

# Correspondence



## INSTRUCTIONS FOR LETTERS TO THE EDITOR

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

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

## Carpal Tunnel Sonography by the Rheumatologist versus Nerve Conduction Study by the Neurologist

To the Editor:

Swen, *et al*<sup>1</sup> reported that 46 of 47 patients (98%) with  $\geq 90\%$  relief of complaints after surgery for carpal tunnel syndrome (CTS) had abnormal median nerve conduction studies (NCS), compared to 33 of 47 (70%) having abnormal sonography (SG). Thirteen patients with abnormal NCS did not have this degree of relief following surgery, compared to 7 patients with abnormal SG. Because the authors chose  $\geq 90\%$  relief of complaints as the gold standard for the diagnosis of CTS, these false positives lowered the specificity, positive predictive value, and accuracy of NCS. Undoubtedly, with more severe and/or longstanding median neuropathies, one may not see such a robust response; the fact that these patients did not have such a response should not be used to argue that they did not have CTS. Thus, I would urge caution not to overinterpret the results of NCS in this study. Although the results of SG are provocative I believe that NCS remains essential in the diagnosis of CTS.

TED M. BURNS, MD, Lahey Clinic, 41 Mall Road, Burlington, MA, USA.

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To the Editor:

I was surprised to read the title of a recent *Journal* article, which opposes rheumatologists performing sonography (SG) and neurologists performing nerve conduction study (NCS)<sup>1</sup>. The second surprise was the use of a surgical procedure as a carpal tunnel syndrome (CTS) diagnostic criterion. The third was the attempt to use sonography to transdermally visualize the pseudo-neuroma described by Pierre Marie et Foix, although it is well known by surgeons that pseudo-neuroma is absent in 30 to 40% of cases.

The last but not least surprise was the incredible 0.19 specificity of the nerve conduction study for CTS diagnosis. These surprises lead me to make some comments.

In France many rheumatologists perform nerve conduction studies and many neurologists perform sonography for vascular investigations. In my experience both investigations are essentially complementary and not at all in competition. Considering the gold standard, it seems unethical that patients with normal conduction study should undergo surgery. This is also true for mild median nerve lesion, which logically should first be treated with corticosteroid injection or splinting. I am astonished that one can propose such a protocol to patients. It is well known among surgeons that 30 to 40% of CTS cases with abnormal NCS and cured by surgical release had no pseudoneuroma and normal median size and morphology. So it is not surprising that sonography remains normal in CTS with mild or moderate median nerve lesion and also explains the 14 false negative cases.

Finally, if the specificity of CTS electrodiagnosis is so poor, then I and most other electromyographers would have stopped performing EMG examinations long ago. Only inappropriate methodology can explain the result, and the authors wonder themselves why they had such findings when others<sup>2,7</sup> found a specificity of 90 to 100%. Redmond<sup>4</sup>, quoted many times, found a 92% specificity for the 0.4 ms cutoff (4th digit test). In fact analysis of the study shows that much of their methodology was not appropriate.

1. For sonography the normal data are determined from 20 controls; this allows the calculation of sensitivity, specificity, positive predictive value, and negative predictive value. This was not performed for their nerve conduction study.

2. Logically, the normal data for sonography and nerve conduction study should have been determined from the same population.

3. The electrodiagnostic study criteria used for CTS diagnoses in their study are not sufficient. Electrodiagnosis must not only show the median nerve lesion but also systematically demonstrate normal needle examination of C5 to T1 myotomes<sup>3</sup>, normal ulnar nerve conduction at the wrist and elbow, and if possible normal conduction of the medial antebrachial cutaneous nerve (thoracic outlet syndrome).

4. Their gold standard may be considered as unethical and inappropriate, as one clearly knows by experience<sup>6</sup> that only 80% of patients referred with typical CTS complaints by specialists (rheumatologist, neurologist, orthopedic, or hand surgeon) really have CTS. The other 20% of patients have either ulnar nerve lesions at the elbow, mono or multiroot disease, cervicoharthrosis myelopathy, or thoracic outlet syndrome demonstrated by a complete electrodiagnosis. These patients are very unlikely to experience 90% relief of their complaints after CTS surgery, which explains the rate of true negative NCS.

5. CTS surgery failed in about 5% of cases by incomplete median nerve decompression. In 5 to 10% of CTS cases, electrodiagnosis reveals severe median nerve lesion (axonal loss = 95 to 100%); these severe cases rarely have dramatic improvement after surgery. A further 10 to 20% of patients with CTS demonstrated (by complete electrodiagnostic) associated nerve lesion (ulnar nerve lesion, root diseases, thoracic outlet syndrome...). These lesions were not evaluated by the NCS protocol used in this study and may explain why some patients did not improve as the associated pathology was not treated.

6. On the whole, 20 to 35% of the 63 CTS cases (i.e., 12 to 22 potential false positive CTS) would be expected to have partial or no relief of complaints after surgery. And by chance in this study there are 13 with false positive nerve conduction study.

Contrary to the author's opinion, this study essentially demonstrates that "90% relief of the complaints after surgery" is not a valuable gold standard for CTS diagnosis and that SG is unable to detect mild CTS or to conduct a complete neurologic evaluation of the upper limb. Finally, regarding NCS specificity, the specificity determination (from the cutoff) is the easiest and the first stage for any nerve conduction test study. Generally the cutoff is the mean + 2.5 (or more) standard deviations that provides a speci-

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ficacy of 97.5% (or more). Only after this can the sensitivity, positive predictive value, and negative predictive value be studied.

Generally speaking, in 2001 clinical examination serves to select patients with "CTS complaints"; electrodiagnostic examination serves to reveal the presence and severity of median nerve lesion at the wrist and to evaluate associated nerve lesions. Sonography, radiography, clinical, and biological examinations are essential to determine if CTS is idiopathic or not. In any case, the first treatment to propose to the patient is certainly not surgery, except when the patient has frequent or rapid progression of complaints after corticosteroid injection (or other medical treatment) or when electrodiagnosis reveals a very severe median nerve lesion (which was not specified in this study).

PAUL SEROR, MD, Paris, France.

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## Dr. Swen, et al reply

To the Editor:

We appreciate the interest of Dr. Burns in our paper<sup>1</sup>. He raises the important issue that with severe and/or longstanding median neuropathies, one might not be able to see a robust beneficial response. We chose as a gold standard  $\geq 90\%$  relief of complaints 3 months after surgery, a high cutoff point to definitely eliminate a possible placebo effect. Dr. Burns is quite right to stress that false positives for nerve conduction studies (NCS) might be attributable to our high cutoff point and therefore lower the specificity, positive predictive value, and accuracy for NCS. However, this applies also to sonography (SG). SG investigation is quite different from NCS: the former gives an anatomical picture and the latter is a function test. Both investigations can be complementary; it would be interesting to investigate whether with sonography nonreversible neuropathy can be differentiated from reversible neuropathy, a differentiation that cannot be made with NCS. It could be that in a patient with longstanding nerve compression, swelling can no longer be seen at SG; however, this is a hypothesis.

Dr. Seror has interesting comments on our paper.

A. *Visualization of pseudo-neuroma.* We did not attempt to visualize pseudo-neuromas, but chose the most reliable sonographic characteristic of median nerve compression, being swelling of the nerve. Pseudo-neuroma is a term to describe macroscopic swelling of the median nerve at surgery; indeed, often it is not present. Also in our study the surgeon looked at macroscopical swelling of the nerve and in most cases did not find it. Our point is that the sonographical feature of swelling of the median nerve as a

sign of compression is not the same as the feature of pseudo-neuroma.

B. *Patients with normal NCS undergoing surgery and NCS criteria.* All patients were selected for the study by a neurologist on the basis of typical clinical signs of CTS. It is known that patients with a clinical diagnosis of CTS and a negative NCS often benefit from surgery, as is also the case for patients in our study. Further, there are no generally internationally accepted criteria for a positive NCS. We did not want to define criteria for SG or NCS to use them as a cutoff point for the diagnosis of CTS; we sought only to investigate the possible utility of SG as an investigation for CTS.

C. *Possible selection for our study of patients having neurological problems other than CTS.* The patients were selected by a neurologist on the basis of clinical features (signs and symptoms) typical of CTS.

D. *Surgery instead of local corticosteroid injections.* In our experimental study we chose surgery as therapy because otherwise we could have introduced bias. If a patient would not have had a beneficial effect after injection it could be due to the wrong injection technique. The fact that in this study we chose surgery does not mean that we choose surgery as conventional daily practice for all our patients.

E. *Gold standard  $\geq 90\%$  relief after surgery.* Dr. Burns also raised this point: we would like to refer to our answer to his letter.

We only investigated whether sonography might have a place in detection of CTS. We agree with Dr. Seror that further investigation is warranted: the place of sonography in CTS has further to be defined by additional investigation.

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## Abundant Expression of Common Cytokine Receptor Chain (CD132) in Rheumatoid Joints

To the Editor:

An interesting paper concerning the expression of the common cytokine receptor  $\gamma$  chain (CD132) in the rheumatoid arthritis (RA) synovium was recently published in *The Journal*<sup>1</sup>.

I believe there is an error in the Materials and Methods of this paper, which states that immunohistochemical staining of the RA synovial tissue was performed using streptavidin linked alkaline phosphatase, visualized with 3,3'-diaminobenzidine tetrahydrochloride (DAB). The method as stated would not produce any staining as DAB is a substrate for the immunoperoxidase, not the immunoalkaline phosphatase technique. Can the authors please confirm which technique and substrate they used, as it is not possible to deduce this from the black and white Figure 1 in the paper, and the method as described in the paper is not correct.

I believe there is an alternative explanation for the results the authors have presented. It is well known that the major source of tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and interleukin 1 $\beta$  (IL-1 $\beta$ ) in the RA synovial membrane is the macrophage lineage cell in the lining, not the sublining macrophage<sup>2,3</sup>. It is also clear that macrophages differentiate as they migrate through the synovial membrane into the lining layer, and one of the cell surface markers that is downregulated is CD14. Therefore lining layer macrophages are more likely to be CD68 positive with less CD14 expression.

When the results presented in the paper by Nishio, et al<sup>1</sup> are analyzed, the most obvious finding is that, while there is CD132 expression in the sublining region of the synovial membrane, there is little, if any, in the lining region where most of the TNF- $\alpha$  and IL-1 $\beta$  is made. The authors also

demonstrate by flow cytometry that most of the cells expressing CD132 are CD14 positive macrophages, but it is possible that these are all sublining macrophages and that the further differentiated CD68 positive, CD14 negative lining macrophages are not expressing CD132. This would suggest that CD132 is performing as a negative marker of macrophage differentiation, with the more differentiated lining macrophages failing to express either CD14 or CD132, but being the major source of synovial TNF- $\alpha$  and IL-1 $\beta$ . This would then explain the immunohistochemical staining results shown in Figure 1 and would suggest that CD132 expression is not related to the production of TNF- $\alpha$  and IL-1 $\beta$  by macrophages in the RA synovial membrane. This could be confirmed, of course, by either dual immunohistochemical labelling for CD132 and the inflammatory cytokines, TNF- $\alpha$  or IL-1 $\beta$ , or by combining *in situ* hybridization for the mRNA of TNF- $\alpha$  and IL-1 $\beta$  with immunohistochemical labelling for CD132.

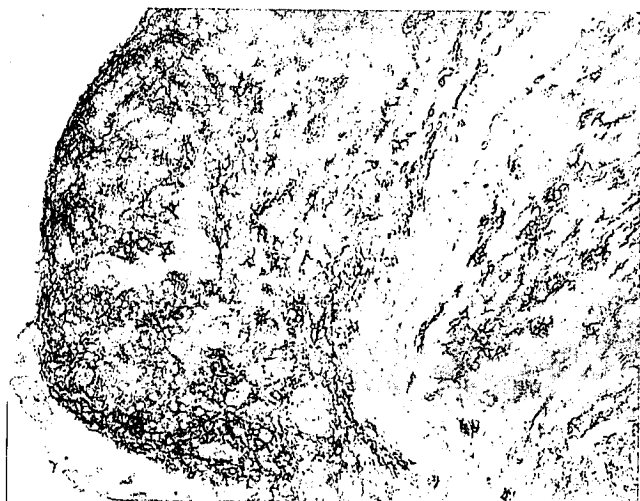


Figure 1. Anti-CD132 antibody staining of rheumatoid synovial tissue. Subsequent to incubation with the antibody, the tissue was treated with streptavidin linked peroxidase and then with DAB.

It is also possible that the high levels of soluble CD132 in the synovial fluid (SF) are due to diffusion from the synovial source into the SF due to the lack of any ligand within the synovial membrane to prevent such diffusion, as is likely with soluble IL-2 receptor levels in the SF.

In conclusion, while the authors have shown CD132 expression on synovial sublining macrophages, there is no evidence that expression of CD132 occurs on the macrophages that are the predominant source of proinflammatory cytokines in the RA synovial tissue, and the role of CD132 in the production of TNF- $\alpha$  and IL-1 $\beta$  remains unproven.

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#### Dr. Nishio, *et al* reply

To the Editor:

Ref: Lost expression of CD14 and CD132; markers of functional or non-functional synovial macrophages? We apologize sincerely to readers for the

incorrect description of the immunohistochemical technique. The antibody binding was visualized with streptavidin linked peroxidase, instead of alkaline phosphatase, which reacted with 3,3'-diaminobenzidine tetrahydrochloride (DAB)<sup>1</sup>.

As pointed out by Dr. Smith, it is likely that maturation or exhaustion of the synovial macrophages downregulates surface expression of CD14 via an unknown pathway. However, it is also true that lining layers of the rheumatoid synovial tissue contain quite a few CD14 positive macrophages<sup>2,3</sup>. In accord with this, we found CD132 positive cells in the lining and sublining layers of the rheumatoid synovial tissues (Figure 1). However, CD132 staining was generally fainter than that in the sublining cells, and thus was not emphasized in our paper<sup>1</sup>. Additionally, it has been reported that a majority of the synovial cells that secrete tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and interleukin 1 $\beta$  (IL-1 $\beta$ ) are CD14 positive macrophages<sup>4,5</sup>. TNF- $\alpha$  production in rheumatoid synovial tissues depends on nuclear factor  $\kappa$ B, which is expressed by a majority of CD14 positive cells in the lining and sublining layers<sup>6,7</sup>. Undifferentiated macrophage cell line, U937, starts expressing CD14 when cells are stimulated and become competent for TNF- $\alpha$  secretion. These facts suggest that synovial macrophages that produce TNF- $\alpha$  at the lining layer still express CD14.

Nevertheless, the synovial sublining layer contains more CD14 positive macrophages than the lining layer. As discussed by Dr. Smith, it has been an enigma that immunohistochemical labelling has revealed the most intensive staining of anti-TNF- $\alpha$  and anti-IL-1 antibodies at the synovial lining layer. Differentiation of the synovial macrophages in relation to cytokine production must be further investigated to solve this issue.

We would like to point out that high levels of soluble receptors in synovial fluid (SF) are not necessarily attributable to lack of ligands in the synovial tissues. Soluble TNF receptors are abundant in rheumatoid SF, although TNF- $\alpha$  is secreted on a large scale and stimulates synovial cells via membrane-bound TNF receptors<sup>8</sup>. Recently, it was reported that fibroblast-like synoviocytes (FLS) also express CD132 on their surface<sup>9</sup>. Using flow cytometric analysis, we observed that most of the cells with high level expression of CD132 are confined to the CD14 positive cell population<sup>3</sup>. Thus, FLS should express CD132 at a lower level, but could be another source of soluble CD132 in SF.

At present, we can provide no direct evidence that the signal through CD132 promotes secretion of TNF- $\alpha$  or IL-1 $\beta$  from CD14 positive macrophages. However, it appears possible that triggering CD132 might activate synovial macrophages, thus exacerbating arthritis.

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## Hyaluronic Acid Serum Levels in Fibromyalgia, Nonspecific Arm Disorder, and Controls

To the Editor:

Yaron, *et al*<sup>1</sup> reported clearly higher hyaluronic acid levels in fibromyalgia (FM) than in controls or rheumatoid arthritis (RA) cases. Barkhuizen, *et al*<sup>2</sup> failed to confirm this finding with a small sample of FM cases. Yaron, *et al*<sup>2</sup> in a second study showed a much less definite difference than initially reported. Yaron's findings have not been confirmed in this study of physical and psychological features in women with FM, nonspecific upper limb disorder (chronic regional arm pain), and volunteer controls without pain<sup>3</sup>.

Methods: The Pharmacia HA test (Kabi Pharmacia Diagnostics AB S-752, Upsala, Sweden) was used for the estimations<sup>4</sup>.

Results: During one to 3 years' wait for this study, 9 cases originally selected as having FM no longer had sufficiently widespread pain or tender points to diagnose FM. These have been transferred to the arm pain category. This did not change the result.

The mean hyaluronate level in the remaining 14 FM cases was 27  $\mu$ g/l, in 32 arm pain cases 24  $\mu$ g/l, and in 20 controls 20  $\mu$ g/l. There was a positive association with age, as expected from the manufacturer's data<sup>4</sup>. After adjusting for age there was no difference between the 3 groups. All levels were within the normal range<sup>4</sup>.

No association was found between hyaluronic level and height, weight, duration of symptoms, number of tender points, number of pain areas<sup>5</sup>, time at a computer keyboard, or an activities of daily living score.

A diurnal variation in RA<sup>3</sup> showed a peak early in the morning. In this study samples were taken in midafternoon, so the possibility arose that the differences might be greater if samples had been taken in the morning. Five subjects with FM with a mean American College of Rheumatology tender point count of 15.5 out of 18 had blood samples taken at 8 AM, 9 AM, and 3 PM. The mean levels at these times were 56, 41, and 35  $\mu$ g/l. For the original 21 FM cases with a lower mean tender point count of 12.5 the mean serum level was 27  $\mu$ g/l for the afternoon samples.

Conclusion: Serum hyaluronic acid estimation was not found to be helpful as either a research or a diagnostic tool in FM or nonspecific arm pain syndrome.

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### Dr. Yaron replies

To the Editor:

We read with interest the report by Dr. Wigley, *et al*, who found no significant differences between serum hyaluronic acid levels in 3 groups: fibromyalgia (FM, n = 14), arm pain (n = 32), and controls (n = 20).

These results are in contrast to ours<sup>1,2</sup> and in accord with those of Barkhuizen<sup>3</sup>.

We have now reviewed serum hyaluronic acid in 28 patients with FM from our clinic and compared them to 13 age matched controls and 32 patients with rheumatoid arthritis (RA). The results were (mean  $\pm$  SEM  $\mu$ g/l) as follows: 26.7  $\pm$  2.05, 49  $\pm$  4.8, 128  $\pm$  2.3 for controls, FM, and RA patients, respectively. The values for FM and RA patients were significantly higher than controls (p < 0.01), but levels of our FM patients were much lower than those in the Beer Sheba FM patients reported<sup>1</sup>. Results reported by Wigley and Barkhuizen as well as our followup observations do not support our initial suggestions for the specificity and sensitivity of HA serum level determinations in patients with FM.

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## Fish Oils Are Beneficial to Patients with Established Rheumatoid Arthritis

To the Editor:

Metaanalysis has shown that fish oils are beneficial to patients with established rheumatoid arthritis (RA)<sup>1</sup>. We were therefore interested to read the recent publication by Volker, *et al*, which examined the effect of fish oil supplementation in RA<sup>2</sup>. In this study, patients randomized to receive omega-3 fatty acids (fish oil) had less active disease than those who received placebo, after 15 weeks. However, we wish to raise a number of concerns in relation to the study methodology.

The abstract is misleading, in that it claims that 50 RA patients were studied. In fact, data are only presented for 26 patients (13 in each group). The remaining 24 were excluded due to "change in RA treatment drugs" (n = 14) or supplement noncompliance (n = 10). No further information is provided for these patients, either at baseline or followup. The authors state that "change in treatment regime was a predetermined criterion for withdrawal from the study." They do not state why this was necessary, or to what it refers (change in dose/type of drug, etc). We feel it is inappropriate, and that an intention-to-treat analysis should have been performed.

The primary outcome investigated was not stated. The American College of Rheumatology (ACR) preliminary criteria for improvement in RA have been recommended to assess treatment in RA clinical trials<sup>3</sup>. In this study, 5/13 (39%) patients in the fish oil group satisfied the ACR-20

improvement criteria, compared to 3/13 (23%) in the placebo group. This gives a risk difference of 15%, 95% confidence interval -19, 50, suggesting the study did not recruit sufficient patients to detect a modest improvement in the intervention group.

We were surprised to find that compliance was higher in the fish oil group (88%) in comparison to placebo (72%). This raises the possibility that patients were not blind to the intervention, since fish oil capsules usually leave a mild but distinctly fishy taste or cause eructation. Therefore patients may have been aware that they were taking an active treatment, which may be beneficial to their disease.

Finally, the study design seriously limits the generalizability of the data. Only those patients with a diet naturally low in omega-6 fatty acids were recruited. However, as the authors themselves mention, omega-6 is now abundant in most Western diets. Previous studies have already shown that fish oils are beneficial in unselected patients. If the authors wished to determine whether fish oils might be more beneficial in patients with low dietary omega-6, then they should have compared patients with high and low levels in the diet.

We agree that further research is directed to identifying effective ways to increase omega-3 intake in RA patients<sup>4</sup>. Supplements are conveniently prescribed or purchased over-the-counter, yet compliance is poor<sup>5</sup>, and many contain small amounts of omega-3. Moderate doses of short and long chain omega-3 fatty acids can be obtained easily from the diet, for example from oil-rich fish, walnuts, and rapeseed oils<sup>6</sup>, and achieves better compliance than from supplements<sup>7,8</sup>. Furthermore, these diets will reduce intake of omega-6, thereby increasing the amount of omega-3 incorporated into cells<sup>9</sup>. In a randomized controlled trial of dietary advice following cardioversion for atrial fibrillation, over 90% of patients eat 2-3 portions of oil-rich fish per week, equivalent to around 1 gram per day of omega-3, or 5 large capsules of some fish oil supplements<sup>10</sup>. We suggest that dietary modification is feasible for patients with RA, and justifies further research.

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## Drs. Volker and Garg reply

To the Editor:

The authors appreciate the interest in our recent paper<sup>1</sup>, which demonstrated that patients with rheumatoid arthritis (RA) who received omega-3 fatty acids (fish oil concentrate) had less active disease than those who received placebo (equivalent amount of olive oil). We would like to suggest that the editorial protocols of *The Journal of Rheumatology* required that this paper be reduced from approximately 6000 words and 40 references to 2000 words and 16 references. The reduction in the scope of discussion and presentation of patient details may well have resulted in an incomplete picture.

Your suggestion that the abstract was misleading results from the lack of detail about the patient group through editorial restrictions. Fifty patients were enrolled and most completed the study. Change in treatment regime (whether a change of dose or drug) would influence the assessment of n-3 fatty acid antiinflammatory effect. In most cases, the change in treatment resulted from intraarticular injections. The compliance requirement was 95% compliance in capsule intake and dietary n-6 < 10 g/day requirement. The dose of n-3 fatty acids was set at 40 mg/kg body weight/day, which was a much smaller dose than had been utilized in previous studies<sup>2,6</sup>. Failure of subjects to consume the required number of capsules could have affected the dose response rate.

The primary outcome of the study was to determine if a dietary supplement, administered with concurrent drug regime, could result in an improvement in the clinical status of RA patients. Your comments about the power of the study are well founded. The subjects were drawn from 5 practices in a provincial city and 250 patient diets were assessed prior to the recruitment of 50 patients. There were no more patients available and the recruitment process took 18 months. The naturally low n-6 background diet was an important consideration because n-6 and n-3 are competitive antagonists for the elongation and desaturase enzymes and of the cyclooxygenase and lipoxygenase systems<sup>7</sup>. In fact, one of the novel aspects of this study was that for the first time in a fish oil supplementation study the background diets of the patients were recorded and analyzed to ensure that n-6 fatty acids were not interfering with the antiinflammatory effect of the fish oil supplement<sup>8,9</sup>.

The study was a double blinded study and the fish oil supplement used did not give rise to reports on eructation. It should be noted that the capsules, supplied by Lube AS, Denmark, contained 60% n-3 fatty acids and did not have a fishy odor. We disagree that the design of the study limits the generalizability of the data, it is now an accepted requirement for n-3 fatty acid studies<sup>5</sup>. We also agree that supplement compliance is often poor; however our group was interested in developing a dose response rate for long chain n-3 fatty acids and this could only be achieved through supplementation. Our group would also suggest that in this study we were not investigating atrial fibrillation; in fact we studied suppression of the pro-inflammatory n-6 derived eicosanoids by the antiinflammatory n-3 derived eicosanoids. Indeed dietary modification to achieve the desired level of omega-3 fatty acids for prevention of RA and other inflammatory conditions is feasible and preferred; however, the levels required for treatment of these conditions are more likely to be achieved by supplementation. The issue of the efficacy of plant sources of omega-3 fatty acids, originating from walnuts, flaxseeds, canola, soybeans, etc. is debatable.

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## Epidemiological Aspects of Behçet's Disease in Galicia

To the Editor:

Behçet's disease (BD) is a vasculitic syndrome with a low incidence in Europe, but which is found in countries around the Mediterranean Basin. Galicia, a northwestern region of Spain, has a Celtic background, and the incidence of BD in Galicia might be expected to be low and similar to that of other Celtic populations in Europe.

Gonzalez-Gay, *et al* recently reported the epidemiological and clinical features of BD in Lugo, a province of Galicia. The authors point out that the annual incidence and clinical spectrum of the disease were not previously well defined in the northwest of Spain<sup>1</sup>.

We believe that Gonzalez-Gay, *et al* were probably not aware of previously published epidemiological and clinical data on BD<sup>2,3</sup>, and we would like to contribute to the knowledge about this rare disease. The average annual incidence rate of complete BD in the province of La Coruña, which is next to the province of Lugo, both of which are in Galicia, was 0.32/100,000 (95% CI 0.14-0.73); and for men 0.53/100,000 (95% CI 0.17-0.16) (Tables 1 and 2). The prevalence rate was 5.6/100,000 (95% CI 7.56 ± 3.64). We also described the clinical features of the patients.

Additional clinical aspects are described in the next report about HLA and arthritis in BD<sup>4</sup>. Of the 32 patients with BD, 27 (84%) presented arthritis. Our study showed that the frequency of arthritis in patients with BD was high compared to most reports, around 50% according to Gonzalez-Gay, *et al*<sup>1</sup>. We found a statistically significant association between HLA-

Table 1. Average annual incidence of BD in health area of La Coruña (Galicia, Spain) per 100,000 population (1978-90).

Age	1978-82	1983-87	1988-90	Total
20-29	0 (0)	2 (0.25)	1 (0.21)	3 (0.14)
30-39	2 (0.27)	5 (0.68)	1 (0.23)	8 (0.42)
40-49	1 (0.15)	3 (0.46)	4 (1.02)	8 (0.47)
50-59	2 (0.15)	5 (0.73)	0 (0)	7 (0.39)
60-69	0 (0)	2 (0.39)	0 (0)	2 (0.15)
Total	5 (0.15)	17 (0.50)	6 (0.29)	28 (0.32)

Table 2. Male average annual incidence of BD in health area of La Coruña (Galicia, Spain) per 100,000 population (1978-90).

Age	1978-82	1983-87	1988-90	Total
20-29	0 (0)	2 (0.51)	1 (0.42)	3 (0.29)
30-39	2 (0.56)	5 (1.4)	1 (0.47)	8 (0.86)
40-49	0 (0)	2 (0.64)	3 (1.61)	5 (0.62)
50-59	1 (0.32)	4 (1.26)	0 (0)	5 (0.61)
60-69	0 (0)	1 (0.45)	0 (0)	1 (0.17)
Total	3 (0.19)	14 (0.87)	5 (0.52)	22 (0.53)

B51 and BD, with a relative risk of 4.71. The attempt to relate markers B51 and B27 to the presence of arthritis and its further development was not conclusive. We observed a relationship between oral ulcers and arthritis in patients carrying the B12 allele. Other manifestations were not correlated with any antigen, and joint episodes were not related to mucocutaneous symptoms.

We have no explanation for the difference between Gonzalez-Gay, *et al* data and ours. They believe that BD incidence may have been underestimated and we agree with their reasoning; however, we observed a reduction in the annual cases of BD in recent years. There might be several reasons for this decrease; for instance, an increase in the awareness of BD by other physicians could account for the reduction of patients with BD seen in our rheumatology department. Thus, from an area serving 500,000 people there are 54 active charts of BD patients that make periodic visits to our hospital (we have lost 12 patients for several reasons).

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## Drs. Gonzalez-Gay, *et al* reply

To the Editor:

We appreciate the interest in our work<sup>1</sup> shown by Dr. Graña. However, we would like to make clear some points that may be valuable for readers interested in this form of vasculitis.

First, our hospital provides medical care to a very specified area, which is not the province of Lugo as a whole; rather, it serves the area surrounding Lugo city, in the middle of the province. This long neglected area of inner Galicia has important peculiarities reported elsewhere<sup>2,3</sup>. Of note, it is not a coastal area. Moreover this area was isolated from the rest of Galicia for many centuries due to geographical problems. Second, the article and abstract discussed by Dr. Graña as References 2 and 3 were not found in a Medline database search performed by our group before submitting our epidemiological



data for publication. Third, in our study we retrospectively classified our patients according to the International Study Group Criteria for Behçet's disease (BD). Thus, patients who did not fulfill such criteria were not discussed in that report. Also, we used adjusted rates. However, in Dr Graña's letter no information about adjusted rates is provided. Indeed, we are surprised at the rapid and unexpected dramatic changes and variations in the incidence of BD in so short a time, as described by these authors. These amazing changes among different periods of study raise our concern about possible bias in the diagnosis of their patients. To avoid problems like these, we paid special attention in our study to exclude other conditions mimicking BD. Because of that, the frequency of severe neurological manifestations in Lugo was relatively high, which relates to the more strict criteria for the diagnosis of patients with this condition in our hospital.

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## Quadriceptal Tendon Enthesitis in Psoriatic Arthritis and Rheumatoid Arthritis: Ultrasound Examinations and Clinical Correlations

To the Editor:

Enthesitis is an inflammatory lesion of the tendon, ligament, and capsular insertions on the periosteum, and it is considered a fundamental element in the diagnosis of seronegative arthritis<sup>1,2</sup>. Psoriatic arthritis (PsA) is a chronic inflammatory arthropathy belonging to the group of seronegative arthritic pathologies; PsA is characterized by its association with the cutaneous and/or ungual lesions typical of psoriasis, frequent inflammatory involvement of periarticular structures such as tendons or entheses, and the new formation of periosteal bone<sup>3,4</sup>. Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by a progressive polyarthritis that mainly affects the small joints and tendons and may result in disabling deformities<sup>5,6</sup>. We investigated the clinical and sonographic prevalence of quadriceptal tendon enthesitis in patients with PsA and RA, and identified any sonographically demonstrable morphostructural differences between the type of enthesitis associated with the 2 diseases. We also verified whether there is a correlation between enthesitis and peripatellar psoriatic skin lesions.

Enthesitis is characterized by an early phase involving edema, inflammatory infiltration, and destructive fibrocartilage microlesions, which subsequently evolve into periosteal fibro-cicatricial erosions leading to new bone deposition (enthesophytosis)<sup>7,8</sup>. It is clinically manifested by the onset of spontaneous pain and tenderness upon pressure or in the case of obstructed movement, but is frequently asymptomatic<sup>9</sup>. Sonography is the method of choice for studying periarticular soft tissues because it is capable of detecting both the early (edema, thickening) and late alterations (erosions and calcification); it is also a cheap, harmless, and easily repeatable technique<sup>10</sup>.

Forty consecutive patients with PsA (mean age 51.7 yrs; 22 men, 18 women; M/F ratio 1.2) and 40 consecutive patients with RA (mean age 50.3 yrs; 4 men, 36 women; M/F ratio 0.1), classified according to the criteria of the American Rheumatism Association<sup>11</sup>, were clinically and sonographically evaluated in our outpatient department between November 1997 and October 1998 (mean time since diagnosis  $3 \pm 2$  yrs) by 4 experienced rheumatologists. Eighty healthy controls (27 men, 53 women; mean age 54.2 yrs) were evaluated in the same manner.

Of the PsA patients, 9/22 men and 8/18 women had active cutaneous psoriasis; they were not further divided into disease subsets (according to Wright and Moll<sup>12</sup>) because not all of the clinical variants of PsA were represented.

The clinical examination involved determining the presence or absence of pain (spontaneous, upon finger pressure, or in the case of contrasted movement — knee extension) at the level of the quadriceptal entheses, the presence of effusion on the joint, and the presence of any psoriatic lesions in the peripatellar extensor region.

The ultrasound examination was performed by one experienced sonographer (blinded to diagnosis) using a Toshiba SAL 240 with a 7.5-MHz linear electronic probe and a Kitecho gel pad. The quadriceptal enthesitis was evaluated by axial and longitudinal scans of the supine patient, with the knee extended at rest, with quadriceptal contraction, and subsequently in 30° flexion in order to increase the distention of the tendinous fibers and thus avoid the "empty tendon" artefact<sup>13</sup>. The following findings were considered indicative of quadriceptal enthesitis: the presence of thickening, hypoechogenicity localized to the enthesitis, the loss of normal fibrillar structure, gross irregularity of the patella (> 2 mm), and insertional calcifications (enthesophytes) of > 5 mm<sup>13,14</sup>. Further, all the patients were evaluated for the presence of articular effusion in the suprapatellar recess (hypochoic fluid collection > 4 mm in contraction)<sup>15</sup>. The percentages obtained were compared by Fisher's exact test and the chi-square test.

Eighteen (45%) of the patients with PsA had sonographic signs of quadriceptal enthesitis, a significantly higher frequency ( $p < 0.01$ ) than the 7.5% found in the patients with RA (Figure 1). In contrast, ultrasound examination showed a higher prevalence of articular effusion in RA (38/40, 95%) than in PsA (24/40, 60%;  $p < 0.05$ ) (Figure 1). In these patients with sonographic alteration, clinical examination revealed articular effusion in 87% in PsA and 90% in RA, whereas quadriceptal enthesitis was found in only 45% in PsA and in 66% in RA.

Another statistically significant observation ( $p < 0.01$ ) was that quadriceptal enthesitis may be the only manifestation of inflammatory involvement of the knee in PsA patients regardless of the presence of articular effusion, whereas no case of isolated enthesitis was observed among the patients with RA (Figure 2).

Quadriceptal enthesitis was more frequent in the male patients with PsA (14/18, 77%). Only 4 cases of enthesitis were found among the healthy controls (3 men and one woman), a prevalence that was significantly less ( $p < 0.0001$ ) than that observed in the PsA patients, but not significantly different from that observed in the RA patients. An association between psoriatic skin lesions (whatever the site) and quadriceptal enthesitis was observed in 8/17 patients (47%), only 4 of whom presented psoriasis in the peripatellar extensor region (all with isolated enthesitis and no effusion).

Ultrasound examinations of the 18 PsA patients with enthesitis revealed that 17 had irregular bone profiles, 9 enthesophytosis, and 9 thickening and hypoechogenicity of the entheses. In the 3 RA patients with quadriceptal



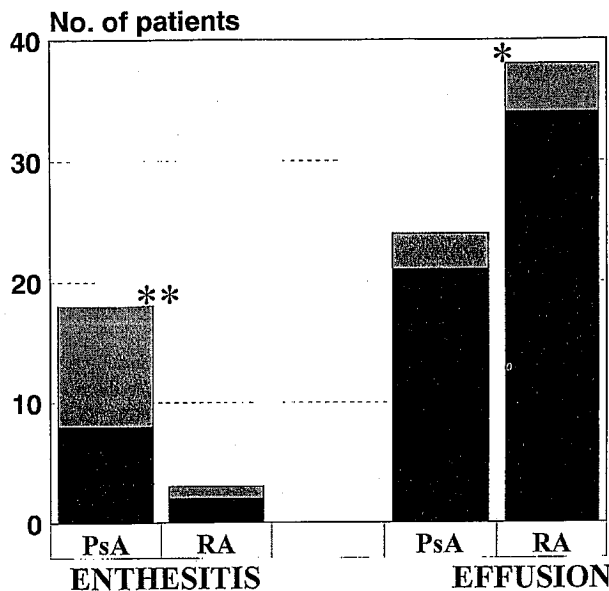


Figure 1. Prevalence of quadriceptal enthesitis and knee effusion in PsA and in RA patients at ultrasound examination. Black panels: symptomatic patients; shaded panels: asymptomatic patients. \* $p < 0.05$ ; \*\* $p < 0.01$ .

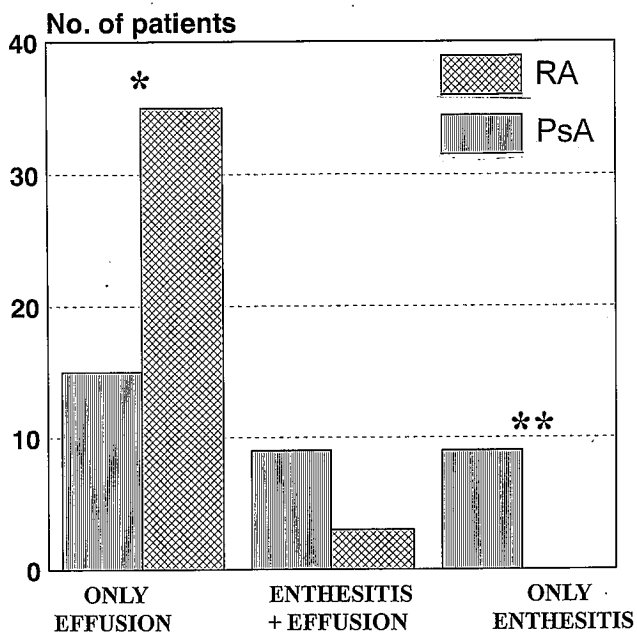


Figure 2. Patients with RA showed a prevalence of articular effusion, with no case of isolated quadriceptal enthesitis; in PsA patients enthesitis may represent the only manifestation of inflammatory knee involvement. \* $p < 0.05$ ; \*\* $p < 0.01$ .

enthesitis, echography revealed an irregular bone profile in one case and hypoechoogenicity in 2. No patient showed any signs of erosions (Table 1).

As in the case of all forms of seronegative spondyloarthritis, enthesitis inflammatory involvement is a very important criterion for the diagnosis of PsA, whereas the prevalence of enthesitis is relatively low in RA. This is confirmed by our results, in which the frequency of enthesitis in PsA

Table 1. Sonographic features of quadriceptal enthesitis in patients with PsA and RA.

	PsA	RA
Enthesophytes > 5 mm	9	0
Irregularities > 2 mm	17	1
Thickening / hypoechoogenicity	9	2
Erosions	0	0

patients is significantly higher than in RA patients; thus enthesitis, in PsA, can be considered a clinical sign of arthritis that almost reaches the importance of articular effusion. Echography proved to be a highly sensitive means of revealing articular and periarticular alterations, particularly given that more than half our PsA patients with enthesitis were asymptomatic. The prevalence of enthesitis was higher in the men of both our PsA and control populations, a gender difference that may be due to factors such as heavy physical work, sport, greater body weight, or possibly dysmetabolism. However, it is notable that this prevalence was significantly higher in the male PsA subjects than in the healthy controls, and that the presence of quadriceptal enthesitis was significantly less in the women with RA than in those with PsA. The presence of psoriatic skin lesions (regardless of their site) does not seem to be associated with the presence of enthesitis. Further studies could verify whether the presence of psoriatic skin blotches increases the probability of finding inflammatory alterations in the articular and periarticular structures closest to the lesion.

The structural alterations observed by ultrasound were different in the 2 diseases: the patients with RA showed a prevalent inflammatory component consisting of edema, thickening, and focal hypoechoogenicity, whereas those with PsA also showed major new periosteal bone depositions leading to the formation of enthesophytes (which were only observed in our PsA subjects).

In the case of suspected PsA, we therefore think it is important to perform systematic multijoint echographic examinations that include the articular and periarticular structures of the knee (with particular reference to the quadriceptal entheses — in addition to the proximal and distal patellar entheses and anserine bursa), even if physical examination fails to reveal any electively tender areas, swelling, or positive patella ballottement. Further studies should be undertaken to determine if sonography can be useful to differentiate the various types of polyarthritides.

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### Dolorimetry Performed at 3 Paired Tender Points Highly Predicts Overall Tenderness

To the Editor:

Psychophysical and other studies have shown that fibromyalgia (FM) is characterized by a global decrease in pressure pain threshold rather than by specific changes limited to the tender point areas<sup>1,2</sup>. In clinical routine, tenderness is assessed by manual palpation of tender and control points, while in research settings a pressure gauge is more often used to measure an actual pain threshold (dolorimetry). It has, however, become clear that manual tender point counts are significantly influenced by psychological factors, like an individual's distress<sup>3</sup>, while dolorimetry is less affected and is thus a more pure measure of tenderness<sup>4</sup>.

Dolorimetry has typically been performed at all the 18 designated tender points or various subsets of them, as well as a number of variable control points<sup>5</sup>. Little is known about the efficiency of performing dolorimetry at all of these points compared to fewer sites<sup>7</sup>. We investigated whether the measurement of pain threshold with dolorimetry at fewer paired tender and/or control points is a sufficiently precise substitute for the overall pressure pain threshold determined at all tender points.

We studied 40 female patients with FM (average age 41.4 ± 9.2 yrs) meeting the American College of Rheumatology diagnostic criteria<sup>8</sup> and an age matched cohort of 40 healthy female controls (average age 40.8 ± 9.6 yrs). Patients were unselected attendees of the rheumatology clinic; controls were selected from a pool of 104 patients obtaining a routine history and examination at a primary care clinic. Dolorimeters with rubber heads (surface area 3.14 cm<sup>2</sup>, Chatillon Instruments) were applied over the 18 tender points and 2 pairs of control points, i.e., bilateral thumbnails and tibialis anterior muscles. Pressure was increased at a rate of 1 kg/s, and subjects indicated when they first felt pain (pain threshold). If no pain was reported, the threshold maximum of 12 kg/3.14 cm<sup>2</sup> was recorded.

The correlations between the right and left threshold readings ranged from a low of 0.78 (epicondyle) to a high of 0.90 (occiput) for the total sample of 80 subjects. Correlations in the 2 groups were similar, although slightly smaller in the controls due to range restriction. This validated the practice of averaging the paired threshold readings, which were used in the subsequent analysis.

Given that the 22 intraindividual pain thresholds obtained were not truly independent measures, we decided *a priori* to restrict the analysis to 2 models using paired points, one based on empirical, the other on clinical findings. The empirical model was based on the correlation of each site with the average of the respective 10 other sites to avoid a part-whole correlation. The sites were rank ordered by the size of their correlation with the total sample, and the first 3 (supraspinatus, epicondyle, occiput) were selected (Table 1). The clinical model was based on clinical experience as well as accessibility of the sites — thumbnail, mid-trapezius, and epicondyle were selected. Both models were evaluated with an analysis of accuracy by calculating coefficient alpha and discriminant function analysis by calculating the canonical correlation, Wilkes lambda, and jackknifed classifications.

Coefficient alpha for the empirical model was 0.940 and thus slightly higher than for the clinical model (0.870). For comparison, Table 2 shows the decrease of coefficient alpha in an example of a random reduction of sites included in the accuracy analysis, indicating a superior fit for the empirical, but also an adequate fit for the clinical model.

Using all 11 paired sites the ability to discriminate the patients with FM from the controls was highly accurate. The canonical correlation was 0.95, Wilkes lambda 0.089, with  $F_{1,68} = 63.1$  and  $p < 0.0001$ . Jackknifed classifications correctly identified all 40 (100%) patients with FM and 37 (93%) controls. For the empirical model, classification accuracy was reduced, but still substantial. The canonical correlation was 0.64, Wilkes lambda 0.585, with  $F_{3,76} = 17.9$  and  $p < 0.0001$ . Jackknifed classifications correctly identi-

Table 1. Correlation between the pressure pain thresholds at each paired site with the total pain threshold at the respective 10 other sites.

Site	Total Sample	Fibromyalgia	Controls
Spinatus	0.92	0.91	0.84
Epicondyle	0.89	0.88	0.81
Occiput	0.88	0.90	0.77
Gluteal	0.87	0.84	0.67
Knee	0.86	0.84	0.70
Rib	0.84	0.85	0.80
Trochanter	0.83	0.83	0.57
Trapezius	0.83	0.74	0.79
Anterior tibial	0.83	0.85	0.53
Thumb	0.79	0.76	0.71
Cervical	0.75	0.56	0.69

Table 2. Accuracy for total sample based on random reduction of the number of included sites from 11 to 1. Coefficient alpha of the 2 models is given for comparison.

Number of Sites	Coefficient alpha
11	0.97
10	0.967
9	0.964
8	0.959
7	0.954
6	0.946
Empirical model	0.940
5	0.936
4	0.922
3	0.898
Clinical model	0.870
2	0.855
1	0.746

fied 33 (83%) patients with FM and 30 (75%) controls. The clinical model was as accurate as the classifications based on all sites. The canonical correlation was 0.95, Wilks lambda 0.102, with  $F_{3,76} = 17.9$  and  $p < 0.0001$ . Jackknifed classifications again correctly classified all 40 (100%) patients with FM and 37 (93%) controls.

These data suggest that examination of tenderness by dolorimetry at only 3 paired sites is a reliable and clinically useful assessment of an individual's overall pain threshold. The sites used in both models are easy to locate and examine, and may serve as a quick survey of an individual's overall tenderness. These results also provide a rationale to argue that a limited dolorimeter examination is a feasible and valid substitute for a tender point count as a measure of tenderness in both research and clinical settings. This is desirable, given the significant relation between the manual tender point count and an individual's level of distress, which may be a feature of the method and not an inherent feature of persons who are tender<sup>9</sup>.

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