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 4 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, 365 Bloor Street East, Suite 901, Toronto, ON CANADA M4W 3L4. 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.**

The Fate of Abstracts: Without Publication, Science Is Dead

To the Editor:

We read with interest the article by Hashkes and Uziel[1]. The authors mention that there were no studies of the publication rates from general rheumatology meetings. We agree; we are completing a similar study.

We wished to determine the publication rate in Medline–indexed journals of the abstracts presented at the XXII Spanish Society for Rheumatology meeting held in Zaragoza in 1996 and published in *Revista Española de Reumatología*[2]. A computer search was performed with the Medline data base to determine if the abstract had been published in a peer-reviewed journal from 1995 to 2001. All presentations in either poster or oral form were reviewed. The searches began with the first author's name. If a match was not found, all the authors' names were used. If a match was still not found it was assumed that the article was not published in a journal retrievable by Medline.

A total of 249 abstracts were reviewed, 200 posters (80%) and 49 (20%) oral comunications. Of these 249 abstracts, 52 were published in peer-reviewed journals, giving an overall publication rate of 21%. The average delay between the meeting and publication was 18.5 months. The majority of the papers were published in rheumatologic journals (63%). *The Journal of Rheumatology* was the preferred journal (Table 1). Four of the abstracts had been published prior to the meeting.

The publication rate of 21% was lower than other meetings, such as the Park City 4 meeting. This might indicate that the presentations were of lesser quality and the meeting less informative. However, it is important to note that language may be a barrier for the final publication of an abstract, particularly if the original language of the meeting is not English.

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Table 1. Journals in which abstracts were published (n = 52).

Journal	n (%)
J Rheumatol	13 (25)
Br J Rheumatol, Rheumatology	7 (13.4)
Arthritis Rheum	6 (11.5)
Lupus	2 (3.8)
Ann Intern Med	2 (3.8)
Tissue Antigens	1 (1.9)
Human Immunol	1 (1.9)
Medicine (Baltimore)	1 (1.9)
Semin Arthritis Rheum	1 (1.9)
Scand J Rheumatol	1 (1.9)
AJR AM J Roentgenol	1 (1.9)
Ann Rheum Dis	1 (1.9)
Inmunogenetics	1 (1.9)
Arzneimittel Forschung	1 (1.9)
Calcif Tiss Int	1 (1.9)
Clin Exp Rheumatol	1 (1.9)
Genes	1 (1.9)
Arteriosclerosis Thromb Vasc Biol	1 (1.9)
Med Clin (Barc)*	6 (11.5)
Rev Clin Esp*	2 (3.8)
Ann Pediatria*	1 (1.9)

* In Spanish.

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Drs. Hashkes and Uziel reply

To the Editor:

The timely dissemination of scientific knowledge is crucial and many important advances may be missed due to lack of publication of findings in peer-reviewed journals. Unfortunately, for various reasons, some noted in our report[1], many studies do not progress from presentation at a scientific meeting to a full, published article.

Olivé, *et al* found that only 21% of the abstracts presented at the XXII Spanish Society for Rheumatology meeting in 1996 were eventually published in peer-reviewed journals. These findings were similar to those from another recent study originating from Spain, in which only 31% of research proposals submitted to a research ethics committee were eventually published[2]. Besides the factors noted by the authors regarding the possible low quality of some presentations at their annual national meeting and the language barrier, we noted in our study that the geographic location of the authors was one of the most significant factors in determining eventual publication[1], even if the original abstract was published in English. Research quality as well as the pressure to publish and the time physicians have to dedicate to writing may differ between countries.

Studies such as those by Olivé, *et al*, ourselves, and others should not be viewed only as an intellectual exercise or as a "pat on the back" for our scientific societies' success. It is important to analyze those factors associated with an increased or decreased rate of publication. Issues of study design (case report, descriptive, analytical), study topic (etiology, epidemiology, clinical manifestations, treatment, etc.), "positivity" of results, novelty of the study, and abstract quality (whether accepted for presentation at a scientific meeting by poster or oral presentation) should be investigated in order to detect those factors that can be addressed and rectified prior to study design and writing of the paper. Only by such a process may we be

able to assist researchers in planning studies that eventually will result in the propagation of scientific knowledge through the most credible method, the peer-review process.

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Serious Gastrointestinal Events from Low Dose Analgesic Use

To the Editor:

Fries and Bruce[1] conclude that over-the-counter (OTC) use of aspirin (ASA), ibuprofen (IBU), or acetaminophen (APAP) carries little risk of serious gastrointestinal (GI) toxicity, and that these 3 analgesics at low or intermediate doses have rates of serious GI toxicity that cannot be distinguished from each other or from background. Their study data do not support the latter conclusions, nor are their conclusions consistent with the results of several previous studies.

On the basis of information obtained from semiannual questionnaires about use of ASA, IBU, APAP, other nonsteroidal antiinflammatory drugs (NSAID), or corticosteroids, each 6 months of followup for each patient from a cohort of people with rheumatoid arthritis (RA) or osteoarthritis (OA) was assigned by Fries and Bruce to one of 9 categories of analgesic use[1]. The categories were defined by use of each of the 3 study analgesics alone (i.e., neither the other 2 study analgesics nor any other NSAID nor corticosteroids were used during the 6 month period), use of each study analgesic with concurrent therapy (i.e., at least one of the other study analgesics or another NSAID was used as well, but no corticosteroids were used), or use of each study analgesic with corticosteroids and concurrent therapy (i.e., corticosteroids and possibly also other analgesics were used as well). The rates of adverse GI events associated with ASA, IBU, and APAP were then compared during periods of use alone, periods of use concurrent with other analgesics, or periods of use with corticosteroids and possibly other analgesics. No attempt was made in these comparisons to adjust for use of other medications (e.g., antihypertensive drugs and cardiovascular medications), which the authors claim are "not known to be associated with serious GI events." In addition, no attempt was made to adjust for chronic diseases other than arthritis, in spite of the authors' admission that comorbid disease conditions would be expected in RA and OA patients.

There may be no combination of drug and disease with a greater potential for confounding by indication than the combination of APAP and adverse GI events[2]. The risk of adverse GI events is increased in people with chronic diseases other than arthritis, such as heart failure and diabetes[3,4]. Anticoagulants increase the risk of GI bleeding more than any other pharmacologic agents, although other drugs such as digoxin and diuretics have also been shown to increase the risk of adverse GI events more than corticosteroids[3,4]. The potential for confounding by indication arises because APAP is preferentially prescribed (rather than NSAID) for patients with a wide variety of chronic diseases[5,6]. As a result of this channeling bias patients taking APAP are much more likely than patients taking NSAID to have a variety of chronic diseases (e.g., heart failure, ischemic heart disease, cancer, or renal failure), to be taking several different types of medications (e.g., corticosteroids, anticoagulants, antihypertensive drugs, or antidiabetic agents), to be taking multiple medications, and to have had a recent hospitalization[7,8]. The fact that people taking APAP are more likely to be chronically or seriously ill leads to profound biases in the estimates of mortality risks in APAP users[9]. In most epidemiologic studies, information on disease history and drug history is inadequate or incomplete. Thus, residual confounding by indication will likely remain in studies of APAP and adverse GI events, even when a thorough statistical adjustment based on all relevant information is attempted[10]. Fries and Bruce failed to adjust for comorbid diseases and classes of medications known to be associated with adverse GI events in their analyses, and hence their risk estimates for APAP are almost certainly positively biased due to confounding by indication[2].

In spite of the likelihood of confounding by indication in the estimates presented by Fries and Bruce, it is noteworthy that in periods in which only a single analgesic was used, APAP had the lowest rate of serious GI events in both the RA and the OA patients, whether the rates were calculated per person (their Table 3) or on the basis of person-years (their Table 4)[1]. Higher rates of GI events for APAP users were observed only in periods in which other drugs were used as well, that is, periods in which confounding by indication would be most likely. Fries and Bruce argue that the appearance of a dose-response for APAP in periods of multiple drug use argues against confounding by indication, but this is almost certainly not the case. Physicians may be particularly careful to prescribe APAP rather than an NSAID to high-risk patients when a full therapeutic dose of an analgesic is needed; that is, even an apparent dose-response can be induced by confounding by indication. Thus the results of the statistical analyses by Fries and Bruce do not support the conclusion that APAP, ASA, and IBU have indistinguishable GI toxicities.

Although Fries and Bruce state in their Abstract that the risk of GI complications at low doses of NSAID "remains unknown," there is ample evidence, including evidence from randomized clinical trials, of increased risk of GI bleeding for ASA doses as low as 75 mg per day[11-15]. A number of studies comparing the risk of adverse GI events in users of APAP and users of ASA or NSAID have concluded that the risk is lower in users of APAP, at both low and high doses[5,16-18]. Moreover, a recent analysis of the ARAMIS data bank that was the basis of the Fries and Bruce study reported a relative risk of 3.9 for serious GI complications for OTC use of NSAID, but reported that APAP "was not associated with increased risk of GI complications."[19]

Fries and Bruce cite 2 studies as being consistent with their conclusion that APAP does not have lower rates of adverse GI events than NSAID at low doses, but neither study supports such a conclusion. The first, a case-control study, reported no increase in the risk of GI complications for APAP at doses of 2000 mg per day or lower[20]. In contrast, the risk of GI complications for low or medium doses of NSAID in the same study was 2.4 (95% confidence interval 1.9, 3.1)[20]. Even the reported increased risk of GI bleeding at higher doses of APAP in this case-control study must be viewed with caution, because of the likely influence of confounding by indication[2]. Adjustment for potential confounding factors resulted in decreases in the relative risk estimates (often substantial decreases) for every measure of APAP use in this study (see their Table 1)[20], suggesting that positive bias due to residual confounding by indication is almost certain to be present in the risk estimates for APAP. The second study cited by Fries and Bruce in support of their conclusions was a retrospective cohort study[7]. This study documented the high degree of confounding by indication that is likely in evaluating adverse GI events associated with APAP (compared to NSAID). Although adjustment using a propensity score was employed, it is unlikely that such adjustment completely eliminated confounding by indication in the estimates of risk for APAP. In spite of the likely presence of residual confounding, however, the risk of adverse GI bleeding events (relative to the risk at high doses of NSAID) was lower for APAP at doses of 2600 mg per day or lower (relative risks ranging from 0.59 to 0.78) than the risk of adverse GI bleeding events for low dose NSAID (relative risk of 0.9) (see results in Table 6)[7]. Thus both studies cited by Fries and Bruce are consistent with a lower risk of adverse GI events at low doses of APAP compared to low doses of NSAID.

The potential for adverse events associated with commonly used drugs must always be considered and balanced against the potential benefits. Based on careful considerations of such risks and benefits, APAP has been proposed as the first-line analgesic therapy for patients with OA and RA[19,21] as well as for people taking low dose ASA for cardioprotection[22]. The absolute risk of adverse GI events is low for ASA and IBU at low doses, but the even lower risk of adverse GI events with APAP should be considered in making decisions about analgesic use.

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To the Editor:

The recent article by Drs. Fries and Bruce[1] states several conclusions that deserve comment and, unless and until confirmed, need to be viewed with cautious skepticism.

The conclusion that risk of gastrointestinal (GI) events with acetaminophen is low is likely correct. However, the conclusion that the risk of GI events for the 3 agents is similar not only runs contrary to conventional wisdom, it contradicts the large, established body of literature that documents that nonsteroidal antiinflammatory drugs (NSAID), aspirin, and ibuprofen have substantial GI risks[2-5] in contrast to non-NSAID analgesics such as acetaminophen. Therefore the authors' observations are likely flawed by significant methodological biases inherent in their assessments and by confounding by indication.

The GI events Fries and Bruce describe are neither numerically nor qualitatively consistent with the number or pattern of GI events described in study populations previously. From a quantitative perspective, the authors expressed GI event rates per 1000 patient-years while the convention for studies of this type is to report event rates per 100 patient-years[6,7]. Well established data indicate that expected rates of GI events with low dose aspirin should be 0.5 to 3.0% per 100 patient-years[2,3]. In the Fries study, GI event rates with aspirin are 4.0% per 1000 patient-years[1], roughly 10% of that expected based on previous reports. Similarly, with low dose ibuprofen the authors report event rates that are likely one-half to one-tenth that expected from previous studies of low dose ibuprofen. Since GI risks of aspirin have previously been extensively evaluated, GI event rates with aspirin should serve as a standard to validate the accuracy of the Fries study's methods and results. Lack of quantitative consistency with well documented GI event rates such as with aspirin indicates that this study lacks external validation.

Since the study appears to under-report GI events, it quite likely lacks sufficient power or sensitivity to accurately capture or compare rates of GI events with aspirin, ibuprofen, or acetaminophen. Thus its conclusion that GI risks of aspirin and ibuprofen are equivalent to background rates is flawed by study methodology that is insufficiently powerful to appreciate the well documented and universally accepted increased GI risk over background conferred by these medications. Similarly, the conclusion that GI risks of acetaminophen, aspirin, and ibuprofen do not differ from one another likely reflects methodology insufficiently sensitive to differentiate GI risks among analgesic therapies.

A widely held tenet of drug induced GI injury is that the extent of GI injury is proportionate to the dose. Yet in the Fries study, just the opposite was observed. With higher doses of acetaminophen, the authors observed lower, or more specifically, no GI event rates (their Table 5)[1]. Osteoarthritis patients who took ibuprofen for less than 10 days each month experienced

a greater number of events than those taking ibuprofen between 11 and 25 days of the month (Table 6). The same inverse frequency relationship was observed with acetaminophen, with infrequent users of acetaminophen experiencing higher event rates than frequent users. It is important that a study's observations be consistent with the known mechanism of action of a medication. The higher GI event rates observed with lower and less frequent analgesic doses imply that the Fries study results are mechanistically implausible.

The authors observed higher GI event rates in acetaminophen users taking concurrent ulcerogenic medications such as NSAID or corticosteroids than in those using aspirin or ibuprofen and also taking concurrent medications. This observation most probably reflects confounding by indication; those at higher risk for GI bleeding would more likely be prescribed acetaminophen. The authors contend that differences in their study groups did not exist because propensity scores, a statistical test to suggest similarity of groups, were similar. In contradiction, they also state that the GI risks of their study groups were not matched and that the ibuprofen study group had a higher percentage of patients at low risk for GI events than the other analgesic groups. Otherwise stated, the acetaminophen study group was disproportionately enriched with patients who, at baseline, were at higher risk to develop significant GI events. Thus, it is to be expected that the acetaminophen cohort would have had a higher incidence of GI events even in the absence of exposure to acetaminophen.

In summary, the conclusions reached by Drs. Fries and Bruce contradict a large body of literature that indicates that ibuprofen and aspirin are associated with increased GI risks compared to acetaminophen. Their conclusions are likely biased by flawed insensitive methodology and confounding by indication.

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Drs. Fries and Bruce reply

To the Editor:

We read with interest the comments of David Peura, Robert Tarone, and their colleagues on our recent article[1], which suggested that at low, intermittent, and over-the-counter (OTC) doses in low risk patients the rates of serious GI complications are low for aspirin (ASA), acetaminophen (APAP), and ibuprofen, and the 3 drugs cannot be statistically distinguished from each other. This sensible finding, granting the dose-effect relationship, had not previously been addressed prospectively because OTC intake is not generally available in prospective datasets. The datasets we used were the ones that we had used to originally establish the epidemiologic boundaries of nonsteroidal antiinflammatory drug (NSAID) gastropathy, and the doses and incidences reported are consistent with previous reports[2,3]. Our drug, dose, and event detection techniques are protocol-driven and were identical for each of the 3 drugs. We adjusted for possible confounding by indication by use of validated propensity scores, which is the standard for observational studies.

Peura's letter is laced with "contrary to conventional wisdom," "contradicts the large, established...," and other unsupported appeals to authority. Rather oddly, of the 6 studies that he cites, 5 do not even mention acetaminophen and the sixth is a telephone survey concerning symptoms rather than serious complications. The toxicity of aspirin and other NSAID at high or prescription doses is not disputed by our article. But the average person takes only 6–10 pills per month of these OTC medications. No prospective comparative study had been reported at these dosages, hence our report.

A need for confirmation of results is requested by Peura. But in our article[1] we had already cited 2 prior articles documenting associations between acetaminophen and serious gastrointestinal (GI) events and suggesting that there might be cracks in the conventional wisdom[4,5]. If the conventional wisdom was always correct we could stop doing studies, but this wisdom held, not too long ago, "no acid, no ulcer."

Definitive confirmation of our results by randomized double-blind controlled trial was reported while our report was in press. Moore and colleagues[6] reported results from the PAIN study of 8633 subjects comparing ASA, APAP, and ibuprofen in low doses, eliminating the possibility of confounding by indication. Outcomes were adverse events, serious adverse events, and serious GI adverse events. The number and nature of concomitant medication proved a more important predictor of serious GI events than the specific OTC analgesic. Absent additional risk factors, aspirin was about 1.5 times as toxic as APAP or ibuprofen, which were closely similar. With 3 or more concomitant medications, APAP was associated with greater toxicity than either of the other 2 drugs ($p < 0.01$).

The mechanism behind these now consistent findings is not completely clear, in part because of only weak evidence of a causal mechanism for acetaminophen GI toxicity. Perhaps it is most reasonable to suggest, as Moore, *et al* imply, that at low doses of these drugs where the incidence of causal events from the analgesic is low, the concomitant background risks for GI bleeding are of greater magnitude than the specific analgesic and mask true differences between drugs. The postulation of drug–drug interactions involving acetaminophen also is not unreasonable.

We think that Tarone and colleagues protest too much. Our article is by no stretch of the imagination an attack upon the GI safety of acetaminophen and we scrupulously avoided, in both the abstract and the text, concluding that APAP was more toxic than ASA and ibuprofen, even though the data trended that way in the more complicated patient groups. We did conclude that at the lowest and most intermittent doses of these 3 OTC analgesics there was insufficient statistical resolving power to show differences between specific medications and noted that all were relatively safe.

Tarone, *et al* discuss the literature quite differently than do the authors of the articles they cite. Thus, Hochberg, *et al* subsequently noted substantial reservations about possible APAP toxicity[7,8], Garcia-Rodriguez and Hernandez-Diaz[4] noted a relative risk of APAP users over nonusers of 3.6 with doses above 2 g/day, consistent with our findings in more complicated patients, and Rahme, *et al*[5] would not agree with Tarone, *et al* that their study documented a high degree of confounding by indication. A report by a former member of our group[9] was never published in full because the APAP data had not been collected in the same way as the NSAID data and APAP use was greatly under-reported; this problem was corrected in the present report.

Moore, *et al*[6], as above, have refuted speculation about a major role for confounding by indication. Confounding by indication cannot easily occur in a randomized controlled trial.

What do we think is happening? Let's assume, as Tarone, *et al* would like to, (1) that APAP is innately twice as safe as NSAID for serious GI toxicity. Let's assume also, as with the PAIN data and ours, (2) that patients at greater risk may have a 6-fold increased risk over healthier patients. And assume also (3), as Avogadro's number and broad clinical data indicate, that toxicity goes to zero as dose goes to zero. Two times zero is zero. It follows then that as dose decreases drugs become progressively safer and ultimately cannot be distinguished from each other, while effects of other risks remain and may dominate the risk profile. This is what we all have been observing.

Why is this more than an academic discussion? This involves patients. Drugs are both safe and toxic. We emphasize toxicity to increase caution about injudicious recommendation. We emphasize safety to reduce the concerns raised by the toxicity. In practice, if it is argued, as Tarone, *et al* would do, that there are large differences in safety between low doses of different OTC analgesics in actual use when there are not (for whatever reason), this balance is disturbed, caution decreased, and risk increased. We hope that these authors and their sponsor can join us in a balanced discussion of patient risks and patient benefits.

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Ophthalmologic Monitoring for Antimalarial Toxicity

To the Editor:

We read with interest the recent article by Bernatsky, *et al* on the adherence to ophthalmologic monitoring for antimalarial toxicity in their lupus cohort[1]. As the authors demonstrate, adherence to the 1996 American College of Rheumatology (ACR) guidelines suggesting repeated ophthalmologic examinations at least yearly[2] was incomplete in their center. Notably, they observed that antimalarial exposure for more than 5 years was predictive of nonadherence. Although only 2 cases of hydroxychloroquine (HCQ)-induced retinopathy, after 15 and 33 years of treatment, were identified among their patients, both of whom had a history of exposure to chloroquine, the authors continue to advocate ophthalmology assessments at least yearly for their patients who are receiving antimalarial agents[1]. Moreover, a recently published survey that examined rheumatologists' attitudes toward routine screening for HCQ retinopathy revealed that 94% of them screen their patients at least once a year because they are unwilling to accept any risk of visual damage[3].

We recently published the results of a prospective study conducted between 1985 and 2000 in our center to define the risk of HCQ-related retinal toxicity in patients with rheumatoid arthritis and systemic lupus erythematosus who are receiving recommended doses of the drug (6.5 mg/kg/day)[4]. Of 400 patients using longterm HCQ at recommended doses, the incidence of retinal toxicity was very low (0.5%), while no case of retinopathy was observed during the first 6 years of treatment. These results allowed as to conclude that after a baseline examination to confirm the absence of preexisting fundus pathology, patients with normal renal function may receive HCQ at a maximal daily dose of 6.5 mg/kg and continue safely for 6 years. However, we suggested annual screening in patients who have taken the drug, even in recommended doses, for more than 6 years[4]. These results substantiate the guidelines developed in 2002 by the American Academy of Ophthalmology (AAO) Task Force for screening for HCQ toxicity[5], stating that ophthalmologic examinations of such patients during the first 5 years of treatment can be at the frequency of regular examinations recommended by the AAO Preferred Practice Pattern[6] for the age of the patient, providing that no concomitant retinal, renal, and/or liver disease exists.

To our knowledge, no documented case exists of HCQ-induced retinopathy in patients who were taking the drug in recommended doses for less than 6 years and had normal renal function. Moreover, among the millions of patients exposed to HCQ worldwide, there are only 5 appropriately-dosed patients who developed irreversible retinal changes within the first 10 years of treatment; all were diagnosed during the seventh or by the end of the eighth year of HCQ exposure[7-10]. Seven additional patients who developed HCQ-induced retinopathy after taking the drug for more than 10 years at doses less than 6.5 mg/kg/day, in the absence of any associated comorbidities, have been reported to date[4]. Based on this evidence, and because frequent visual testing is not only expensive but burdensome to patients, as well as the findings by Bernatsky, *et al* claiming increased nonadherence especially after the first 5 years of treatment[1], it seems appropriate to revise the ACR clinical guidelines of ophthalmologic monitoring for antimalarial toxicity.

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Dr. Bernatsky, *et al* reply

To the Editor:

We welcome the thoughtful letter by Drs. Sfikakis and Mavrikakis. As they indicate, the literature appears to contain no documented case of definite hydroxychloroquine-induced retinopathy in patients taking the drug for *less* than 6 years (properly dosed, with normal renal function), although there are published cases of antimalarial toxicity as early as 6.5 years[1]. We agree that it may very well be time for the American College of Rheumatology (ACR) to reconsider the published guidelines regarding ophthalmologic monitoring for antimalarial toxicity[2], perhaps along the lines of the American Academy of Ophthalmology Task Force[3]. The recent summary of these recommendations in a letter to the journal *Arthritis and Rheumatism* (the official publication of the ACR) suggests that there is some recognition of the importance of this issue[4] by the ACR.

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Diagnostic Value of Anticyclic Citrullinated Peptide Antibody in Rheumatoid Arthritis

To the Editor:

We read with interest the report by Zeng, *et al*[1] on the diagnostic value of anticyclic citrullinated peptide antibody (anti-CCP) in patients with rheumatoid arthritis (RA). The role of anti-CCP remains to be determined for its value as a predictor of erosive disease, as a prognostic factor, and possibly as a diagnostic tool. Zeng, *et al* evaluated a modified ELISA as a diagnostic for detecting RA using anti-CCP antibodies in a Chinese population (n = 511 sera) consisting of 191 patients with RA (37%), 132 patients with other rheumatic diseases (systemic lupus, systemic sclerosis, primary Sjögren's syndrome, etc.), 98 patients with nonrheumatic diseases (postviral diseases, autoimmune hepatitis, etc.), and 90 healthy individuals: they calculated a 45% sensitivity and 97% specificity for anti-CCP as a diagnostic test for RA. But how should this be interpreted? We think a critical evaluation of a diagnostic test deserves some words on the influence of the Chinese population, the relative magnitude of non-RA subgroups, and test characteristics clinically more important than sensitivity and specificity, i.e., predictive value of a positive test result (PPV) to correctly diagnose RA with the anti-CCP, versus the predictive value of a negative test result (NPV) to correctly exclude RA with a negative anti-CCP test result.

In clinical practice a diagnostic test cannot merely be defined by calculating sensitivity and specificity. As clinicians we are not that much interested in ratios of index test results in RA versus non-RA, as described with sensitivity and specificity. For clinicians it is relevant to gain further insight into the merits of a diagnostic test; therefore one needs to calculate PPV, NPV, and likelihood ratios (LR: positive LR ideally reaching to infinity; negative LR ideally reaching to nil). We calculated these test characteristics for Zeng, *et al* (Table 1). For comparison we added test characteristics of data from a recent study investigating a Dutch patient population[2]. Anti-CCP sensitivity ranges did not overlap between the Chinese and Dutch populations. This seems to be because the Chinese patients with RA more often lacked anti-CCP antibodies than the Dutch patients. Is this due to a high number of cases of early RA, is it inherent to the Chinese population with RA, or is this due to their ELISA? The low number of anti-CCP positive RA patients explains the discrepancy in sensitivities but also results in a lower NPV: the probability not to have RA a priori in the study by Zeng, *et al* was 63%, and only increased up to 76% after a negative anti-CCP test result. In contrast, in the Dutch population the a priori probability not to have RA was 68%, which increased up to 92% after a negative anti-CCP.

Therefore one may conclude that as a diagnostic test anti-CCP in Chinese patients is performing less well than in Holland. In China, anti-CCP as a diagnostic test may be less suitable for rheumatologists.

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Table 1. Test characteristics. Data in parentheses are 95% confidence intervals.

	China Study[1]	Netherlands Study[2]
Prevalence RA in serum bank samples, %	37	32
Sensitivity, %	47 (40–54)	82 (78–86)
Specificity, %	98 (96–99)	98 (97–99)
PPV, %	93 (88–98)	96 (93–99)
NPV, %	76 (72–80)	92 (90–94)
LR of positive test	22 (10–47)	41 (35–53)
LR of negative test	0.54 (0.47–0.62)	0.18 (0.14–0.22)

PPV: positive predictive value, NPV: negative predictive value, LR: likelihood ratio.

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Dr. Zeng replies

To the Editor:

We thank Dr. Jansen and Dr. Bruyn for their interest in our article. We agree that a diagnostic test cannot merely be evaluated by its sensitivity and specificity; the positive predictive value and negative predictive value are also very important indexes. However, we think that the value of a diagnostic test can also be interpreted by how it is used in the clinic. As we know that the sensitivity of both anti-Scl-70 antibodies and anti-Sm-antibodies is very low, but they are very useful in the diagnosis and management of systemic sclerosis and systemic lupus erythematosus because of their high specificity[1,2]. Since the cost of the anti-CCP antibody test is very high in China, we tested it only in patients who were in the very early stage of disease or patients whose clinical manifestation was very likely to be RA, but did not fulfill the American College of Rheumatology (ACR) diagnostic criteria to confirm the diagnosis. Therefore, specificity is more important in our practice than sensitivity. Indeed, we diagnose RA based on the ACR criteria, not any single antibody.

As we stated, we had tested 511 serum samples, including 191 patients with definite RA, 132 with other rheumatic disease, 98 with nonrheumatic disease, and 90 healthy individuals (not included in the specificity and negative predictive values). The diagnosis of RA was well defined according to the ACR criteria. The results for sensitivity, specificity, positive predictive value, and negative predictive value were 47%, 97%, 94%, and 69%, respectively. In this study, we did the test using ELISA coated by ourselves. The low sensitivity is most probably due to our ELISA, as Jansen and Bruyn point out in their comments. After this study was completed, we carried out another study (not yet published) using many commercial anti-CCP kits including the new Immunoscan RA mark 2 kit (Euro-Diagnostica, Arnhem, The Netherlands). We tested anti-CCP in the same cohort of patients using Diastat anti-CCP kits (FCCP 200, Axis-Shield Diagnostics, Dundee, UK), and got a higher sensitivity (67% vs 47% as reported in our article) and high specificity (95%). However, the sensitivity is still not as high as that reported by van Venrooij and van de Putte[3]. It is known that the sensitivity of anti-CCP antibody varies from 40% to 80% in different laboratories depending on the cohort of patients studied and ELISA kits used[4-6]. As we stated, further research is required to elucidate these differences, including geographic factors, between our results and those of others. We look forward to a multicenter collaboration with other laboratories.

Finally, we believe that, although there are some limitations in our study (low sensitivity and other statistical data), the anti-CCP antibody is still a useful tool in the diagnosis of RA in China.

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Prevalence of Silent Amyloidosis in Rheumatoid Arthritis and Its Clinical Significance

To the Editor:

We read with interest the article by Wakhlu, *et al*[1] analyzing the prevalence of reactive amyloidosis in a series of Asian North Indian patients with rheumatoid arthritis (RA). In this systematic cross-sectional study (rather than prospective, as the authors assert) using abdominal subcutaneous fat aspiration (ASFA) as the screening method, a high prevalence of amyloid fat deposits was found in patients with RA (26.5%), most of whom (73%) had subclinical amyloidosis. The authors question the clinical significance of these amyloid deposits and whether they may predict future overt clinical visceral amyloid involvement.

A partial answer may be found in our followup study published 2 years ago[2]. In this observational study in a large cohort of Spanish patients with adult RA, the prevalence of amyloid fat deposits was lower (16.3% at the time of the first ASFA test) than that observed by Wakhlu, *et al.* We also found that most patients had no clinical manifestations due to amyloidosis. After a mean followup period of nearly 7 years, 10 out of 35 patients with subclinical amyloidosis developed some type of renal disease, but this was due to amyloid nephropathy in only 5 patients; thus, amyloidosis remained subclinical in most patients throughout the followup, even in patients with followup longer than 10 years[2]. We agree with Wakhlu and colleagues that a longer followup is required to elucidate the exact clinical significance of this finding, but our results seem to confirm that, in a considerable proportion of patients, these deposits should not be considered a sign of poor prognosis and a sure marker of future overt clinical amyloidosis. This suggests that no aggressive cytotoxic therapy should be initiated in patients with silent amyloidosis.

Our study found that patients with marked amyloid deposits are more prone to clinical amyloidosis than patients with moderate to mild deposits. Using the same semiquantitative method, Wakhlu, *et al*[1] seem to confirm our findings, even though the small number of patients studied makes it difficult to draw definite conclusions. However, we believe that patients with marked deposits (massive deposits in > 25% of tissue fragments) should be closely monitored for clinical symptoms or laboratory findings suggestive of amyloidosis in order to treat early when clinical amyloidosis develops.

It is now clear that subclinical amyloidosis is common in RA and other inflammatory rheumatic diseases such as ankylosing spondylitis[3]. The prevalence rates of secondary amyloidosis in systematic studies in RA patients in recent series using the ASFA test[1,2,4] or gastroduodenal biopsies[5] to detect amyloid deposits range from 7% to 26%; most of these patients have subclinical amyloidosis. In contrast, the prevalence of clinical amyloidosis is rather lower; in a Spanish cohort study of a large series of RA patients with a mean disease duration of 10 years, which was specifically designed to search for comorbidities and extrarticular complications (the

EMECAR study)[6,7], clinical amyloidosis was found in only 5 out of 788 registered patients (accumulated prevalence of 0.6%; 95% CI 0.1–1.2%).

A decline in the incidence of secondary amyloidosis in RA has been suggested[8]. We believe this may be true with respect to clinical amyloidosis, but recent studies do not support a low prevalence of subclinical amyloidosis in RA, since the prevalence rates in older studies are similar, or even lower[9,10]. It is probable that in some patients these deposits are true silent deposits, but in others they only reflect preclinical status. However, taking into account our results and the discordance between the prevalence rates of clinical and subclinical amyloidosis, it may be concluded that most of these patients have true silent amyloidosis and they will never develop clinical visceral involvement. It is possible that more effective therapies for the control of inflammatory activity are mainly responsible for the fact that silent amyloidosis remains at this stage during the evolution of the disease, although other factors, including genetic ones, may also be involved[11]. In the last few years, new antirheumatic drugs, including biological therapy, have been shown to be highly effective in controlling inflammatory activity and joint damage. Whether this will result in a lower incidence of subclinical or clinical amyloidosis in the near future remains to be seen.

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Dr. Misra, *et al* reply

To the Editor:

We are thankful to Dr. Sanmarti, *et al* for their critical analysis of our study[1]. We have quoted their study[2] in our report. The issue is whether subclinical amyloidosis is a precursor of clinical disease in rheumatoid arthritis (RA) or not. We agree with their hypothesis, but there are few studies (including theirs) that have looked at patients systematically over a prolonged period of time. We have in mind more than 10–15 years. We have said categorically that any therapeutic intervention such as cytotoxic agents like azathioprine or cyclophosphamide would be unwarranted for subclinical amyloidosis in the light of current findings. Even though their suggestion that massive amyloid deposits, > 25% of tissue fragments, are strongly associated with development of clinical disease, it will still be premature to advocate cytotoxic treatment in these cases. A close followup is perhaps necessary. We reiterate what has been published by the authors themselves, and this has been substantiated by our study in another ethnic group of patients.

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Macrophage Activation Syndrome Due to Methotrexate in a 12-year-old Boy with Dermatomyositis

To the Editor:

We describe a 12-year-old boy with dermatomyositis (DM) who had a reaction to methotrexate (MTX) while under treatment in hospital.

His clinical signs included high temperature, hepatomegaly and splenomegaly, and neurological changes (including expression abnormalities, coprolalia, insomnia, and agitation), with changes observed on brain magnetic resonance imaging studies. He also had melena, severe pancytopenia, abnormalities in prothrombin time, and a decrease in erythrocyte sedimentation rate. He had never experienced these symptoms prior to the use of MTX. All these signs and symptoms became worse after the second dose of MTX, and improved after discontinuation of MTX and the initiation of therapy with additional steroids and cyclosporine, which had been used continuously for his primary disease. He recovered with no further crisis or worsening of his DM.

Eraso, *et al* have suggested that MTX could not be responsible for the development of this syndrome[1], but in our patient we observed a direct relation between the onset of symptoms and the use of MTX. A diagnosis of macrophage activation syndrome was made according to the published criteria[2], and there was no other evidence of a factor that could have triggered this syndrome. We concluded this patient had macrophage activation syndrome secondary to the treatment with MTX, although we could not determine ferritin concentrations. As Ravelli and colleagues recommend[3], we also ruled out other trigger factors for these changes in our patient.

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Drs. Ravelli and Martini reply

To the Editor:

Dr. Sterba and colleagues describe a patient with juvenile dermatomyositis (JDM) who developed a macrophage activation syndrome (MAS) after receiving methotrexate (MTX), in the absence of other potentially eliciting factors.

MAS occurs most frequently in children with systemic juvenile idiopathic arthritis (JIA), but has been observed in other subtypes of JIA and, more rarely, in juvenile systemic lupus erythematosus[1]. In the latter disease, however, it has been suggested that this complication may be more common than previously realized[2]. To our knowledge, MAS has not been previously described in JDM, with the exception of a case with platelet-specific hemophagocytosis[3].

That MAS in Dr. Sterba's patient was apparently triggered by MTX is in keeping with our observations that this drug may act as an inciting factor of this syndrome in children with systemic JIA[4,5]. Because several medications, including nonsteroidal antiinflammatory drugs, sulfasalazine, and gold salts, have been incriminated as possible triggers of MAS[1], it is not surprising that MTX could elicit this syndrome under certain circumstances.

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Breast Implant Related Disease

To the Editor:

The recent article by Vermeulen and Scholte[1] stimulated us to examine our data. The Arthritis Center of Northeast Ohio [as regional expert witness for the presence of symptoms, signs, and diagnoses fulfilling previously established (36) criteria] examined 183 women with silicone-filled breast implants. This included 56 individuals with ruptured/leaking implants and 127 in whom the implants appeared intact.

This analysis confirmed Vermeulen and Scholte's observation[1] of increased sleep disturbance, headache, and memory loss and additionally identified increased sweating among individuals with ruptured implants (Table 1). However, neck pain, photosensitivity, dry eyes (subjective complaint, but not dryness as measured by Schirmer test), and constipation were less common in that group (Table 1). Fatigue, malar rash, alopecia, mucosal ulcers, dysphagia and diarrhea, and associated rheumatologic disorders were equally represented in both groups.

This variation illustrates the need for large-scale, epidemiologically-designed studies (correcting for reporting/participation biases) to further explore these intriguing issues.

Table 1. Differential expression of clinical symptoms with breast implant leakage.

Clinical Symptom	Breast Implant		Chi-square	p
	Leaking, %	Intact, %		
Sleep disturbance	79	43	20.30	< 0.0001
Dry eyes	25	51	10.86	< 0.009
Headache	36	6	21.18	< 0.0001
Excess sweating	50	34	4.26	< 0.05
Memory loss	11	1	10.32	< 0.009
Photosensitivity	9	30	25.76	< 0.0001
Neck pain	29	81	47.16	< 0.0001
Constipation	18	37	6.65	< 0.01

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Drs. Vermeulen and Scholte reply

To the Editor:

The survey of the symptoms occurring in patients with silicone breast implants by Rothschild and Helbling underlines the outcome of our study[1] with respect to the increased expression of several symptoms after rupture of the implants, such as sleep disturbance, headache, and memory loss. Interestingly, they also found symptoms that decreased after rupture. These and other differences between the outcome of the studies are associated with differences in the selection of diagnostic questions and of the patients. Rupture had occurred in only 31% of their patients, contrasting with 74% in ours. But details with regard to patient selection were not given.

The main tenor of our message was that patients who underwent a second operation to replace or remove silicone breast implant(s), complained of signs and symptoms of chronic fatigue syndrome[2], and that the symptoms were more severe in the ruptured group. The pattern of the complaints was different from patients with chronic fatigue syndrome, as relatively more implanted patients complained of multijoint pain and myalgia, and

fewer of impaired short-term memory or concentration, sore throat, unrefreshing sleep, and headache of a new type.

The data from Rothschild and Helbling may add to our knowledge of the silicone exposure disease. Their patients likely represent an earlier stage of the disease than ours, as the chance of the occurrence of rupture increases with time[3].

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Hepatitis C Virus and Rheumatoid Arthritis: Further Pieces to the Puzzle

To the Editor:

Hepatitis C virus (HCV) has been considered one of the leading causes of liver disease worldwide, and has also been reported to be a potent inducer of autoimmunity resulting in a broad spectrum of striking extrahepatic syndromes. Serological markers of autoimmunity and clinically apparent immune-mediated nonhepatic syndromes may be present in up to 70% of patients with chronic hepatitis C infection. Although some reports suggest that HCV might induce rheumatoid arthritis (RA) or be involved in its pathogenesis[1-8,10-14], the relevant data are difficult to interpret (Table 1).

In a recent article, Hsu and colleagues investigated HCV in the pathogenesis of RA, and reported that this virus has probably no role in the etiology of RA in a study based on a US population[8]. Our findings are in accord with these results.

In a prospective study (1998–2001) we evaluated the prevalence and the clinical significance of chronic HCV infection in patients who met the revised diagnostic criteria for RA of the American College of Rheumatology[9]. One hundred patients (76 with early onset and 24 with advanced-stage RA; mean duration of disease 7.2 yrs; mean age of patients 54 ± 17 yrs) were prospectively enrolled and screened for anti-HCV antibodies by third-generation ELISA (Abbott Laboratories, Abbott Park, IL, USA). No serum sample was found to be reactive on ELISA.

Our study indicated that HCV infection is an uncommon finding in patients with RA. In Hungary, where the prevalence of anti-HCV positivity in the adult population is less than 1%, HCV does not seem to be a relevant factor in the induction or perpetuation of RA.

It seems worth emphasizing that patients with RA are prone to contract HCV infection because of the natural immunodeficiency as a consequence of the disease, and immunodeficiency caused by longterm immunosuppressive treatment. Furthermore, it may be the consequence of frequent hospitalization including invasive diagnostic and therapeutic measures. Further prospective studies should be done to clarify this picture and to solve this puzzle.

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Table 1. Prevalence of markers of hepatitis C virus infection in patients with RA.

Report	Country	Patients, n	Duration of Disease, yrs	Anti-HCV Test ELISA	Anti-HCV Test RIBA (generation)	Anti-HCV Positive	HCV-RNA (PCR), %
Theilmann[1]	Germany	41	NG	1	ND	61	ND
Tanaka[10]	Japan	30	NG	1	ND	6.7	ND
Sawada*[2]	Japan	1	7	1	ND	100	ND
Borque[3]	Spain	36	NG	1	ND	33	ND
Marson[11]	Italy	79	NG	1/2	1	5.1	ND
					2	2.5	
Baffoni[4]	Italy	100	NG	2	2	6.0 (ELISA)	ND
						5.0 (RIBA)	
Perrot[12]	France	33	NG	2/3	2/3	3.3	ND
Rosner*[5]	Isreael	3	4 mo–2 yrs	2	ND	100	100
D'Amico[13]	Italy	49	7.5	2	2/3	14.3	ND
Lovy[14]	USA	19	NG	NG	NG	0.5	ND
		600	ND	NG	NG	0.5	ND
Rivera[6]	Spain	303	ND	3	2	7.6 (ELISA)	2.7
						4.3 (RIBA)	
Csepregi[7]	Hungary	80	12.1	3	ND	0	ND
Hsu[8]	USA	196	NG	3	?	1.3	0.7

RIBA: recombinant immunoblot assay, PCR: polymerase chain reaction, ND: not done, NG: not given. * Case report.

Etanercept in Breast Milk

To the Editor:

Etanercept (Enbrel®) is a soluble tumor necrosis factor (TNF) receptor fusion protein that binds and inactivates TNF. Its metabolites are excreted in bile and urine and are not bioactive. Clinical studies have shown that etanercept effectively suppresses arthritis not only in patients with rheumatoid arthritis (RA), but also in juvenile idiopathic arthritis, ankylosing spondylitis, and psoriatic arthritis[1]. The main side effect of etanercept in children and adults is infections, particularly upper respiratory tract infections. However, serious events like sepsis or aseptic meningitis occur in less than 1% of treated patients[1]. In women with child-bearing potential, treatment with etanercept can interfere with pregnancy or lactation. It is not known whether etanercept is secreted into human breast milk. We measured etanercept in breast milk of a patient with RA.

A 30-year-old woman with rheumatoid factor positive RA had active disease throughout pregnancy. Four weeks after delivery, treatment with etanercept injections 25 mg twice weekly was started because of acute flares of arthritis. She did not breastfeed her child, but had milk flow throughout the duration of the study. The first injection of 25 mg etanercept was given 30 days after delivery, and thereafter twice weekly subcutaneously. A blood sample of the mother was taken one day after the fifth etanercept injection, and thereafter milk samples were collected. The maternal plasma and milk samples were kept frozen at –80°C until analyzed by an ELISA test selective for etanercept[3].

The results are summarized in Table 1. The measured concentrations of etanercept in maternal serum corresponds to 2 mg/ml levels reported previously[2]. The maximal etanercept level measured in breast milk was 75 ng/ml on the day after injection and decreasing during the following days (Figure 1). The lack of an increase of etanercept after the second injection was presumably due to the spontaneous cessation of milk secretion in this lactating, but not nursing mother.

To our knowledge this is the first report showing that etanercept is secreted in human breast milk. It is not known whether etanercept can be absorbed orally. Since it is a large protein, bioavailability by oral ingestion can be assumed to be small. However, the nursing infant absorbs immunoglobulins and thus the possibility exists for a fusion protein[3]. The amount of a drug secreted into breast milk varies depending on the frequency of nursing and the composition of milk proteins and lipids. Thus no precise calculation of the amount ingested by a nursing infant can be made in this lactating mother who was not nursing her child. Further, the volume of milk secreted during the day was not recorded. If one assumes that a nursing infant is breastfed 6 times a day with about 200 ml of milk at each feeding, the amount of etanercept ingested by the child is 50 to 90 µg per day. Therefore, the maximum exposure by oral ingestion can be calculated to be 0.1 to 0.05 mg/kg body weight. In comparison, the recommended dose of etanercept for the treatment of children aged 4 years or older is 0.4 mg/kg subcutaneously twice a week. At present, any risk possibly exerted by these small amounts of etanercept, which theoretically could be ingested by a nursing infant, remains speculative and not very likely. Should the

Table 1. Excretion of etanercept in human breast milk.

Day Post Partum of Etanercept Injection	Day Post Partum Milk Sample	Collection Time	Etanercept in Breast Milk, ng/ml	Etanercept in Maternal Serum, ng/ml
44	44	5:00 pm	50.2	
	45	12:00 am	75.4	2057.6
	46	8:00 am	45.2	
	47	11:00 pm	31.0	
48	48	11:00 pm	31.5	
	49	1:30 pm	25.0	

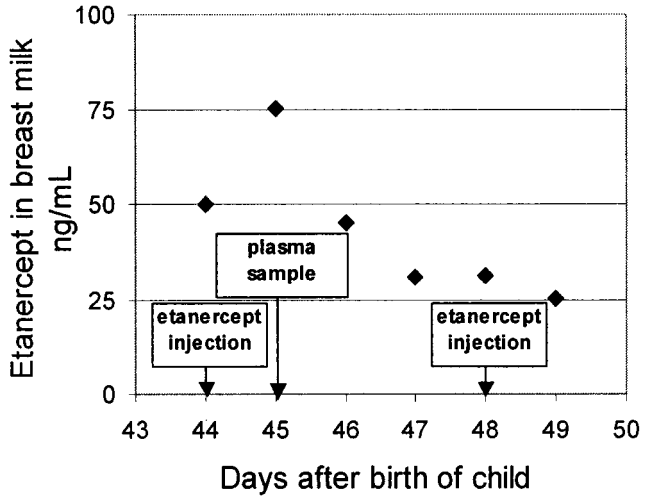

Figure 1. Etanercept in breast milk.

necessity arise to treat a nursing patient who wants to continue breast-feeding during treatment with etanercept, measurement of serum concentrations in the suckling child could solve the question whether orally ingested etanercept is absorbed.

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Severe Recurrent Neurological Disease in the MAGIC Syndrome

To the Editor:

Patients with features of Behçet's disease and relapsing polychondritis have been described as having the MAGIC (mouth and genital ulcers with inflamed cartilage) syndrome. It has been suggested that there may be a particularly close relationship between these 2 diseases, resulting in overlap. This report documents severe recurrent neurological involvement that was clinically, radiologically, and pathologically consistent with neuro-Behçet's even while cartilage inflammation was taking place. Thus, even though there may be common pathways leading to disease expression in the MAGIC syndrome, each manifestation should be evaluated individually to determine if it is primarily related to Behçet's disease or relapsing polychondritis so that appropriate therapy may be given.

A 38-year-old Caucasian man presented with increasing confusion, papulopustular skin lesions on his chest, and scrotal ulcerations. Over the preceding 10 years he had recurrent oral ulcerations 3–6 times per year as well as scrotal ulcers. Two years prior to admission he presented to another institution with oral ulcerations, right-side weakness, and diplopia. A left third nerve palsy was confirmed. There was decreased muscle strength on the right side, with hyperreflexia and clonus at the ankle. Magnetic resonance images (MRI) of the brain revealed a mass-like lesion deep in the left side of the brain. The epicenter was in the left cerebral peduncle with cephalad extension into the basal ganglia and the frontal corona radiata, anterior extension into the left optic tract, and caudal extension into the midbrain and left pons as far as the left inferior cerebellar peduncle. There was also extension into the left cerebellar hemispheric white matter about the left lateral margin of the fourth ventricle. Heterogenous enhancement was noted after intravenous gadolinium injection. Venous sinuses were patent, as were the internal cerebral veins.

A stereotactic brain biopsy was performed. The tissue had patchy inflammatory infiltrates composed primarily of mononuclear lymphocytic cells and microglial rod cells. In a number of foci there were accumulations of foamy macrophages, some of which retained rod-like nuclei. The inflammation was present in both grey matter and striate white matter bundles, and was dispersed throughout the tissue with some accentuation around vascular profiles, often involving small venous channels. Even in the perivascular regions, the majority of the reactive cells appeared to be microglial cells and foamy macrophages. This was felt to be highly consistent with neuro-Behçet's.

He improved with corticosteroid therapy but failed followup appointments and received no further therapy for 2 years. In the month before admission at our institution, he became more confused and developed papulopustular skin lesions and oral and scrotal ulcers. He also gave a one-year history of intermittent redness, swelling, and tenderness of the ears with decreased hearing. The inflammation would persist from several days to several weeks. He had no joint pains or tenderness over the thyroid or the anterior tracheal cartilage.

Pertinent findings on physical examination revealed conjunctival injection of the left eye and a third-nerve palsy, but no evidence of vasculitis on funduscopic examination. There were soft floppy deformities of both ears ("cauliflower ears") with sparing of the noncartilaginous portion of the ear. There was no evidence of a saddle-nose deformity. There were oral ulcerations, but the epiglottis and the vocal cords revealed no abnormality. Skin examination revealed papular lesions on his nose and papulopustular lesions on the thorax and back. He had numerous scrotal ulcerations.

Liver function tests, electrolytes, urinalysis, and rheumatoid factor were all negative or within normal limits. Antinuclear antibody was 1:40 in a speckled pattern with negative anti-Sm, anti-RNP, anti-Ro, anti-La, anti-Scl70, anticentromere, antidouble stranded DNA, anticardiolipin, antichromatin, and antineutrophil cytoplasmic antibodies. Erythrocyte sedimentation rate was 112 mm/h.

MRI of the brain continued to reveal increased T2-weighted signal within the left frontal lobe, the left corona radiata, putamen, internal capsule, thalamus, and left mid-brain, although this was markedly improved in size and intensity compared to the previous MRI. There was also an interval increase in signal intensity on FLAIR (fluid attenuated inversion-recovery), T2, and proton density-weighted images within the right thalamus, right cerebral peduncle, the medulla, and the pons, which was not present previously.

He was treated with prednisone orally 1 mg/kg/day and started azathioprine. His confusion improved and his oral and genital ulcers cleared. He was subsequently lost to followup.

Behçet's disease is a multisystem inflammatory disorder classified among the vasculitides[1]. Chronic progressive central nervous system (CNS) involvement occurs in up to 20% of patients and is characterized by exacerbations and remissions[2]. Neuro-Behçet's disease may present with parenchymal or nonparenchymal involvement. Parenchymal involvement often involves the brain stem, basal ganglia, internal capsules, and peduncles. Low grade inflammation may be present throughout the CNS, and multiple high intensity focal lesions in the brain stem, basal ganglia, and cerebral white matter are seen on T2-weighted MRI. FLAIR sequences

detect even more lesions, particularly in the juxtacortical white matter, suggesting subclinical abnormalities are present[3]. Clinically, aseptic meningitis, meningoencephalitis, cranial nerve palsies, brain stem and cerebellar syndromes, as well as nonspecific psychiatric disturbances may be seen[1,2].

Relapsing polychondritis is an episodic inflammatory disease of the cartilaginous structures including the ear, nose, peripheral joints, trachea, and bronchial tree. Other proteoglycan-rich structures such as the eyes, heart, blood vessels, and inner ear may be affected. Patients present with redness, swelling, and tenderness of the cartilaginous portion of the ear, which becomes damaged and deformed after repeat attacks. The external auditory meatus and eustachian tube may become narrowed by edema or collapse[4]. Relapsing polychondritis may rarely present with multifocal neurological abnormalities[4-6], although this may be a result of a concomitant systemic vasculitis.

Firestein, *et al* described 5 patients with features of coexistent Behçet's and relapsing polychondritis and proposed the MAGIC syndrome as the name for this entity[7]. Since 1985 there have been a few case reports of the syndrome[8-10] and other descriptions of patients with symptoms suggestive of overlap. Most patients had disease presentations and courses in which symptoms and signs most consistent with Behçet's developed earlier in the course and were more prominent. A few had prominent symptoms of polychondritis early in their course, which persisted.

Firestein, *et al* suggested that the similarities between the clinical manifestations of the 2 diseases may imply a common cause or pathogenesis, possibly related to autoimmunity to components of cartilage. Whether there is a particularly close relationship between Behçet's disease and relapsing polychondritis, or the MAGIC syndrome merely represents the overlap of 2 rheumatological diseases, the clinical experience reported suggests that the course and prognosis of each organ involved reflects that of the individual disease most likely responsible for the particular manifestation — either Behçet's disease or relapsing polychondritis. Thus, our patient had neurological involvement clinically, radiologically, and pathologically in a manner classic for neuro-Behçet's disease. This recurred after 2 years, again in a manner classic for Behçet's (along with other symptoms of oral and genital ulcers), even while he had several attacks of polychondritis. Each manifestation should therefore be evaluated to determine whether this is primarily related to Behçet's disease or relapsing polychondritis so that appropriate therapy can be given. This is particularly useful when lesions relatively specific for each process are present[7]. Treatment with immunosuppressive agents such as azathioprine or methotrexate would be reasonable, and preliminary data suggest that there may be a role for anti-tumor necrosis factor-α agents as well.

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Correction

Jaimes-Hernández J, Robles-San Román M, Suárez-Otero R, Dávalos-Zugasti ME, Arroyo-Borrego S. Rheumatoid arthritis treatment with weekly leflunomide: an open-label study. J Rheumatol 2004;31:235-7.

On page 236, in the first paragraph of the Discussion, the eighth sentence should read as follows: "One group received LFN 20 mg/day, the second group received LFN 100 mg/week, and the third group received methotrexate (MTX) 7.5–15 mg/week during 6 months of treatment." We regret the error.