in our editorial, critical care pathways should be subjected to the same rigorous standards of proof of benefit as other medical therapies (i.e., methodologically sound RCT) before they are widely implemented.

Care pathways are complicated by the fact that they include several interventions, some of which are supported by RCT, but others which are not. When the term "evidence based" is added to care pathways, the health care community may be misled to believe that all elements of the pathway are supported by RCT. In addition, care pathways influence care beyond the constellation of interventions that they incorporate. Care pathways can draw on resources to introduce and support their implementation and to meet their requirement for documentation. This, in turn, may have unforeseen consequences on patient care. Therefore, one cannot assume that implementation of "evidence based" care pathways will result in improved clinical outcomes. Rather, as Dr. Russell emphasizes, it is essential to evaluate them with RCT to establish that they achieve their intended result of improving patient outcomes.

I. GARY NAGLIE, MD, FRCPC; SHABBIR M.H. ALIBHAI, MD, FRCPC, Departments of Medicine and Health Administration, University of Toronto, Toronto, Ontario, Canada.

Drs. Syed and Bogoch reply

To the Editor:

Dr. Russell states that the cause of failure by March, *et al*[1] to show a benefit of the use of an integrated pathway for hip fracture care was that the best practice guidelines on which the pathway was based were flawed. He also implies that care pathways in general have this problem, which leads to their not being useful in real-world situations.

As we pointed out in our editorial[2], there are care pathways that have been successful in a variety of circumstances. These were, for the most part, in the setting of elective surgery. It cannot be said that all care pathways are flawed and should be abandoned. A number of factors determine the success of care pathways, including the best practice guidelines on which they are based. We feel that the most important determinant of effectiveness of a care pathway is the appropriateness of the circumstance in which it is implemented. Hence, in the more "controlled" elective setting, care pathways function relatively well. In hip fractures, due to their urgent nature, it is difficult to match needs and resources.

In general, we feel that care pathways can be useful where care processes are homogeneous, elective, and scheduled (e.g., total knee replacement), but in situations where comorbidity is high and complications common, and matching resources to the flow of patients is unpredictable (e.g., hip fracture), it is unlikely that they would work.

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Drs. March, *et al* reply

To the Editor:

Dr. Russell appears to make the point that just because something doesn't show a benefit in a controlled trial doesn't mean it is not a useful intervention. We would make 2 points in response to this. First, we would disagree on the one hand and defend the need for adequately powered controlled trials when deciding on efficacy, particularly in the field of rheumatology, where disease presentation is heterogeneous, natural history fluctuates markedly, and outcome measures are subjective. Second, we would agree to a certain extent in the setting where a study lacked power or when all relevant outcomes were not evaluated. Our paper on clinical pathways for hip fracture[1] did discuss possible explanations for the lack of effect on mortality. Sample size is always an issue in any study, but another important issue is choosing the outcome measures most likely to be influenced by your intervention. In our case, quality of life of hip fracture subjects was not assessed in sufficient numbers to allow analysis, but quality of life adjusted years may have been the more appropriate measure from both an individual and a societal perspective.

Dr. Russell also makes the point that guidelines may fail if not based on proven therapy and laments the existence of numerous and at times conflicting guidelines for the one condition. We agree and strongly advocate the development and implementation of evidence based guidelines that recommend interventions proven in controlled trials wherever possible, and when not available this is made explicit in the guideline. This is a solution to both Dr. Russell's problems and is the basis for our hip fracture pathway.

I believe we also agree on his final point that clinicians should take the responsibility for evaluating the guidelines they develop.

Guidelines aren't going to go away. Clinicians should not ignore them, but should get involved in their development and appraisal so that only the "good" ones are widely implemented.

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To Lump or to Split. The Importance of Tender Points

To the Editor:

Dr. Croft's editorial joins two others[2,3] in the same issue of *The Journal* in a formidable assault on the tender points of fibromyalgia (FM). We will try to deal only with the first of these papers.

We are flattered by Dr. Croft's kind remarks about our work, but we have, sadly, failed to convince him. He does not take issue with our findings that certain tender points (TP) are significantly more prevalent in population subjects with FM than in those with chronic generalized pain (CGP)[4]. He refers to our publications[5,6] and summarizes them well when he states that subjects with FM "tend to be more distressed, more disabled, and more likely to seek health care" than those with CGP[1]. He does not like to use the term fibromyalgia and prefers to talk about patients with CGP with higher or lower TP counts. He asks what the classification of patients "on the basis of a high tender point count" (that is, FM) adds to the management of chronic pain. We agree that it adds very little. That is not the issue, however. What, for instance, did the discovery of rheumatoid factor in the 1940s add to the management of rheumatoid arthritis at that time? We have to start somewhere, and defining a condition is not a bad way of doing it. Is it useful to forget about FM, and deal with CGP only? We don't think so, for several reasons: (1) there is no widely accepted definition of CGP; (2) CGP includes, of necessity, well defined entities such as polyarticular osteoarthritis, rheumatoid arthritis, polymyalgia rheumatica, etc; (3) while FM may be simply the extreme end of an epidemiological spectrum of CGP, it is more likely that we will be able to gain a better understanding of its pathogenesis, and potential treatments, by studying the extreme rather than the whole spectrum; this is the argument that Russell has made[7]; it is an argument Dr. Croft rejects because he does not think that a high TP count represents a measure of risk; in fact, it would seem that it does, not in terms of deaths perhaps, but certainly in terms of disability and distress[5,6].

We don't think there is anything mystical about TP counts. Certainly, high TP counts can occasionally be found in people who report no pain[8]. That is interesting, but it does not help our understanding of CGP or FM. TP counts give us an indirect and not very precise assessment of severity of pain and/or distress. If that were their only purpose we would agree that one should measure the "components of the distress itself"[1]. However, we think that the main reason for doing TP counts is to classify patients as having FM or not; the classification criteria for FM are meant to allow for a common language in which students of this condition can communicate with each other. A second objective, for the clinician, is that of giving the patient a label for a distressing problem. Some have argued that assigning the FM label creates "medicalization and dependency"[9]. Recent evidence shows that this is not the case[10]. Moreover, we doubt that many patients will be satisfied with a diagnosis of chronic pain. Dr. Croft assures us that "we no longer need special pleading to defend the reality of chronic pain and the suffering associated with it"[1]. We, alas, live in a less enlightened environment and deal daily with skeptical colleagues, insurers, and employers who would be less than sympathetic to a diagnosis of chronic widespread pain.

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Dr. Croft replies

To the Editor:

Drs. White and Harth defend the use of tender point counts and the use of the FM label. In response, I would like to return to the distinction between classification for research purposes and labelling in clinical practice.

The clinical syndrome, as I understand it, is "chronic widespread pain without obvious underlying musculoskeletal pathology." To reemphasize an observation from the editorial, there is strong published expert opinion that the number of tender points is not in practice used as a basis for defining this syndrome in the clinic. Further, tender point counts are not used clinically to exclude from the chronic widespread pain (CWP) syndrome those "well-defined entities such as polyarticular osteoarthritis, rheumatoid arthritis, polymyalgia rheumatica," referred to by White and Harth. These conditions have their own features that place them in those other groups.

I do not feel qualified to enter the debate as to whether this syndrome should or should not be labelled "fibromyalgia syndrome" in clinical practice, but I do accept White and Harth's point that a label can be helpful to both doctor and patient as signalling the reality and severity of symptoms. As a scientist, however, I have to ask if clinicians can demonstrate the use of "pathological" labels to be truly of benefit to the patient? Thirty years ago in British general practice, the commonest labels for neck and back pain were "cervical spondylosis" and "spinal osteoarthritis." The shift in textbooks and in practice to "neck pain" and "low back pain" as acceptable labels — although they may be difficult to define and need red flag diagnoses to be excluded — parallels a shift to more active, less radiography obsessed, more symptom and function oriented approaches to these problems. There may be beneficial effects of a label on outcome, but these need to be demonstrated in good scientific studies.

The problematic question is whether a high tender point count should be used in addition in clinical practice to define a separate entity to "chronic widespread pain without obvious underlying musculoskeletal pathology." The analogy used is rheumatoid factor, the implication being that a high tender point count is the equivalent of a definite pathological diagnosis, even though we do not yet know what that pathology might be. White and Harth hint that this then provides a more real or convincing disease entity than "chronic widespread pain without obvious underlying musculoskeletal pathology" for insurers and employers. This seems to me scientifically unjustified at present. It leaves unanswered the question of what the reality of chronic widespread pain without high tender point counts might be and overlooks the absence of evidence on the utility of the tender point count as a diagnostic procedure in clinical practice. For every instance like rheumatoid factor, there are other examples of presumed pathologies and their accompanying diagnostic features from the history of musculoskeletal pain that have disappeared from our textbooks.

However, I certainly agree with White and Harth that tender point counts are worth doing for research classification and communication, since I believe it is important to continue to investigate whether they represent distinctive neurophysiological pathology or provide clinically effective ways to subclassify for prognosis or treatment. I would also accept that carrying out a tender point count may have a clinical function as a means of communication between doctor and patient, and might play a practical part in the management of chronic widespread pain. However, my view remains that such a science of tender points has not reached the stage that gives the count a special value in clinical practice beyond what an assessment of pain and its associated distress, disability, and handicap can more practically provide.

PETER CROFT, MD, Keele University, Keele, UK.

Epstein-Barr Virus and Rheumatoid Arthritis

To the Editor:

We read with interest the article by Blaschke, *et al*[1], addressing EBER 1/2 transcripts found within synovial membrane of 2 (8%) of 25 patients with rheumatoid arthritis (RA). Hybridization signals were confined to lymphocyte infiltrates of the rheumatoid synovium. Epstein-Barr virus (EBV)-carrying cells were identified as isolated cells scattered throughout the subsynovial layer. The nature of these cells, however, could not be identified by histological means. We are confused by these results that the positive cells are lymphocytes but could not be identified. Further, there is discussion that recent experimental data indicate that rheumatoid synoviocytes (besides B lymphocytes) could be a target for EBV infection: an EBV infected fibroblast cell line was established from RA synovial tissue for the first time by Koide, *et al*[2]. However, Koide, *et al* do not say that this fibroblast cell line is a synoviocyte cell line in that paper.

In 1997, we reported the detection of EBV encoded small RNA 1 (EBER-1) and latent membrane protein 1 (LMP-1) in RA synovial lining cells[3]. We reported that EBER was observed in synovial lining cells from 8 (23.5%) of 34 RA patients, but in none of 20 patients with osteoarthritis ($p < 0.05$), nor in the one patient with psoriatic arthritis. Interestingly, EBER was localized in synovial lining cells that were located at the top of villous lesions. This was confirmed also by the 2 monoclonal antibodies to LMP-1.

We believe our article is the first report that rheumatoid lining cells (synoviocytes) — besides B lymphocytes — are a target for EBV infection.

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Dr. Blaschke replies

To the Editor:

Epstein-Barr virus (EBV) infection in the synovial tissue of patients with rheumatoid arthritis (RA) remains controversial — some early studies failed to detect the viral genome (EBV-DNA) within the rheumatoid synovium[1,2]. Using highly sensitive techniques several investigators were able to localize EBV infection in synovial tissue samples of RA patients in comparison to controls with osteoarthritis[2-7]. However, conflicting results exist with respect to the frequency of infected cells and the cell type in which EBV could be identified, as follows.

Lymphocytes. We analyzed EBV infection by *in situ* hybridization for the small EBV encoded RNA (EBER)[8]. Distribution and morphology of EBER-RNA positive cells within the rheumatoid synovium led to the hypothesis that these cells could represent lymphocytes known to be the primary target site of latent EBV infection in the peripheral blood. Until publication of the data, we failed to further characterize these cells by double staining experiments required to prove this hypothesis. By combination of *in situ* hybridization for EBER-RNA and immunohistochemistry for CD antigens 2 recent studies report the detection of EBV infection within lymphocytes of the rheumatoid synovium[6,7]. In addition, Niedobitek, *et al*[6], using double staining for the CD20 and CD79a B cell antigens, showed that these EBV infected lymphocytes belong to the B cell subset.

Synovial fibroblasts. Takei, *et al*[3] first hypothesized that synovial fibroblasts (previously defined as type B synoviocytes) also might be infected with EBV in the rheumatoid synovium: expression of EBER-RNA and the latent membrane protein 1 (LMP-1) of EBV was described in the synovial tissue from 8 of 34 patients with RA. In that study, infected cells were characterized as synovial lining cells only by histological means. Results of negative staining of EBV infected cells for the anti-pan B cell antibody (anti-CD19) were not shown. In addition, the staining pattern (an accumulation of EBER-1 positive cells at the apex of villous lesions of the synovial lining cells) was not observed in other studies[6,7].

The most important evidence for the hypothesis that rheumatoid synoviocytes could be a target for EBV infection results from the isolation of an EBV-carrying fibroblast cell line from RA synovial tissue[9]. This fibroblast cell line, designated DSEK, was studied for the expression of certain cell surface markers and cytokines known to be characteristic for synovial fibroblasts: DSEK cells were shown to be negative for lymphocyte and macrophage markers, but expressed CD44, CD58, and HLA-DR antigens and spontaneously produced interleukin 10, basic fibroblast growth factor, and transforming growth factor ß1.

In a recent study[7], the same research group reported on the frequent detection of lytic EBV infection in both lymphocytes and synovial lining cells of RA synovial tissues. These results differ from the findings of Niedobitek, *et al*[6], who could not localize EBV infection within the synovial lining cells using the same techniques. These discrepancies may perhaps be dependent on the EBV isolate or on the disease stage of the patient population studied. Thus, larger studies are still required to address this issue and to further elucidate the role of synovial Epstein-Barr virus infection for the pathogenesis of RA.

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Risk Factors for Development of Lower Limb Pain in Adolescents

To the Editor:

I read with interest the article by Shrier, *et al*[1]. This very impressive study indicates that lower limb pain in adolescents is not associated with *decreased* flexibility. However, it is my clinical impression that musculoskeletal pains in adolescents are much more commonly associated with hypermobility rather than hypomobility. The literature also generally supports this association[2-4], although one recent study failed to find a relationship between musculoskeletal pain and hypermobility in preadolescents[5]. I am unclear from my reading of their study if the authors were able to evaluate whether those individuals with the most flexibility by the 3 tests used had more lower limb pain than the rest of the group. If the most flexible individuals did not have the highest frequency of lower limb pain, this would be interesting information. It would either suggest that the tests of flexibility used are not good at measuring hypermobility, or that our clinical impression and the literature are mistaken.

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Dr. Shrier replies

To the Editor:

We thank Dr. Malleson for bringing up an important point not mentioned in our article[1]. We used flexibility to refer to limitations of range of motion due to muscle, whereas the papers cited by Dr. Malleson use the term "hypermobility" to refer to limitations of range of motion due to ligaments and/or capsule. For example, we tested the hamstring range of motion by extending the knee while the hip was flexed at 90 degrees to ensure that limitations were not due to hip or knee capsule/ligament. In contrast, hypermobility in the articles cited was defined by Beighton's criteria: (1) passive dorsiflexion of the little fingers beyond 90 degrees, (2) passive apposition of thumbs to the flexor aspect of the forearm, (3) hyperextension of the elbows beyond 10 degrees, (4) hyperextension of the knees beyond 10 degrees, and (5) forward flexion of the trunk so that the palms of hands rest easily on the floor. The first 4 of these tests clearly test ligamentous laxity and not muscle flexibility. Although the last test is an extreme measure of the Sit and Reach Test, no previous papers cited reported data associating the result of this test alone with the occurrence of musculoskeletal pain.

Although previous papers discussed ligament laxity[2-4], we have rerun our analysis dichotomizing our flexibility measures as hyperflexible (top 25%) and non-hyperflexible (bottom 75%). None of the measures predicted a risk of injury, with p values ranging from 0.4 to 0.8.

We thank Dr. Malleson for the opportunity to distinguish between these subtle but important differences in determinants of range of motion.

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Insulin-like Growth Factor and RA

To the Editor:

The recent article[1] showing an association between low levels of insulin-like growth factor (IGF-1) proteins in rheumatoid arthritis (RA) patients who are sedentary is certainly an interesting observation and not unexpected. It would be interesting to know how may patients in the study had fibromyalgia (FM), since it is known that many FM patients have low levels of IGF-1[2,3]. This is not simply of academic interest because RA and FM often coexist[4]. Clearly, increasing the level of activity in sedentary RA patients would be desirable. However, if these RA patients also have FM, but the diagnosis of FM is not made, then appropriate therapies to decrease the pain due to the FM might not be instituted, thus making an attempt to increase physical activity in such patients much more difficult and, in fact, in some patients unrealistic. Many of my patients with RA are quite active. However, many RA patients who have concomitant FM are not as active as their counterparts without FM, all other things being equal.

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Dr. Maddison replies

To the Editor:

We thank Dr. Romano for his interest in our work. We agree that he makes an important point that the presence of fibromyalgia (FM), itself associated with low levels of insulin-like growth factor (IGF-1), might have contributed to the low serum levels of IGF-1 seen in our patients with rheumatoid arthritis. However, in this study, the presence or absence of FM features was not recorded in the rheumatoid population we studied and this question cannot be addressed.

On the other hand, it is unlikely that FM made a significant contribution to the results in the nonrheumatoid group with other rheumatic complaints, the majority of whom did not have a generalized pain syndrome. Further, the 5 patients with primary FM showed a range of serum IGF-1 results from low normal levels to low (one patient).

In our study, level of exercise was the variable most closely associated with low circulating levels of IGF-1 and IGFBP-3. Currently we are examining the effect of an exercise intervention on growth hormone and IGF status.

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Clinical Correlates of Avascular Necrosis in Systemic Lupus Erythematosus

To the Editor:

I read with interest the article by Gladman, *et al* and their review of the literature analyzing predictive factors of symptomatic osteonecrosis in patients with lupus[1]. Although they give due credit for Lew Cozen's landmark work with Edmund Dubois[2] describing the syndrome in 1960, Gladman, *et al* should know of a more recent effort spearheaded by Dr. Cozen.

Now 90 years of age, Dr. Cozen is still a vibrant, active member of our medical staff. In 1998, he published an analysis similar to Gladman, *et al*, but in the orthopedic literature[2]. He spent 2 years following osteonecrosis patients and compared them with SLE patients without osteonecrosis. Analyzing numerous comparisons of 488 patients, he found statistically increased prevalences for hypertension, pleural effusions, cerebritis, nephritis, anemia, and hemolytic anemia among patients with osteonecrosis. No serologic feature, including antiphospholipid antibodies, was predictive. This information should be added to Gladman's informative review.

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Drs. Gladman and Urowitz reply

To the Editor:

We thank Dr. Wallace for his letter and the confirmation that anticardiolipin antibodies were not associated with avascular necrosis (AVN, osteonecrosis), by Dr. Cozen in *The American Journal of Orthopedics,* which we neglected to include in our reference list. However, it should be noted that while Dr. Cozen's paper describes items associated with the presence of AVN, patients were not matched for disease duration and followup. Indeed, patients without AVN had a shorter followup duration than patients with AVN, therefore it is possible that some items present in the patients with

AVN had not had a chance to develop in patients without AVN. Moreover, the analysis provided is only univariate and the p values for the items identified are very small. Nonetheless, it is important for readers to appreciate the work with these reservations in mind.

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Dermatomyositis with Normal Creatine Kinase and Elevated Aldolase Levels

To the Editor:

The literature dictates that 5–10% of cases of dermatomyositis (DM) and polymyositis (PM) can present with normal creatine kinase (CK) levels[1,2]. It has not, however, been established if one of the other less specific muscle enzymes may be a better marker of disease activity in this subset of patients with DM or PM. We describe a patient with "definite" DM[1] who had normal CK levels at the time of diagnosis and all subsequent followup visits. Interestingly, this patient had persistently elevated aldolase levels that paralleled her clinical course.

The patient is a 38-year-old woman who presented with a one year history of rash on her face, shoulders, and the anterior surface of her neck and chest. She had been admitted to hospital 4 months earlier with a one month history of daily fevers (up to 102°F), myalgias of her arms and legs, weakness primarily of the proximal muscle groups, bilateral ankle arthralgias, and the rash. She had a nondiagnostic examination at that time; however an aldolase test was not ordered (Table 1). She was then seen at our facility for worsening of her symptoms. On examination, she appeared ill. She had an erythematous, macular rash in a malar distribution on her face. There was a similar rash on her neck, chest, and shoulders. She had a purplish discoloration of her eyelids. She had no Gottron's plaques or periungual erythema. Her muscle strength was 3/5 in the proximal muscle groups of her upper extremities and 4/5 in the proximal muscle groups of her lower extremities. She did not have significant muscle atrophy.

CK level was normal (97 IU/l). Aldolase level was slightly elevated at 8.5 IU/l (normal 1.2–7.6 IU/l). Her electromyograph was consistent with myositis. The muscle biopsy showed interstitial inflammation with a few foci of endomysial pericapillary inflammation, with some spillage into the endomysium and some accompanying myophagocytosis.

Over 3 years of followup, her DM has been difficult to treat. She finally required intravenous cyclophosphamide to control her disease. Throughout the whole course of her illness her CK levels remained normal, but aldolase levels mirrored her strength and clinical symptoms (Table 2). AST levels were normal for the first 2 years of her illness and then later seemed to fluctuate with her disease state.

Reports of DM and PM with normal CK levels were first described in the 1970s[1-3]. In these original data, there is a suggestion that aldolase levels may be a useful diagnostic marker for this subset of patients. Bohan and Peter described 153 patients with DM or PM in their review article in 1977. Seven (4.6%) of these 153 patients presented with normal CK levels and 6 (3.9%) had normal aldolase levels. This contradicts suggestions that CK is a more sensitive marker for muscle diseases than aldolase[4]. They did not address if aldolase levels were increased in the cases with normal CK. They further stated that only 1.3% of these 153 patients had normal muscle enzymes when including CK, aldolase, transaminases, and lactate dehydrogenase. Vignos, *et al* addressed the evaluation of laboratory tests in the diagnosis and management of PM. They found that 4 out of 20 patients had a normal CK. Of these 4 patients, 2 had elevated aldolase levels[2].

Table 1. Patient's initial laboratory results.

Laboratory Test	Value	Normal
Creatine kinase	50 IU/l	38–174 IU/l
AST	17 U/l	0–45 U/l
ALT	32 U/l	0–50 U/l
LDH	148 U/l	0–240 U/l
C-reactive protein	0.9 mg/dl	< 0.8 mg/dl
Thyroid stimulating hormone	3.1 mU/l	0.4–5 mU/l
C3, C4	141 mg/dl, 35 mg/dl	88–200, 15–47 mg/dl
Uric acid	4.2 mg/dl	2.2–7.7 mg/dl
RF, ANA, DS-DNA, SSA, SSB, anti-Smith, anti-RNP	Negative	Negative

In 1986, Fudman and Schnitzer described 7 cases of DM without CK elevation[5]. Aldolase levels were reported for 5 of these 7. Four of the 5 patients had aldolase levels that were increased or were at the very upper limits of normal (range 11–14 units/ml, normal 3–11). The fifth patient, with normal CK and aldolase levels, had only "possible" DM with a nonspecific muscle biopsy.

Geisker and Bowers addressed the comparative utility of serum CK levels versus serum aldolase levels in the evaluation of muscle disorders in 1979[6]. They concluded that testing serum aldolase levels adds little information in these cases. While this is true in cases that have increased CK, it does not answer the question posed here. They also stated that aldolase level is of limited utility in cases with normal CK levels because it is less specific, and other disorders can elevate aldolase level, for example, hepatic or erythrocyte disorders. Simply because a test is less specific, its utility is not negated, as illustrated by this case and the others reviewed.

There have been several theories why these patients have normal CK levels. These include a circulating inhibitor of CK activity[7], late stage disease with severe atrophy[5], patients with coexistent connective tissue disease[8], simultaneous hepatic disease[9,10], or patients undergoing treatment with steroids[11]. It has also been shown that increased uric acid and cystine levels can interfere with the CK assay, yielding inaccurately low results[12,13]. These observations suggest it is useful to follow less specific muscle enzymes in patients with DM or PM and normal CK levels. Aldolase is the most sensitive and specific muscle enzyme after CK[1,2].

What is most intriguing is the evidence of a CK inhibitor in some patients with muscle diseases, as described by Kagen and Aram[7]. They propose that there may be a CK inhibitor in the muscle that is released into the circulation along with CK as a consequence of muscle cell damage in some patients. This could certainly account for patients with DM or PM who have normal CK levels. In addition, a CK inhibitor would not interfere with serum aldolase levels.

When evaluating patients for DM or PM the initial blood test should be a serum CK level. If this is elevated, then serum aldolase levels add nothing further. However, in the 5–10% of cases with normal CK levels, serum aldolase levels may be of benefit in diagnosing and following these patients.

Table 2. Patient's progressive laboratory results. Normal values shown in parentheses.

Date	CK (38–174 IU/l)	Aldolase (1.27–.6 IU/l)	AST (0–45 U/l)	ALT (0–50 U/l)	Muscle Strength/ Clinical Condition	Therapy
2/21/97	97	8.5	32	34	BUE: 3/5 BLE: 4/5	None
4/04/97	138	9.4	48	39	BUE: 4/5 BLE: 4/5	Pred 30 mg bid
12/29/97	36	10.3	23	58	BUE: 4/5 BLE: 3/5	MTX 15 mg qwk Pred 20 mg bid
4/07/98	38	9.5	44	51	BUE: 5/5 / less BLE: 4/5 / rash	CYC 1.5 g qm Pred 15 mg qd
5/12/98	41	10.4	35	69	BUE: 4/5 BLE: 4/5	CYC 1.8 g qm Pred 15 mg qd
10/23/98	48	18.9	102	Not measured	BUE: 4/5 / rash BLE: 3/5 / worse	Pred 15 mg qd
4/19/99	50	17.0	59	60	BUE: 4/5 BLE: 4/5	AZA 100 mg qd Pred 7.5 mg qd
5/24/99	59	17.2	147	86	BUE: 4/5 BLE: 4/5	AZA 125 mg qd Pred 15 mg qd
6/17/99	53	19.2	124	Not measured	BUE: 4/5 BLE: 3/5	AZA 150 mg qd Pred 12.5 mg/qd
8/24/99	41	12.0	32	63	BUE: 4/5 BLE: 4/5	CYC 1.0 g qm Pred 7.5 mg qd
9/16/99	55	8.5	34	63	BUE: 5/5/ less BLE: 4/5 / rash	CYC 1.5 g qm Pred 7.5 mg qd
10/25/99	59	11.3	51	76	BUE: 5/5 BLE: 4/5	CYC 1.5 g qm Pred 7.5 mg qd
12/02/99	48	8.1	19	36	BUE: 5/5 / no BLE: 5/5 / rash	CYC 1.5 g qm Pred 10 mg qd
1/19/00	39	9.3	41	58	BUE: 5/5 BLE: 5/5	CYC 1.5 g qm Pred 7.5 mg qd

BUE: bilateral upper extremities, BLE: bilateral lower extremities, Pred: prednisone, MTX: methotrexate, CYC: cyclophosphamide, AZA: azathioprine.

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Natural Killer Cell Ig-like Receptor Alleles in Patients with Rheumatoid Arthritis

To the Editor:

Natural killer (NK) cells are bone marrow derived lymphocytes that share a common progenitor with T cells. The NK cell function appears to be reg-

ulated by a balance between the positive effect initiated by costimulatory receptors and the specific inhibitory effect provided by receptors that are ligands for MHC class I molecules[1,2]. Human NK cells use 2 types of structures as their HLA class I receptors: the CD 94:NKG 2, a heterodimer related to C-type lectins that recognizes HLA-E molecules and a peptide derived from HLA-A, B, C, or G leader sequences; and the molecules of the immunoglobulin superfamily called the killer cell immunoglobulin-like receptors (KIR). At present, 12 KIR belonging to 2 families (KIR 2D and KIR 3D) and based on diversity throughout the extracellular, transmembrane, and intracellular domains are recognized. Since KIR have opposing effects on signal transduction pathways and effector function, it is likely that polymorphisms in KIR genes play an important role in transplantation (e.g., stem cell) and development of autoimmune diseases. In fact, it has been reported that in mice with disrupted CTLA-4 gene, CD28 stimulation via CD80 or CD86 in the absence of negative regulation by CTLA-4 leads to lethal self-aggression by T cell proliferation[3,4]. Similarly, motheaten mice carrying mutation in SHP-1 suffer from autoimmunity that results in death[5]. We investigated the role of polymorphisms in KIR genes in susceptibility to rheumatoid arthritis (RA).

We studied 98 adult Caucasian patients with RA who attended the rheumatology clinics at the McMaster University Medical Centre and the St. Joseph's Hospital in Hamilton, Canada. All patients had definite classical seropositive RA according to the American College of Rheumatology 1987 revised criteria[6]. Eighty-one unrelated normal healthy Caucasian subjects from the same geographical area served as controls. Genomic DNA was prepared from peripheral blood lymphocytes and typed for all KIR by the polymerase chain reaction (PCR) using a pair of sense and antisense primers, each possessing a 3′ residue matching a polymorphic position on a given NK cell receptor gene. The sequences of the primers for PCR amplification of KIR are essentially the same as described by Uhrberg, *et al*[7]. The amplification was performed under the following conditions: initial denaturation for 3 min at 94°C, then touchdown PCR for first 6 cycles for 30 s at 94°C, 40 s at 62°C down to 57°C, and 90 s at 72°C. This was followed by amplification for 30 cycles at 94°C for 30 s, 56°C for 40 s, and 72°C for 90 s. Amplification products were analyzed on ethidium bromide.

Statistical analysis of the distribution of KIR alleles in patients with RA and healthy controls was by Fisher's exact test. P values were corrected (pc) by multiplication with the number of comparisons made.

We examined KIR belonging to 2 families (KIR 2D and KIR 3D): KIR with long cytoplasmic domains containing immunoreceptor tyrosine-based inhibitory motifs (ITIM) responsible for inhibitory function — 2DL1, 2DL2, 2DL3, 3DL1, and 3DL2; and KIR with short cytoplasmic domains lacking ITIM and possessing a charged amino acid in the transmembrane domain that potentially activate NK cell function — 2DS1, 2DS2, 2DS3, 2DS4, 2DS5, and 3DS1. We compared the prevalence of these KIR alleles in patients with RA with those in normal healthy individuals (Table 1). It can be seen that no differences were observed in the prevalence of KIR alleles in RA patients and healthy controls. Two KIR groups of the inhibitory type, KIR 2DL1 and KIR 3DL2, were represented in all individuals typed. Among healthy subjects, 80 of 81 carried either 2DL2 or 2DL3. Similarly, 94 of 98 patients with RA carried either 2DL2 or 2DL3 ($p = 0.38$). Since KIR 2DL1 represents one HLA-C inhibitory specificity and KIR 2DL2 or KIR 2DL3 represents the other, most of the subjects thus carried KIR with 2 different HLA-C inhibitory specificities.

Every individual expressed between 3 and 5 inhibitory KIR, and between 1 and 5 noninhibitory KIR (Table 2). The prevalence of 4 inhibitory KIR was significantly ($p = 0.035$) lower in patients with RA (43.9%) compared to healthy controls (60.5%). On the other hand, a significantly ($p = 0.008$) larger proportion of patients (46.9%) carried 5 inhibitory KIR than healthy controls (27.2%). Differences were also observed in the numbers of RA patients and healthy subjects that carried 5 noninhibitory KIR (patients 5.1%, controls 14.8%; $p = 0.039$).

KIR interact with class I molecules in a fashion specific to certain alleles or set of alleles[1,2]. The KIR mediate opposing functions on signal transduction pathways and may thus play a crucial role in development of autoimmune diseases[3-5], and to control certain bacterial, parasitic, and viral infections[8,9]. In this regard, the diversity in KIR and the number of KIR that an individual expresses may have the potential to modify NK cell responses. In addition, it is evident that a balance is achieved to eliminate pathogens but avoid autoimmunity. It is likely therefore that differences in expression of the number of inhibitory and noninhibitory KIR may cause imbalance in immune response and result in development of RA. The results in our study are preliminary and need to be confirmed by other independent studies. It is also likely that the investigations of the cell to surface expression of KIR genes may be more informative to elucidate their role in susceptibility to RA.

Table 1. Prevalence (%) of KIR alleles in patients with RA and healthy subjects.

Allele	Controls, n = 81	Patients, n = 98	p
2DL1	100.0	100.0	NS
2DL2	43.2	55.1	NS
2DL3	88.9	88.8	NS
3DL1	82.7	93.9	0.03*
3DL2	100.0	100.0	NS
2DS1	48.1	41.8	NS
2DS2	32.1	43.9	NS
2DS3	37.0	28.6	NS
2DS4	83.9	80.6	NS
2SD5	0	0	NS
3DS1	49.4	45.9	NS

* Corrected p = NS.

Table 2. Prevalence (%) of the number of KIR alleles in patients with RA and healthy subjects.

	Inhibitory KIR			Noninhibitory KIR		
No. of Genes	Controls, n = 81	Patients, n = 98	p	Controls, n = 81	Patients, n = 98	p
1	–	–	–	32.1	29.6	NS
2	–	–	–	23.5	24.5	NS
3	12.3	9.2	NS	21.0	26.5	NS
4	60.5	43.9	0.035	8.6	14.3	NS
5	27.2	46.9	0.008	14.8	5.1	0.039

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Corrections

H. Abe, N. Tsuboi, S. Suzuki, et al. Anti-apolipoprotein A-I autoantibody: characterization of monoclonal autoantibodies from patients with systemic lupus erythematosus. J Rheumatol 2001;28:990-5. Figure 2 was printed incorrectly. The correct Figure 2 appears here. We regret the error.

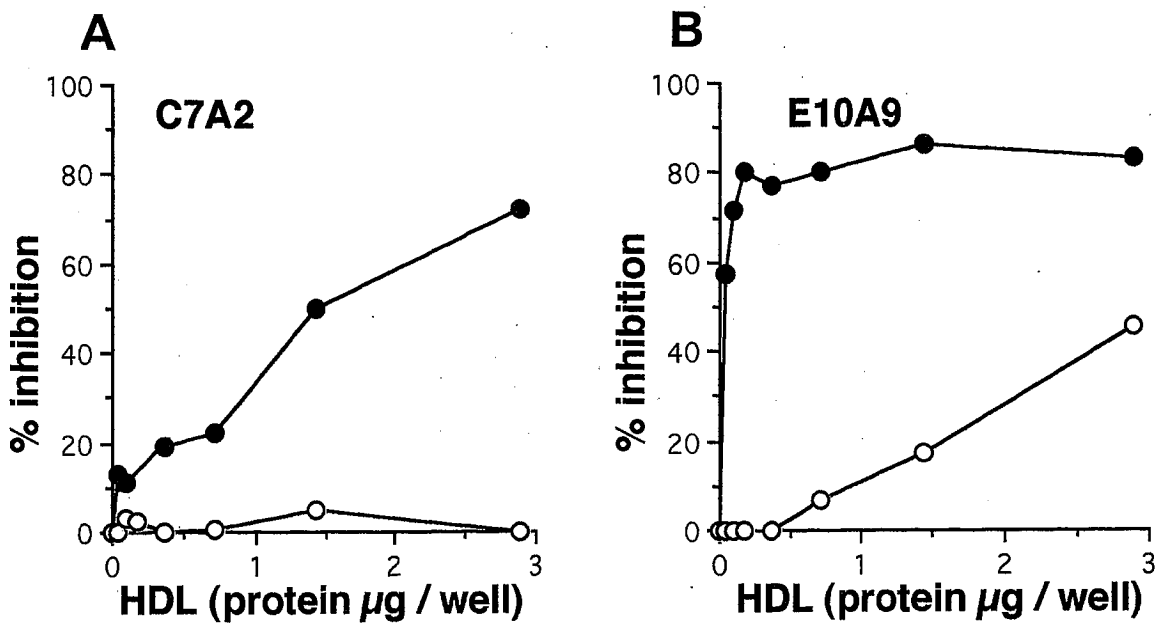

Figure 2. Inhibition of binding of MAAI to apoA-I by oxidized HDL. MAAI [C7A2 (A), E10A9 (B)] were preincubated with various amounts of native HDL (○) or oxidized HDL (●) for 1 h at room temperature. The mixture was transferred to wells preincubated with purified human apoA-I (0.25 μg/well) for 2 h. MAAI binding to apoA-I was detected by biotinylated anti-human IgM and HRP streptavidin. Inhibition of MAAI binding is shown as percentage inhibition of the binding of MAAI to apoA-I in the presence of native or oxidized HDL compared with the binding of MAAI to apoA-I in the absence of native or oxidized HDL.

Prahalad S, Bove KE, Dickens D, Lovell DJ, Grom AA. Etanercept in the treatment of macrophage activation syndrome. J Rheumatol 2001;28:2120–4. Table 1 did not appear within the article; it is reprinted here. We regret the error.

Table 1. Serial hematological variables in patient with MAS. The patient received IV solumedrol on days 4, 5, and 6. Steroids were changed to PO route on day 7. Therapy with etanercept was started on day 33. Prednisone taper was started on day 42 and was completed on day 77. Etanercept was discontinued on day 113.

Day	0	4	5	6	7	9	14	27	42	125
Leukocytes, K/µl	32.0	17.9	7.2	10.3	3.8	23.2	62.9	42.3	14	7.9
Hemoglobin, g/dl	11.3	9.8	10.2	9	9.6	10.8	9.5	10	11.7	12.2
Platelet count, K/µl	176	99	115	160	38	431	698	423	348	287
ESR, mm/h	72	91	—	—	45	—	115	80	15	10