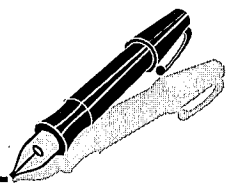


# Correspondence



## 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 M4W 3C7, 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.

## Relationship of Length of Clinical Rotation to Achievement of Skills Necessary for Clinical Management of Musculoskeletal Disease

To the Editor:

Smith, *et al*<sup>1</sup> "suggest that medical graduates are poorly trained in this area [musculoskeletal disease] of medicine." While they very nicely demonstrate one difficulty in addressing this problem, perhaps equally important to availability of adequately trained teachers is inadequacy of curriculum time.

Duration of clinical experience required for attainment of skills appropriate to management of musculoskeletal disease has been a source of contention<sup>2,3</sup>. As 30–40% of primary care relates to musculoskeletal disease<sup>4</sup> and most training programs allow no more than one month (less than 3% of the training program and that often not mandatory) of rheumatology training, adequacy of training is a very pertinent question to examine, specifically, the effect of clinical rotation length on attainment of knowledge and management skills.

Twenty hours of clinical rheumatology patient experience were provided each week. Rotations of 2, 3, 4, and 5 weeks (duration exclusive of vacation time) were assigned by the internal medicine program director. All residents also participated in biweekly rheumatology conferences during their entire residency and during the elective, read the primary care text, and partook of the 60 hours of slide cassette/videotape programs. Pre-tests (37 disease recognition/knowledge "regurgitation" and 10 management questions) and post-tests (63 regurgitation and 30 management questions) were utilized.

Performance in pre-test was uniform across the 5 groups ( $t = 0.08$ , NS), documenting extremely limited pre-elective ability to manage musculoskeletal disease (Table 1).

Management performance was indistinguishable from pre-test for those enrolled in only 2 or 3 week rotations, marginally better for 4 week rotations, and significantly improved only at 5 weeks (Table 1). Analysis of the various rotation completers did illustrate data retention. While regurgitation

Table 1. Relationship of elective rotation length to performance.

Test Score, %	Rotation Length			
	2 Weeks	3 Weeks	4 Weeks	5 Weeks
Initial total	57	49	52	51
Regurgitation	68	57	54	59
Management	20	20	30	10
Final total	67	69	76	81
Regurgitation	84	86	93	92
Management	30	33	40	57
Improvement	9	20	25	30
Regurgitation	16	29	39	33
Management	10	13	10	47

ability improved at 4 weeks ( $t = 9.90$ ,  $p = 0.04$ ), significant improvement in management was only observed at 5 weeks ( $t = 14.70$ ,  $p < 0.01$ )! At 5 weeks, residents illustrated ability not only to regurgitate information, but to actually starting applying it.

This analysis is based upon a concerted data based program, with rheumatology lectures intricately incorporated into the internal medicine lecture curriculum, and cannot be extrapolated to less intensive programs. Elective time rotations (exclusive of vacation time) of at least 5 weeks are required for meaningful training in management of musculoskeletal disease. Concern is expressed that primary care training programs offering less rotation time are not meeting their public welfare responsibility.

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## Drs. Smith, *et al* reply

To the Editor:

We thank Dr. Rothschild for his letter concerning our recent paper relating to teaching clinical skills in musculoskeletal medicine<sup>1</sup>.

It should be noted that the subject of our paper was a different method of teaching clinical skills to optimize the use of limited teaching resources and was not assessing methods of teaching the knowledge component of musculoskeletal medicine, which is predominantly the subject of Dr. Rothschild's letter. The structured clinical instruction modules method of teaching clinical skills was integrated with a musculoskeletal module that included some lectures but was based on problem based learning using several problem based learning cases with a musculoskeletal theme. We do, however, agree with the fundamental point of Dr. Rothschild's letter that musculoskeletal medicine is under-represented in the medical school cur-

riculum, considering the number of patients presenting to a doctor in primary care with a musculoskeletal problem.

Unfortunately, the availability of medically trained teachers is one of the most limited resources in a medical school, so methods to optimize the utility of this valuable but limited resource are needed. Teaching clinical skills optimally requires the use of a medically trained teacher, although we (and others) have already published papers concerning an alternative method of teaching clinical skills utilizing patient partners<sup>2</sup>. Also, unlike imparting knowledge, teaching clinical skills in musculoskeletal medicine ideally requires small tutorial groups with a low student:teacher ratio.

While a greater time commitment for musculoskeletal medicine in the medical curriculum is clearly important, it is essential to have adequate resources to teach musculoskeletal medicine and, if they are limited, to optimize the use of such limited resources. The recent paper from our group presents one strategy to achieve this goal in teaching clinical skills in musculoskeletal medicine.

We strongly endorse Dr. Rothschild's statement about the contrast between the importance of musculoskeletal medicine in primary care compared with its small representation in the medical curriculum. It is questionable whether increasing the time spent in a rheumatology rotation is an efficient use of limited teaching resources and whether it improves longterm retention of knowledge and clinical skills in the area of musculoskeletal medicine. We look forward to more research in the area of teaching of musculoskeletal medicine to address these and many other issues.

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### Intensity and Duration of Oral Anticoagulation in Antiphospholipid Antibody Associated Thrombosis

To the Editor:

We were delighted to see the report by the McMaster group and Universities of Cincinnati and Toronto<sup>1</sup>, which by using decision analysis showed the same conclusion that we came to<sup>2</sup>: that patients with antiphospholipid syndrome presenting with thrombosis have a better outcome if longterm warfarin (target international normalized ratio (INR) 3.0–4.0) is used. We also agree that the use of aspirin does not offer clear additional benefit.

We were, however, disappointed that our work and that of others was incorrectly quoted. For example (p. 491), the authors state that "Others have recommended more vigorous anticoagulation, targeting an INR between 3.0 and 4.0" and cite 2 articles by Ginsberg, *et al*<sup>3</sup> and Schulman, *et al*<sup>4</sup> that do not support their argument. Similarly (p.499) they state that "In some studies with close monitoring of the anticoagulant therapy, no patient taking warfarin (INR 2–3) had recurrent thrombotic events" and cite our paper<sup>5</sup>, which does not support their view.

Despite these shortcomings we wholeheartedly concur with the conclusions of the authors. We agree that the lack of prospective studies in the management of antiphospholipid antibody associated thrombosis is a major drawback. We feel, however, that recruitment into randomized prospective

trials comparing target INR of 2.0–3.0 and 3.0–4.0 will be difficult in view of resistance of both clinicians and patients due to the data suggesting an INR of 3.0–4.0 is preferable.

BEVERLY J. HUNT, MD, FRCP, FRCPath; MUNTHER A. KHAMASHTA, MD, MRCP, PhD, Lupus Unit, St. Thomas' Hospital, London SE1 7EH, UK.

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### Drs. Brunner and Feldman reply

To the Editor:

We highly appreciate the interest in our article. We are especially delighted at Drs. Hunt and Khamashta's approval regarding our final conclusions. With regard to their concerns of the citation referring to recommendation of higher intensity anticoagulation on page 491, the statement that INR 3.0 and higher is recommended by some is mentioned in the publication of Ginsberg, *et al*<sup>1</sup>. However, we agree with Drs. Hunt and Khamashta that we erroneously referred to Schulman, *et al* (citation 12) instead of Khamashta, *et al* (citation 8). Additional concerns regarding the citation used to support the statement that in some instances anticoagulation using a target INR between 2.0 and 3.0 was sufficient to prevent recurrent venous thrombotic events, citation 9 (Krnice-Barrie, *et al*), instead of citation 8 (Khamashta, *et al*), should have been mentioned. The lack of recurrent thromboses in some series is also supported by Ginsberg, *et al*<sup>1</sup>.

As mentioned in the article and emphasized by Drs. Hunt and Khamashta, there is urgent need for prospective studies to identify the optimal approach for the treatment of patients who test positive for antiphospholipid antibodies (aPL). The recent identification of certain subtypes of aPL with differential risks for recurrent arterial or venous thromboses appears to offer an additional opportunity to develop treatment approaches that offer the best risk to benefit profile for any given patient.

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### Silicone Gel Breast Implants

To the Editor:

In my recent letter<sup>1</sup> I challenged Brown, *et al*'s finding of an association

between extracapsular ruptured breast implants and fibromyalgia (FM)<sup>2</sup>. I argued that they inappropriately merged patients with intact implants and those with intracapsular ruptures and used this group as the comparison for patients with extracapsular rupture. This consequently led to a spurious finding. From an epidemiologic and clinical perspective, I find Drs. Brown and Pennello's justification<sup>1</sup> of their analytic approach illogical, lacking merit, and requiring further thoughtful comment.

They justified their pooling by stating: "if extracapsular silicone was the sole cause of FM, then ruptures without extracapsular silicone could be combined with intact implants particularly since there was no association with rupture (i.e., intracapsular and extracapsular) when compared to all others (i.e., intact and indeterminate)" — italics mine. The authors' justification seems at least partially grounded in a hypothesis that extracapsular silicone is "the sole cause of FM," but their data, when analyzed properly, do not support the hypothesis, and thus should be rejected (but are not) by the investigators. Also, discovering that FM has "no association with rupture when compared to all others" clearly fails, as explained below, to justify their decision when all the data across implant rupture status groups are examined.

The relationship between FM and implant status shows that the protection of intracapsular rupture against FM is stronger (odds ratio = 0.50; the reciprocal is an odds ratio of 2.0) than the increased risk with extracapsular rupture (odds ratio = 1.88) when each rupture type is individually compared against intact implants<sup>1</sup>. (Note that neither of these odds ratios are statistically significant.) These numbers suggest that those with extracapsular rupture, not those with intracapsular rupture, are more like those with intact devices. If the authors are intent on combining the intact group with one of the rupture groups, the data suggest the more appropriate combination would be intact implants and extracapsular ruptures. Of course, doing this leads to a different study conclusion — that intracapsular ruptures protect against FM! Combining the data this way shows a statistically significant protection against FM by intracapsular rupture (odds ratio = 0.37, 95% confidence interval 0.17–0.77). Clearly, the appropriate findings to report should be based on an analysis that does not collapse any rupture status categories, because the FM results are so different by rupture status. I believe this analytic and reporting approach is what most clinicians and epidemiologists would consider correct.

If I understand the authors, they found a statistically significant difference ( $p = 0.003$ ) among intact, intracapsular, and extracapsular devices — presumably for FM<sup>1</sup>. This finding further supports that pooling rupture groups is incorrect. This situation highlights a well known epidemiologic problem of when to "lump" or "split" categories. Generally, epidemiologic principles dictate against lumping categories when evidence suggests they are substantially different. For example, the risk of a disease (e.g., as measured by an odds ratio) for males and for females generally should not be pooled into one risk measure when substantial gender differences exist — such combining hides gender differences. The authors tell us they found statistically significant differences in the association of FM across the three implant status categories. Consequently, this is precisely the type of dataset where collapsing should not be done because it gives misleading findings.

The authors correctly state that I found in their data a non-statistically significant odds ratio of 1.88 for FM and extracapsular rupture. They use this finding to continue to justify their conclusions by stating: "it [being the 1.88] is still highly suggestive of an association between FM and extracapsular rupture." What troubles me is their selective use of information. I also state<sup>1</sup> in the next sentence after I report the 1.88 odds ratio, that I found an odds ratio of 0.50 between FM and intracapsular rupture. Why did they not use this finding to say that it is highly suggestive that intracapsular rupture protects against FM? How can they embrace and highlight the one association yet completely ignore the other? Without a doubt, this second association undermines their study conclusions. From a biological and clinical perspective, how can intracapsular rupture on the one hand protect a woman against FM, and an extracapsular rupture, on the other, increase a woman's risk, and all this found in the same dataset? The researchers claim their findings indicate and suggest an association. With all due respect to

my FDA colleagues — How? To me, an impartial and balanced view of their data suggests otherwise.

In light of what the authors' data show with straightforward analysis, I'm left, unfortunately, wondering about their objectivity. Did they have preconceived biases about ruptured implants and FM that led to the way they analyzed and presented their data? Did the authors have strong preconceived notions (even unconsciously) that needed confirmation? Where is the empirical method of allowing the results of proper data analysis to modify incorrect ideas/hypotheses? If this concern is unwarranted, then I'm left asking myself, did the authors overlook (inadvertently or not) basic epidemiologic analysis principles and practices? Whatever the reason, in the end, the rational conclusion from examining the investigators' information across all implant status categories is that no consistent pattern between FM and breast implant rupture exists in this study.

STEVEN J. BOWLIN, DO, MPH, PhD, Dow Corning Corporation, Midland, Michigan, USA.

*Dr. Bowlin is an employee of Dow Corning Corporation.*

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## Drs. Brown and Pennello reply

*To the Editor:*

We appreciate the opportunity to respond to the letter commenting on the results of our study. In his second letter, Dr. Bowlin reiterates criticism to which we have already responded<sup>1</sup>. He also suggests that the proper analyses would have been to combine women with intact implants with women with extracapsular rupture, in which case, he says, it appears as if intracapsular silicone *protects* against fibromyalgia. Previously, he questioned the biological, clinical, and epidemiologic basis for our analysis. But obviously, silicone from extracapsular rupture can spread throughout the body whereas silicone from a ruptured implant maintained within the capsule is less likely to spread as freely.

In Table 1, we show further comparisons of intact implants, intracapsular ruptured implants, and extracapsular ruptured implants using the same logistic regression model we used in our paper<sup>2</sup> ( $p = 1001$ ). The logistic regression model adjusted for self-perceived health, self-perceived implant rupture, site of surgery practice, implant location (subglandular or submuscular), implant age, implant manufacturer, implant type (single or double lumen), implant manufacturer by implant age interaction, and implant manufacturer by site interaction. The last 8 covariables were included because they were associated with rupture, as explained<sup>3</sup>. As we reported previously, when women with extracapsular rupture are compared with other women, the odds ratio of fibromyalgia is 2.8 and significantly greater than 1 ( $p = 0.013$ ). Two new comparisons were made to address Dr. Bowlin's concerns. When women with extracapsular rupture are compared with only women with intact implants, the odds ratio of fibromyalgia is 2.6, about the same as before, but not significant ( $p = 0.11$ ), evidently because fewer women were analyzed. When women with intracapsular rupture are compared with women with intact implants, the odds ratio of fibromyalgia is 0.87, which is not significant ( $p = 0.793$ ). The magnitude of the odds ratio is much less for this comparison (the reciprocal is  $1/0.87 = 1.15$ ) than with the comparison of extracapsular rupture and intact implants (2.6). Thus, when the comparisons of the 3 groups of implants are adjusted for co-variables, the "protective" effect of intracapsular rupture pointed out by Dr. Bowlin is no longer suggested by either the magnitude of the effect or its significance. For comparison, we also list the same comparisons for the diagnoses of Raynaud's syndrome and other connective disease (for a def-

Table 1. Comparisons of intracapsular rupture, extracapsular rupture, and intact implants for diagnosis of fibromyalgia, Raynaud's syndrome, and other connective tissue disease (other) as defined<sup>2</sup>.

Diagnosis	OR	95% CI	p	Degree of Freedom
Intracapsular vs intact				
Raynaud's syndrome	1.44	0.22, 9.42	0.70	231
Fibromyalgia	0.87	0.31, 2.46	0.79	231
Other	0.67	0.12, 3.74	0.65	231
Extracapsular vs intact				
Raynaud's syndrome	4.54	0.54, 38.1	0.16	162
Fibromyalgia	2.60	0.80, 8.44	0.11	162
Other	2.08	0.38, 11.29	0.39	162
Extracapsular vs intracapsular + intact				
Raynaud's syndrome	4.17	1.09, 15.98	0.04	301
Fibromyalgia	2.83	1.25, 6.42	0.01	301
Other	2.66	0.83, 8.57	0.10	301

inition, see our paper), as our study also suggested an association of these diagnoses with extracapsular rupture.

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patients with AS show intestinal inflammation, and inflammatory gut lesions are found on histology in about 60% of cases, even in the absence of any abdominal symptoms. On the other hand, SpA also represent the most frequent extraintestinal manifestation of both ulcerative colitis (UC) and Crohn's disease (CD), the 2 main types of inflammatory bowel disease (IBD)<sup>2</sup>; in the case of CD, complications due to SpA are generally present in 20% of the patients, and radiological findings can be observed in more than 40% of asymptomatic subjects.

CD and AS, or at least their common features, are believed to result from an aberrant response to bacteria, and this finds strong confirmation in animal models, where germ-free conditions prevent the manifestation of both diseases<sup>3</sup>. Together with the overlap in their clinical features, it is therefore conceivable that CD and AS might share a common genetic predisposing background. In the case of AS, a role for HLA-B27 histocompatibility gene has been well established both in humans and in transgenic animal models<sup>4</sup>. However, despite extensive research, a clear pathogenetic role for HLA-B27 molecule has not yet been established, and from twin and family studies it is estimated that more than 50% of the AS-predisposing genetic background remains to be identified<sup>5</sup>. As for CD, a major breakthrough has come from the recent discovery of mutations in the NOD2 gene in a subset of patients with CD<sup>6,8</sup>. The product of NOD2 gene appears to be involved in the inflammatory response to bacteria via the activation of the nuclear factor- $\kappa$ B (NF- $\kappa$ B) pathway, following its interaction with bacterial components such as lipopolysaccharide. NOD2 is therefore regarded as an intracellular sensor of bacteria, and alterations in its ability to activate NF- $\kappa$ B might lead to unwanted reactions underlying inflammatory diseases<sup>9</sup>. Thus, based on its function, and the overlapping features of CD and AS, we were prompted to assess whether NOD2 could also directly influence genetic susceptibility to AS.

Three NOD2 polymorphisms have been shown to associate with increased susceptibility to CD<sup>6,8</sup>, the strongest association being observed with an insertion mutation, 3020insC, which determines a premature truncation of the corresponding protein. As a preliminary test of our hypothesis, we focused our analysis on identification of this variant, and a polymerase chain reaction-restriction fragment length polymorphism investigation was set up to characterize all subjects enrolled in this study (details available upon request). Fifty-three patients with AS with no CD manifestation (38 HLA-B27+ and 15 HLA-B27-) and 58 matched healthy controls were recruited and genotyped for NOD2 3020insC. The results are shown in Table 1. The 3020insC mutation was present with a frequency of 2.5% in the control sample (3/116 chromosomes), consistent with reports for other populations<sup>6,8</sup>. In the AS group, only a single instance of 3020insC was found, corresponding to a frequency lower than 1% (1/106 chromosomes). No differences were observed between HLA-B27+ and HLA-B27- patients (data not shown). Thus, the frequency of 3020insC



### The Crohn's Associated NOD2 3020insC Frameshift Mutation Does Not Confer Susceptibility to Ankylosing Spondylitis

To the Editor:

Spondyloarthropathies (SpA) are a group of relatively common diseases of unknown etiology, whose manifestation is thought to result from the interaction of strong environmental factors with the genetic background in predisposed individuals. These disorders are characterized by inflammation of the spine and sacroiliac joints and by peripheral arthritis. In addition, SpA often show extraskeletal manifestations like iritis/uveitis, psoriasis, and, remarkably, gut inflammation<sup>1</sup>. The association between bowel and joint disease has been extensively investigated, and is strikingly exemplified by one of the most common SpA, ankylosing spondylitis (AS): 20% of

Table 1. NOD2 3020insC mutation in Italian patients with AS and controls.

Genotype	Patients, n = 53	Controls, n = 58
-/-	0	0
-/+	1	3
+/+	0	0

+ denotes mutation, - denotes wild-type.

did not differ substantially in our AS and control groups, and is far from reaching that previously reported in patients with CD (8–16% in different studies<sup>6,8</sup>).

As a result, our analysis does not support the hypothesis of a pathogenic role for NOD2 in the development of AS. It is conceivable that the size of our sample only allowed detection of major genetic effects (with an estimated 80% power to exclude an association with relative risk > 5), and extended analysis of larger samples and different ethnic groups will be necessary to conclusively rule out a NOD2 contribution to AS. However, the fact that we found only a single 3020insC mutation out of 106 AS chromosomes (53 patients) strongly suggests that opposite trends are unlikely to be observed in future studies. The virtual absence of 3020insC mutation in AS is not surprising, as lack of association with NOD2 has also been reported for ulcerative colitis<sup>6,8</sup>, the other common form of IBD and, more recently, for psoriasis<sup>10</sup>. It is tempting to speculate that this observation might reflect the presence of different pathogenetic mechanisms, or the involvement of non-NOD2 response-eliciting bacteria, as the basis of ankylosing spondylitis, ulcerative colitis, and psoriasis, in contrast to Crohn's disease.

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## Book Review

### Epidemiology of the Rheumatic Diseases 2nd edition.

ALAN J SILMAN, MD; MARC C. HOCHBERG, MD, EDITORS. Oxford University Press: New York, 2001, 382 pages, price \$134.95 US

The first edition of *Epidemiology of the Rheumatic Diseases* was a key reference for descriptive and risk factor data for a range of rheumatologic conditions. This revised edition promises to continue in this role. The book begins with an overview of population based approaches to the study of musculoskeletal epidemiology, followed by chapters on rheumatic conditions including inflammatory joint diseases, connective tissue disorders, degenerative and metabolic bone and joint diseases, and regional and widespread pain disorders. Review of morbidity and mortality statistics, and risk factor study results, is provided for each disease. New to this edition is the population studies overview and expanded scope of diseases represented.

Each chapter provides a current and extensive review of descriptive and analytic epidemiologic knowledge, with an international perspective. While chapters are densely packed with information, they are well written, organized logically and systematically, and very readable. Graphs and other illustrations enhance the practicality and accessibility of the text. Prognostic aspects are discussed for some conditions, including osteoarthritis and gout, but a notable omission is the absence for other diseases, especially those with adverse prognostic implications such as systemic lupus erythematosus. If the book has a fault, it is the lack of systematic discussion on the current controversies and methodologic limitations of rheumatologic epidemiology. The population studies section provides an introductory level sketch but is incomplete, and these issues are addressed sporadically throughout the remainder of the text (e.g., ACR classification criteria sensitivity/specificity issues described in the rheumatoid arthritis chapter). For this reason, the book is more a comprehensive review than a tool to facilitate rigorous evaluation of the rheumatic disease epidemiology literature.

This is a strong companion to current epidemiology and clinical rheumatology texts. It is suited for those seeking a quick reference, or an extensive review, of descriptive statistics and etiologic determinants. Recommended audiences include rheumatologists, medical trainees, and researchers in epidemiology and the basic sciences, including graduate students.

Louise Murphy, Department of Public Health Sciences, University of Toronto, Toronto, Ontario, Canada.

## Correction

Goldring SR. Bone and joint destruction in rheumatoid arthritis: What is really happening? *J Rheumatol* 2002;29 Suppl 65:44-9. Permission to reprint Figure 2 was obtained but not acknowledged. The legend should read, "Reprinted with permission, *Arthritis Research* 2001;3:6-12." We regret the error.

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